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Conformational Analysis. V. The Reaction of *cis*- and *trans*-4-*t*-Butylcyclohexanol and *trans*-4-Methylcyclohexanol with Phosphorus Pentabromide. Syntheses of Alkylcyclohexyl Bromides[1]

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Reaction of *cis*-4-*t*-butylcyclohexanol with phosphorus pentabromide gives *trans*-4-*t*-butylcyclohexyl bromide, a mixture of 1-, 3-, and 4-*t*-butylcyclohexenes and a dibromide which appears to be *trans*-3-*cis*-4-dibromo-*t*-butylcyclohexane. An easier route to *trans*-4-*t*-butylcyclohexyl bromide involves catalytic hydrogenation of 4-*t*-butylbenzoic acid followed by a Hunsdiecker reaction to give a mixture of *cis*- and *trans*-4-*t*-butylcyclohexyl bromides rich in the latter; the *cis*-contaminant may be removed by preferential destruction by base. *trans*-4-*t*-Butylcyclohexanol and phosphorus pentabromide yield *cis*-4-*t*-butylcyclohexyl bromide (which may be purified by crystallization) and a small amount of a position isomer, as well as a dibromide fraction apparently consisting of a major amount of *cis*-3-*trans*-4-dibromo-*t*-butylcyclohexane and a minor amount of the *trans*-3-*cis*-4 isomer. A mixture of the same two dibromides but in reversed proportion is obtained by the addition of bromine to 4-*t*-butylcyclohexene.

Reaction of commercial (*trans*-rich)-4-*t*-butylcyclohexanol with hydrogen bromide leads to a complex mixture of positional as well as configurational isomers. Treatment of *trans*-4-methylcyclohexanol, obtained by fractional distillation of the commercial *cis-trans* mixture, with phosphorus pentabromide leads to *cis*-4-methylcyclohexyl bromide among other products. The stereochemical and mechanistic implications of these results are discussed.

In connection with another problem[2] we have studied the preparation of *cis*- and *trans*-4-*t*-butylcyclohexyl bromide and *cis*-4-methylcyclohexyl bromide.

cis-4-*t*-Butylcyclohexyl bromide was prepared from pure *trans*-4-*t*-butylcyclohexanol—readily available by reduction of the corresponding ketone with lithium aluminum hydride—aluminum chloride, followed by equilibration with acetone[4]— by treatment with phosphorus pentabromide.[5] This reaction produced, in addition to the desired *cis*-bromide, a minor amount of at least one isomeric bromide, possibly a 3-*t*-butylcyclohexyl bromide, as well as a substantial quantity of dibromide. The nature of the dibromide is discussed further below.

From the preparative point of view it was also satisfactory to prepare *cis*-4-*t*-butylcyclohexyl bromide from the commercially available mixed 4-*t*-butylcyclohexanols (containing about 80% of the *trans* isomer). In this case, 4-*t*-butylcyclohexene and *trans*-4-*t*-butylcyclohexyl bromide were additional contaminants of the desired product (having presumably originated from the *cis* alcohol). The crude monobromide was obtained from the mixed alcohol in 27% yield and was purified by repeated low-temperature recrystallization from pentane with a 32% recovery of the pure, crystalline *cis* isomer.

The presumed 3-*t*-butylcyclohexyl bromide contaminant was shown not to be a product of ring contraction, since hydrogenation of a mixture rich in this product, using Raney nickel in base as

(1) (a) Presented in part before the Division of Organic Chemistry at the San Francisco meeting of the American Chemical Society, April 15, 1958. (b) Paper IV: E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, 79, 5995 (1957).

(2) E. L. Eliel and R. G. Haber, *Chem. & Ind. (London)*, 264 (1958); in connection with this problem *cf.* also ref. 3.

(3) P. Klaeboe, J. J. Lothe, and K. Lunde, *Acta Chem. Scand.*, 11, 1677 (1957).

(4) M. Rerick and E. L. Eliel, Abstracts, San Francisco Natl. Meeting, Am. Chem. Soc., 4N (1958).

(5) Regarding the preparation of cyclohexyl halides from the alcohols and its steric course, *cf.* (a) R. J. Bridgewater and C. W. Shoppee, *J. Chem. Soc.*, 1709 (1953); (b) W. Hückel and H. Pietrzok, *Ann.*, 540, 250 (1939); (c) M. Mousseron, R. Granger, and J. Valette, *Bull. soc. chim. France*, 244 (1946); (d) see also E. L. Eliel in M. Newman's "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1956, pp. 128–130.

catalyst, gave *t*-butylcyclohexane. The 3-*t*-butylcyclohexyl bromide may have originated from 4-*t*-butylcyclohexene by addition of hydrogen bromide in the reaction mixture. This hypothesis appears unattractive, however, since pure *trans*-4-*t*-butylcyclohexanol gave the isomeric bromide, even though it gave almost no olefin; whereas the *cis* isomer, which gave much olefin, yielded almost none of the isomeric bromide. More likely, the 3-bromide resulted from a carbonium ion type rearrangement observed also in other conversions of alcohols to halides with phosphorus pentahalide.[5c,6] The characteristic infrared band of this bromide at 14.7μ as well as its stability to base suggested that it was an equatorial bromide, as might be expected to result from a carbonium ion,[7] whereas addition of hydrogen bromide to an olefin would more likely have yielded an axial bromide as the main product.[8] A weak band at 15.4μ suggests that traces of the axial isomer may have been formed also.

Other methods of synthesis of *cis*-4-*t*-butylcyclohexyl bromide were examined. Reaction of *trans* rich, commercial 4-*t*-butylcyclohexanol with phosphorus tribromide gave an olefin fraction and (in poor yield) a monobromide fraction. In this case no dibromide resulted, but appreciable amounts of phosphite ester were formed. This ester could be pyrolyzed to a mixture of *t*-butylcyclohexene isomers with the 4-*t*-butyl compound predominating. Treatment of the *trans* rich alcohol with 48% hydrobromic acid at reflux produced a monobromide fraction in high yield, but from infrared evidence, this material was a mixture of not only *cis*- and *trans*-4-*t*-butylcyclohexyl bromide but probably two other compounds (3-*t*-butylcyclohexyl bromides?) in such proportions that separation appeared quite unpromising.[9] No reaction took place when gaseous hydrogen bromide was passed through a pentane solution of the alcohol at 0°.

cis-4-Methylcyclohexyl bromide was synthesized, similarly as the 4-*t*-butyl homolog, from *trans*-4-methylcyclohexanol[10] and phosphorus pentabromide. The bromide obtained from it was again separated, by distillation into a monobromide fraction and a dibromide fraction. The monobromide appeared to be a mixture of *cis*-4-methylcyclohexyl bromide and an isomer, possibly a 3-bromide, which latter could be removed by low-temperature crystallization. The dibromide fraction in this case was not examined.

Impure *trans*-4-*t*-butylcyclohexyl bromide was obtained in only 8% yield from the relatively inaccessible pure *cis*-4-*t*-butylcyclohexanol[11] and phosphorus pentabromide. The crude monobromide fraction contained a little *cis* isomer and traces of the third bromide previously described. These traces may have been formed by the addition of hydrogen bromide to the olefin by-product. The dibromide fraction (main product) is discussed further below. There was also obtained, in this case, a substantial amount of olefin which, according to infrared spectrum, was a mixture of 1-, 3- and 4-*t*-butylcyclohexene.[12] It was not established whether the 1- and 3-*t*-butylcyclohexenes were rearrangement products of 4-*t*-butylcyclohexene formed initially by diaxial elimination, or whether they were primary rearrangement products formed directly from the alcohol by a carbonium-type rearrangement.

Because of the low yield in the above-described preparation of *trans*-4-*t*-butylcyclohexyl bromide, alternative routes to this compound were sought. *cis*-4-*t*-Butylcyclohexyl tosylate[13,1b] was treated with lithium bromide in acetone.[14] Not unexpectedly,[14] this led to much 4-*t*-butylcyclohexene, but, in addition, the desired *trans*-4-*t*-butylcyclohexyl bromide was contaminated with condensation products of acetone, which proved to be hard to remove, as well as with a small amount of *cis* isomer, probably resulting from inversion of the *trans* bromide by lithium bromide. An attempted inversion of *cis*-4-*t*-butylcyclohexyl bromide to the *trans* isomer with lithium bromide in acetone was even less promising, for the reaction was extremely slow and in addition to much unreacted starting material and acetone condensation products there was obtained not only the desired *trans*-4-*t*-butylcyclohexyl bromide but also the previously encountered third bromide (3-isomer?) which seemed impossible to remove.

Finally a method was developed which, though not affording much higher yields, employed a starting material more readily available than *cis*-4-*t*-butylcyclohexanol. 4-*t*-Butylbenzoic acid was hy-

(6) *Cf.* W. Hückel and K. Kummerle, *Ber.*, **75**, 115 (1942); L. H. Darling, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 1364 (1953); R. Cornubert and K. Nadjme-Abadi, *Compt. rend.*, **241**, 7 (1955); N. D. Zelinsky and K. A. Kozeschkov, *Ber.*, **60**, 1104 (1927); L. Palfray and B. Rothstein, *Compt. rend.*, **190**, 942 (1929).

(7) *Cf.* W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

(8) *Cf.* G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(9) We have been quite unsuccessful in separating any of these bromides by column chromatography on alumina. Low-activity alumina failed to give separation, high-activity alumina led to dehydrohalogenation.

(10) E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **23**, 2041 (1958).

(11) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

(12) The spectrum of pure 4-*t*-butylcyclohexene was recorded on a sample kindly supplied by Prof. Saul Winstein; *cf.* Ref. 13. The infrared spectra of pure 1- and 3-*t*-butylcyclohexene were taken from the thesis of Richard L. Reeves, University of Wisconsin, Madison, Wis. We thank Prof. Harlan L. Goering for making this thesis available to us. *Cf.* also H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Am. Chem. Soc.*, **78**, 4926 (1956).

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

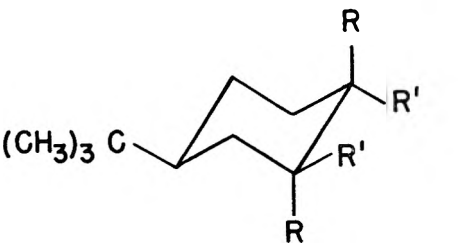
(14) S. Winstein, D. Darwish, and N. J. Holness, *J. Am. Chem. Soc.*, **78**, 2915 (1956).

drogenated to the corresponding cyclohexanecarboxylic acid (*cis* and *trans* isomer) which was subjected to the Hunsdiecker reaction.[15] A mixture of *cis*- and *trans*-4-*t*-butylcyclohexyl bromides rich in the *trans* isomer resulted here, and though it contained more of the *cis* contaminant than that obtained in the treatment of the *cis* alcohol with phosphorus pentabromide, both samples of the *trans* bromide could be purified by preferential destruction of the *cis* isomer with mineral base.[13]

Structural confirmations. The structure and configuration of the above-described *cis*-4-*t*-butylcyclohexyl bromide was confirmed by reaction with sodium thiophenolate. This led to a mixture of 4-*t*-butylcyclohexene and *trans*-4-*t*-butylcyclohexyl phenyl thioether, identical in infrared spectrum with an authentic sample.[1b] Since the thiophenolate reaction followed second-order kinetics,[2] application of Ingold's S_N2 rule[16] allows one to conclude that the starting *t*-butylcyclohexyl bromide was the *cis*-4 isomer. The structure and configuration of *cis*-4-methylcyclohexyl bromide was assigned by analogy and is in accordance with kinetic results, to be published later, which indicate that in the rate of its reaction with thiophenolate, *cis*-4-methylcyclohexyl bromide was intermediate between *cis*-4-butylcyclohexyl bromide and cyclohexyl bromide itself. The structure and configuration of *trans*-4-*t*-butylcyclohexyl bromide was deduced from the fact that it produced *cis*-4-*t*-butylcyclohexyl phenyl thioether,[1b] in addition to some 4-*t*-butylcyclohexene, upon prolonged boiling with alcoholic sodium thiophenolate.

The mixture of 1-, 3-, and 4-*t*-butylcyclohexenes mentioned earlier was subjected to catalytic hydrogenation. The mass spectrum and infrared spectrum of the resulting product indicated it to be mainly *t*-butylcyclohexane, by comparison with authentic spectra (API). A characteristic contaminant was 1-*t*-butylcyclohexene,[12] a not unexpected result, since this olefin, for steric reasons, should be hydrogenated more slowly than its 3- and 4-isomers.

The dibromides. The dibromide "A" obtained from *cis*-4-*t*-butylcyclohexanol with phosphorus pentabromide appeared to be a homogeneous substance, crystalline at low temperatures, and showed only two well-shaped carbon-bromine stretching bands in the infrared spectrum at 14.85 and 15.5μ. In contrast, the dibromide obtained similarly from *trans*-4-*t*-butylcyclohexanol appeared to be a mixture of at least two isomers. The major component "B" had C—Br stretching bands at 14.3 and 14.7μ, but there were also minor bands at 14.85 and 15.5μ which could be attributed to the above-described isomer A. Both dibromides were shown to be 3,4-dibromo-1-*t*-butylcyclohexanes on the basis of elementary analysis and the fact that both were dehalogenated in a variety of ways to 4-*t*-butylcyclohexene. Moreover, a mixture of the two bromides A and B was obtained by addition of bromine to 4-*t*-butylcyclohexene. Since A predominated in this bromine addition product, it is likely that A is the diaxial dibromide, *trans*-3-*cis*-4-dibromo-*t*-butylcyclohexane (I) whereas B is the diequatorial dibromide, *cis*-3-*trans*-4-*t*-butylcyclohexane (II); for it has been found[8] in the steroid series that



I. R = Br, R′ = H II. R = H, R′ = Br

addition of bromine to cyclohexenes gives predominantly the diaxial bromine addition product with minor amounts of the diequatorial isomer.

The configurational assignment of the dibromides is in agreement with the infrared spectral evidence (discussed further below) and the fact that the presumed diaxial dibromide A, upon prolonged heating by itself or in boiling alcohol solution was converted to a mixture of A and B. Interconversion of epimeric diaxial and diequatorial vicinal *trans* dihalides by heating has already been demonstrated in the steroid series,[8,17] whereas there is no precedent for the interconversion of a *cis*-(equatorial-axial)dibromide with either of its *trans* epimers. The fact that B had a higher boiling point than A is also in agreement with the assigned configurations II and I, inasmuch as II undoubtedly has the higher dipole moment and the Dipole Rule[18] predicts that the isomer of higher dipole moment should have the higher boiling point.

Several attempts were made to put the configurational assignment of A and B as I and II, respectively, on a firmer basis and, at the same time, to obtain a pure sample of the isomer B. These attempts were based on the following known facts: (1) Potassium iodide dehalogenates diaxial *trans* dihalides more rapidly than either diequatorial

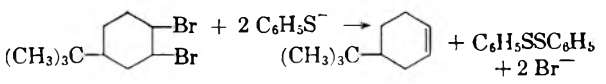
(15) *Cf.* E. L. Eliel and R. V. Acharya, *J. Org. Chem.*, 24, 151 (1959).

(16) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapter VII.

(17) In the steroid cases which have been studied, the equilibrium is almost entirely on the side of the diequatorial dibromide, whereas in the present case this is evidently not so. The difference is readily explained by the presence of the angular methyl groups at C_{10} in the steroids. This crowds the axial bromine substituent at C_2, C_4, or C_6 and forces the equilibrium all the way over to the diequatorial side. *Cf.* D. H. R. Barton and A. J. Head, *J. Chem. Soc.*, 932 (1956).

(18) N. L. Allinger, *J. Am. Chem. Soc.*, 79, 3443 (1957). The rule has usually been applied to olefins but may apply to alicyclic diastereoisomers as well.

trans dihalides[8,19a] or equatorial-axial *cis* dihalides.[19b] (2) Axial halides suffer elimination with base more readily than equatorial halides.[13,20] (3) Axial bromine is more easily displaced by thiophenolate than is equatorial bromine.[2] Unfortunately, none of these attempts was very successful. Treatment of mixtures of A and B (as obtained from *trans*-4-*t*-butylcyclohexanol and phosphorus pentabromide) with potassium iodide in boiling ethanol for a short time produced enrichment of B in the residual dibromide. When the reaction time was extended, however, almost complete conversion of both A and B to 4-*t*-butylcyclohexene occurred. This is probably due to the relatively rapid interconversion of A and B, which would cause the presumed diequatorial dibromide B to be transformed to the presumed diaxial isomer A which would then be dehalogenated.[21] Treatment of the mixture of A and B with alcoholic sodium hydroxide produced a complex mixture in which B appeared to be somewhat enriched, but which still contained unchanged A in addition to a number of other components. Finally, sodium thiophenolate unexpectedly reacted with the mixture of A and B at room temperature to produce 4-*t*-butylcyclohexene and diphenyl disulfide, according to the equation



A search of the literature revealed that similar reactions of vicinal dihalides have been described many years ago.[22a] The reaction seems to show little discrimination between diequatorial and diaxial isomers—being, in this respect, similar to the zinc dehalogenation[22b]—since both A and B were dehalogenated readily at room temperature. The stereochemical aspect of this reaction merits further investigation.

Infrared spectra. The frequencies of absorption in the infrared region (in cm.$^{-1}$) due to the C—Br stretching motion for the compounds here prepared and some related ones are listed in Table I.

TABLE I

INFRARED FREQUENCIES DUE TO C—BR STRETCHING

Compound	Peak	
	Axial	Equatorial
cis-4-*t*-Butylcyclohexyl bromide	670	...
trans-4-*t*-Butylcyclohexyl bromide	...	692
cis-4-Methylcyclohexyl bromide	684	708
Cyclohexyl bromide	685	709
trans-4-*cis*-3-Dibromo-*t*-butylcyclohexane	...	680, 699
cis-4-*trans*-3-Dibromo-*t*-butylcyclohexane	646, 672	...
trans-1,2-Dibromocyclohexane[3]	663	684, 693

The equatorial bands are in the 690–710 cm.$^{-1}$ region with a second band at slightly lower frequency in the diequatorial dibromides. The axial bands fall in the 670–685 cm.$^{-1}$ region with a splitting and shift to lower frequencies in the dibromides. This conclusion is generally similar to that reached by Barton[23] from examination of a series of steroidal bromides. It might be noted, however, that our equatorial bromides lie near the lower end of the frequency region (682–833 cm.$^{-1}$) given by Barton whereas our axial bromides absorb near the upper end of his frequency range (542–692 cm.$^{-1}$). Moroever, the shift in frequency in our diaxial dibromide (from 670–685 cm.$^{-1}$ to 646 and 672 cm.$^{-1}$) is much less than the shift in the steroids where the diaxial dibromides absorb around 550 cm.$^{-1}$ [24]

DISCUSSION

The major monobromide products obtained by treatment of *cis*- and *trans*-4-*t*-butylcyclohexanol with phosphorus pentabromide have configurations opposite to those of the starting materials. This is in agreement with the steric course of the reaction of cholestanol and epicholestanol with phosphorus pentahalides.[5a] In contrast, treatment of the alcohols with hydrogen bromide gives complex mixtures of positional as well as configurational isomers, in contradistinction to what has been reported in the 3-methylcyclohexanol series.[5c,5d,25]

(19) (a) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951). (b) H. L. Goering and H. H. Espy, *J. Am. Chem. Soc.*, 77, 5023 (1955).

(20) H. L. Goering and H. H. Espy, *J. Am. Chem. Soc.*, 78, 1454 (1956).

(21) Unfortunately, we were not able to demonstrate that the presumed diequatorial isomer B is converted to a mixture of A and B by heating. It appears that the mixtures of A and B which we obtained by action of phosphorus pentabromide on *trans*-4-*t*-butylcyclohexanol were so close to the presumed equilibrium mixture that heating them produced no appreciable change in composition. However, if thermal conversion of A to an A-B mixture is indeed equilibration, as appears highly likely, the equilibrium must also be approachable from the side of pure B and at about the same rate as it is approached from pure A; for the equilibrium mixture contains appreciable amounts of *both* isomers, *i.e.*, *K* is not too far from unity.

(22) (a) R. Otto, *J. prakt. Chem.*, [2], 51, 299 (1895). Elimination seems to occur with all vicinal dibromides more highly branched than ethylene or propylene bromide (which undergo substitution only); *cf.* also J. Hine and W. H. Brader, *J. Am. Chem. Soc.*, 75, 3964 (1953). This reaction, to which little attention has been paid, may be quite useful from the preparative point of view. (b) *cf.* D. R. James, R. W. Rees, and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).

(23) D. H. R. Barton, *Experientia suppl.*, II, 121 (1955); see also D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(24) With our instrument we could not observe the spectra below 625 cm. However, there is little doubt that our bands at 646 and 672 cm.$^{-1}$ correspond to the steroidal bands at 542 and 548 cm.$^{-1}$

(25) M. Mousseron and R. Jacquier, *Bull. soc. chim. France*, 80C (1951). We are somewhat at a loss to understand how these investigators were able to reach definite conclusions as to the identity of the 3-methylcyclohexyl bromides without the benefit of infrared spectroscopy.

Not unexpectedly,[26] olefins are obtained as major by-products in the reaction of the (axial) *cis*-alcohol, but not of the (equatorial) *trans*-alcohol.

The formation of major amounts of vicinal dibromides in the treatment of both *cis*- and *trans*-4-*t*-butylcyclohexanol with phosphorus pentabromide, though at first sight surprising, is in agreement with observations of other investigators for this reagent[5a] as well as for phosphorus pentachloride.[5b,27] Goering and McCarron[27] have shown that the formation of a vicinal dichloride from 3,3-dimethylcyclohexanol does not involve the olefin as an intermediate, for optically active alcohol gives active dichloride whereas both possible olefin intermediates are symmetrical. Our results corroborate this point, for if 4-*t*-butylcyclohexene were an intermediate in the conversion of *cis*- and *trans*-4-*t*-butylcyclohexanol to 3,4-dibromo-*t*-butylcyclohexanes, the two epimeric alcohols should give rise to the same dibromide (or dibromide mixture), whereas in fact they do not. It has been proposed[27,28] that the reaction leading to the dihalide proceeds *via* an alkoxyphosphorus tetrahalide, π-complex of a carbonium ion, and π-complex of a halonium ion as shown in Figure 1.

This reaction scheme may be readily applied to *cis*-4-*t*-butylcyclohexanol where—assuming diaxial ring opening[28,29] in the last step—the predicted product is the diaxial dibromide, as actually found. It is more difficult to see how the π-complex can be formed from *trans*-4-*t*-butylcyclohexanol (equatorial hydroxyl) in view of the requirement[8] that a neighboring group must be *conformationally trans* to the functional substituent in whose reaction it participates. On this basis, *trans*-4-*t*-butylcyclohexanol is properly disposed for ring contraction (which does not, however, occur) but not for participation of an adjacent hydrogen. Possibly the molecule may flip over into the conformation in which hydroxyl (or the $-OPBr_4$ grouping) is axial. In this conformation, the system is stereoelectronically disposed for the same sequence of events described above for the *cis*-alcohol (Fig. 1). This sequence would eventually lead to a diaxial dibromide which could then flip back to the observed diequatorial product. However, if in the course of this reaction sequence either the *t*-butyl group has to become axial or the ring has to become boat-shaped (*cf.* Fig. 2) the activation energy for the process would be improbably high. Perhaps the molecule can distort itself sufficiently to allow the course of events shown in Fig. 1 to

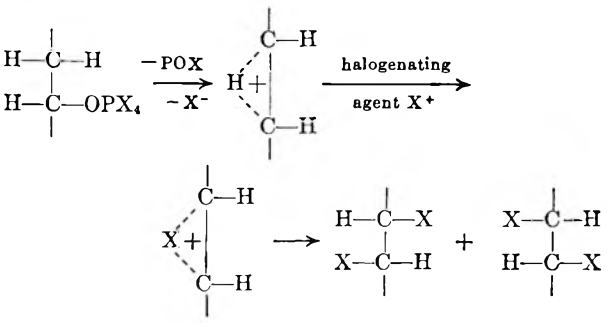


Figure 1

happen without completely taking up the unfavorable conformations shown in Fig. 2. This would involve some intermediate conformation in the transition state where neither the $-OPBr_4$ grouping nor the *t*-butyl group are *completely* axial. It may or may not be significant that dibromide formation from the *trans* alcohol appears to be less stereospecific than that from the *cis* alcohol in that it leads to two diastereoisomeric products.[30]

EXPERIMENTAL[31]

cis-4-t-Butylcyclohexyl bromide. From commercial 4-t-butylcyclohexanol and phosphorus pentabromide. Ninety g. of bromine dissolved in 100 ml. of methylene chloride was slowly added to a cooled (ice bath) solution of 150 g. of phosphorus tribromide, in 150 ml. of methylene chloride, with stirring. A yellow precipitate was formed. Seventy-seven g. of commercial 4-*t*-butylcyclohexanol (about 80% *trans* isomer), dissolved in the minimum amount of methylene chloride, was slowly added to the cooled and well-stirred mixture. The addition was completed in 1 hr. but stirring was continued for 3 hr. more, resulting in evolution of hydrogen bromide. Ice water (500 g.) was then added and stirring continued for an additional hour to decompose the phosphorus halides. After separating the layers, the organic phase was washed with water, sodium bicarbonate solution, and brine. After stripping the dried methylene chloride, the residue was distilled through a 12-in. helix-packed column under reduced pressure. The first fraction (a few drops) distilled at 57–65°/14 mm. and consisted mainly of 4-*t*-butylcyclohexene (infrared spectrum).

The second fraction distilled at 104–110°/14 mm. and constituted a *t*-butylcyclohexyl bromide mixture. After a small intermediate fraction another compound came over at 142°/15 mm. It was shown to be a mixture of 4-*t*-butylcyclohexyl dibromides. Fraction 2 (30 g.) was recrystallized nine times from pentane between room temperature and −70°. *cis*-4-*t*-Butylcyclohexyl bromide (9.3 g.), m.p. 23–25°, b.p. 70°/2 mm. n_D^{25} 1.4912 (supercooled liquid) was obtained. The characteristic infrared bands (neat supercooled liquid)

(26) (a) D. H. R. Barton, *Experientia*, 6, 316 (1950); (b) See also D. H. R. Barton and R. Cookson, *Quart. Revs.*, 10, 44 (1956).

(27) H. L. Goering and F. H. McCarron, *J. Am. Chem. Soc.*, 78, 2270 (1956).

(28) *Cf.* G. A. Russel and H. C. Brown, *J. Am. Chem. Soc.*, 77, 4025 (1955).

(29) Ref. 5d, pp. 130–134.

(30) The significance of this fact may be impaired because (a) diaxial dibromide from equatorial alcohol may result through a mechanistically distinct path, *viz.* addition of free bromine to 4-*t*-butyleyclohexene; (b) some of the diaxial dibromide may have originated through isomerization of the diequatorial isomer during fractionation (*vide supra*). This seems less likely, since the diaxial dibromide can be obtained quite free of the diequatorial isomer by distillation, even though it, also, is not stable to prolonged heating.

(31) Infrared analyses on a Baird double-beam instrument by Mr. Rolland S. Ro and the authors. Mass spectral analysis by Mr. George Young. Microanalyses by Midwest Microlab, Indianapolis, Ind., and Mr. Josef Nemeth, Urbana, Ill.

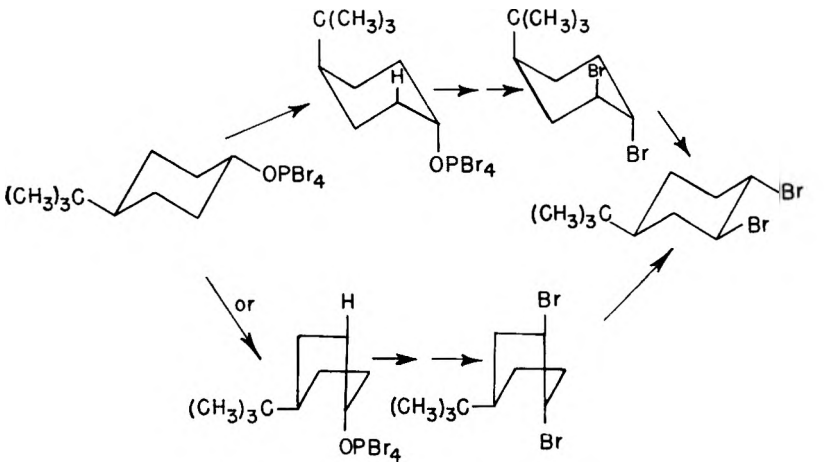


Fig. 2

of this compound (not shared by the *trans* isomer) were at 6.91, 6.97, 7.60, 7.95, 8.05, 9.28, 9.75, 10.87, 11.03, 11.65, 11.97, and 14.92μ.

Anal. Calcd. for $C_{10}H_{19}Br$: C, 54.79; H, 8.74; Br, 36.46. Found: C, 54.72; H, 8.61; Br, 36.54.

The dibromide fraction was chromatographed on alumina from pentane to remove traces of oxygenated impurities and then redistilled, a fraction boiling at 116–124°/5 mm., n_D^{23} 1.5251 being submitted for analysis.

Anal. Calcd. for $C_{10}H_{18}Br_2$: Br, 53.62. Found: Br, 53.53.

This dibromide, to which the *cis*-3-*trans*-4-dibromo-*t*-butylcyclohexane structure was assigned, had characteristic infrared bands at 7.72, 8.65, 8.87, 10.12, 10.34, 11.21, 12.35 (prominent), 14.3, and 14.7μ. The analytical sample had in addition, however, a number of the characteristic bands of the diaxial (*trans*-3-*cis*-4-) isomer (*vide infra*). The sample was not changed in infrared spectrum by six hours heating at 125–130°.

From pure trans-4-t-butylcyclohexanol and phosphorus pentabromide. Forty-one g. of *trans*-4-*t*-butylcyclohexanol prepared by the reduction of the ketone with mixed hydride[4] were treated with phosphorus pentabromide prepared *in situ* from 110 g. of phosphorus tribromide and 55 g. of bromine, as described above. After the same work-up, a monobromide was obtained whose I.R. spectrum showed it to be *cis*-4-*t*-butylcyclohexyl bromide contaminated with the third bromide (I.R. bands at 13.2, 14.7, and 15.4μ.) There was no indication for the presence of *trans*-4-*t*-butylcyclohexyl bromide. Again a very small amount of olefin was obtained in the first distillation fraction. A dibromide fraction boiling at 142°/15 mm. consisted mainly of the diequatorial dibromide but contained also some of the diaxial isomer.

From commercial 4-t-butylcyclohexanol and phosphorus tribromide. Commercial 4-*t*-butylcyclohexanol (10.9 g.) was dissolved in 50 ml of benzene. Phosphorus tribromide (25 ml.) was slowly added (stirring) and the mixture then refluxed for 1 hr. A yellow precipitate formed on boiling. The mixture was cooled in an ice bath and ice water added. The benzene layer was separated and washed with water, bicarbonate solution, and brine. The bicarbonate washing produced a white (acid soluble) precipitate which was filtered off. The dried organic solution was stripped leaving a yellow oil (5.9 g.) which, on distillation yielded four fractions:

Fraction 1, b.p. 60–100°/15 mm.—mainly 4-*t*-butylcyclohexene and its isomers.

Fractions 2 and 3, b.p. 100–104°/15 mm.—monobromide fraction (4 g.).

After this, at a pot temperature of 230°, pyrolysis of the residue occured, giving again 4-*t*-butylcyclohexene and its isomers.

Fractions 2 and 3 were identical in I.R. spectrum and consisted of *cis*-4-*t*-butylcyclohexyl bromide, the *trans* isomer and the third bromide. The pure *cis* isomer could be obtained by repeated crystallization from pentane at −70°.

From commercial 4-t-butylcyclohexanol and phosphorus tribromide under varied conditions. (a) One g. of the above alcohol was dissolved in 5 ml. of pyridine, and 0.4 ml. phosphorus tribromide was added. A yellow precipitate formed immediately. The mixture was left at room temperature.

(b) One g. of the alcohol was dissolved in 5 ml. chloroform, and 1 g. anhydrous calcium carbonate and 0.4 ml. of phosphorus tribromide were added. The mixture was left at room temperature.

(c) One g. of the alcohol was dissolved in 4.5 ml. of benzene, and 0.4 ml. of phosphorus tribromide was added at room temperature.

After 9 hr. samples of the three reaction mixtures were withdrawn, poured into water, extracted with pentane, dried and concentrated. The product of reaction (a) was a solid. The products from reactions (b) and (c) were liquids and contained bromides but many bands indicating phosphorus were seen in the I.R. spectrum, at 4.15 (P—H), 7.95 (P=O), 8.95, 9.5 (C—O—P), 10.3, and 12.43μ.

After 3 days the reactions were worked up as above except that methylene chloride was used as the organic solvent. The crude yield from (a) was 0.70 g., (b) 0.86 g., (c) 0.86 g. Each of the products was percolated through a small alumina (Merck 20 g.) column to eliminate phosphorus esters. The yield after that: (a) 0.05 g., (b) 0.36 g., (c) 0.42 g. The infrared spectra showed (a) not to contain any of the desired bromide; (b) contained at least three bromides; (c) as (b) except that the band at 14.7μ (of the third bromide) was weaker. These tests were considered unpromising.

The reaction of commercial 4-t-butylcyclohexanol and hydrogen bromide. Commercial 4-*t*-butylcyclohexanol (5.4 g.) was boiled with 35 ml. hydrobromic acid (48%) in a flask connected through a 10-in. Vigreux column to a distillation apparatus. Slow distillation was permitted to occur and continued till all organic material distilled over. Water was added to the distillate, the layers were separated, and the aqueous layer was extracted with pentane. The combined organic extracts were washed, dried, and stripped. The residue was distilled. After a very small forerun the bulk of the material distilled at 104°/15 mm., n_D^{20} 1.4908. Yield almost quantitative. The bromide so obtained contained both the *cis*- and the *trans*-4-*t*-butylcyclohexyl bromide as seen from the infrared spectrum. The *trans* isomer seemed to predominate. However strong extraneous bands were found at 7.98, 8.88, 9.45, 10.20, 11.80, 12.40, 13.30, 14.72, and 15.40μ. By treating this mixture with alcoholic base the *cis*-4-*t*-butylcyclohexyl bromide could be selectively destroyed (infrared evidence). However the other extraneous bromide survived. Chromatography over alumina (Merck, acid washed), 100-1, using pentane as solvent did not lead to appreciable sepa-

ration. Using alumina (Woelm) activity I, neutral, acid, or basic, only olefins (the three isomeric *t*-butylcyclohexenes) came off the column, even after periods as short as 15 min.

Using a starting material containing the two stereoisomeric alcohols in almost identical proportions (50:50) the reaction product seemed to consist of the same mixture as above.

trans-4-t-Butylcyclohexyl bromide. From cis-4-t-butylcyclohexanol and phosphorus pentabromide. Seventy-four g. of *cis*-4-*t*-butylcyclohexanol[11] was treated with phosphorus pentabromide prepared from 135 g. phosphorus tribromide and 80 g. bromine in the same way as described for its isomer. The residue after work-up was distilled under reduced pressure. Fraction 1, b.p. 55–56°/13 mm. consisted mainly of 4-*t*-butylcyclohexene contaminated with its two isomers as evidenced by bands at 7.85, 9.63, 11.90, 12.50 (1-*t*-butylcyclohexene) and bands at 8.80, 11.25, 11.60, 13.10, and 13.85μ (3-*t*-butylcyclohexene).[12]

Fraction 2 was an intermediate fraction (b.p. 58–103°/13 mm.).

Fraction 3, b.p. 103–105°/13 mm. and fraction 4, b.p. 105–108°/13 mm. consisted of *trans*-4-*t*-butylcyclohexyl bromide contaminated with a little *cis* isomer and a trace of the third isomer. It appears that fraction 4 was slightly purer than fraction 3.

Fraction 5, b.p. 108–142°/13 mm. consisted mainly of dibromide.

Fractions 3 and 4 were combined and redistilled. Eight g. of middle cut, b.p. 104–107/13 mm. was obtained and further purified as explained below.

Fraction 5 was redistilled and a middle cut was collected at 142°/13 mm. This was the main product of the reaction and consisted of a dibromide which crystallized from pentane at −70°.

Anal. Calcd. for $C_{10}H_{18}Br_2$: Br, 53.62. Found: 53.57.

This dibromide seems to be *trans*-3-*cis*-4-dibromo-*t*-butylcyclohexane. Characteristic infrared bands are found at 8.82, 9.67, 11.81, 14.9, and 15.5μ. The characteristic bands of the diequatorial (*cis*-3-*trans*-4) isomer (*vide supra*) were absent. After 6 hr. heating at 125–130°, the infrared spectrum of the material had changed considerably and now resembled closely that of the (impure) *cis*-3-*trans*-4-isomer described above. A similar change in spectrum was observed when the dibromide was boiled for 3 days in 90% ethanol solution.

From 4-t-Butylcyclohexanecarboxylic acid. p-t-Butylbenzoic acid was hydrogenated and the product submitted to a Hunsdiecker reaction.[15] The product so obtained consisted of a mixture of only the two 4-*t*-butylcyclohexyl bromides with the *trans*-isomer predominating.

Purification of trans-4-t-Butylcyclohexyl Bromide. The crude bromide obtained by the Hunsdiecker reaction (9.1 g.) was boiled with 0.4 g. potassium hydroxide in 25 ml. ethanol for 13 hr. The reaction mixture was poured into water and extracted with pentane. The organic extracts were washed with 20% calcium chloride solution, dried, and stripped. Most of the *cis* isomer had been dehydrobrominated. To this crude residue was added 8 g. of the bromide obtained from *cis*-4-*t*-butylcyclohexanol and together they were boiled with 0.4 g. potassium hydroxide in 35 ml. ethanol for another 13 hr. The product was worked up as above. The olefin formed was separated from the bromide by distillation. Nine g. of essentially pure *trans* bromide was obtained. This sample was percolated through alumina (Merck, acid washed) in pentane, to remove possible traces of ethers, recrystallized once from pentane at −70° and distilled at 120°/24 mm. ($n_D^{20.2}$ 1.4868). It had infrared bands at 7.85, 8.55, 9.10, 9.62, 11.1, 11.4, 12.25, and 14.45μ. The characteristic bands of the *cis*-isomer and the third compound (above) were absent.

Anal. Calcd. for $C_{10}H_{19}Br$: C, 54.79; H, 8.74; Br, 36.46. Found: C, 55.02; H, 8.93; Br, 36.17.

cis-4-Methylcyclohexyl Bromide. Seventy-two g. of *trans*-4-methylcyclohexanol[10] b.p. 172.6–173°/734 mm., was treated with phosphorus pentabromide prepared *in situ* from 170 g. phosphorus tribromide and 100 g. bromine in the same manner as described above. After the usual work-up, the product was distilled. No olefin was detected. Fraction 1, b.p. 64–65°/14 mm., 22.9 g., consisted mainly of *cis*-4-methylcyclohexyl bromide but extraneous bands at 7.98, 8.20, 9.53, 9.65, 9.92, 14.4, and 15.05μ were observed in the infrared spectrum.

Fraction 2 was a mixed fraction. Fraction 3, b.p. 64°/1.5 mm. consisted of dibromide(s?). Fraction 1 was recrystallized repeatedly from pentane at −70°, till all the above-mentioned extraneous infrared bands disappeared. It was then percolated through alumina and redistilled. Yield 9.5 g. Characteristic infrared bands at 14.11 and 14.6μ.

Anal. Calcd. for $C_7H_{13}Br$: C, 47.46; H, 7.40; Br, 45.12. Found: C, 47.44; 47.29; H, 7.45; Br, 44.66.

Reaction of cis-4-t-Butylcyclohexyl Bromide with Sodium Thiophenolate. cis-4-*t*-Butylcyclohexyl bromide (1.85 g.) was added to a solution of 0.21 g. sodium and 1.1 g. thiophenol in 10 ml. methanol. The mixture was refluxed for 36 hr. under nitrogen. Most of the methanol was then distilled *in vacuo* and the residue poured into water and extracted with ether. The organic layer was washed with sodium hydroxide solution, dilute acid, bicarbonate, and brine. The residue after stripping was distilled at 14 mm. Two fractions were collected. The first b.p. 65°/14 mm. consisted of pure 4-*t*-butylcyclohexene and the second, b.p. 185°/14 mm., was shown to be *trans*-4-*t*-butylcyclohexyl phenyl thioether, since its infrared spectrum was identical with that of an authentic sample[1b] and contained none of the bands of the *cis*-isomer.

Reaction of trans-4-t-butylcyclohexyl bromide with sodium thiophenolate. One-half g. of *trans*-4-*t*-butylcyclohexyl bromide was added to a solution of 0.1 g. sodium and 3 g. thiophenol in 40 ml. ethanol. The reaction mixture was kept on a steam bath for 3 days, under nitrogen. It was worked up as described for the *cis* isomer. This time, a little starting material had not yet reacted but again 4-*t*-butylcyclohexene had been formed. The *cis*-4-*t*-butylcyclohexyl phenyl thioether obtained had the same infrared spectrum as an authentic sample[1b] and no bands of its isomer were found.

Reaction of cis-4-t-butylcyclohexyl tosylate with lithium bromide.[14] *cis*-4-*t*-Butylcyclohexyl tosylate[1b,13] (6.16 g.) and 1.6 g. lithium bromide were dissolved in 50 ml. acetone (freshly distilled over potassium carbonate) and the mixture refluxed for 20 hr. The acetone was evaporated and the residue taken up in water and pentane. The organic layer was stripped and the residue distilled under reduced pressure. Four fractions were collected.

Fraction (a) b.p. 40–46°/17 mm., n_D 1.4500, was mesityl oxide.

Fraction (b) b.p. 52–60°/17 mm. was mainly 4-*t*-butylcyclohexene.

Fraction (c) b.p. 77–104°/17 mm. unidentified mixture.

Fraction (d) b.p. 104–108°/17 mm. consisted mainly of *trans*-4-*t*-butylcyclohexyl bromide contaminated with an olefinic ketone (infrared bands at 5.95, 6.03, 6.2, 8.2, 9.0, 9.18, 9.7, 11.5, and 12.9μ). It was chromatographed on an alumina (Merck acid washed) column using pentane as eluent. Most of the interfering ketone was removed. The infrared spectrum of this sample showed it to be *trans*-4-*t*-butylcyclohexyl bromide with traces of the *cis* isomer.

Reaction of cis-4-t-butylcyclohexyl bromide with lithium bromide. cis-4-*t*-Butylcyclohexyl bromide (1.3 g.) was refluxed with a saturated solution of lithium bromide in 20 ml. acetone for two days. The acetone was removed *in vacuo* and the residue taken up in pentane. The organic solution was washed with sodium bicarbonate soln., dried, and stripped. The infrared spectrum of the crude residue showed the presence of mesityl oxide, *trans*-4-*t*-butylcyclohexyl bromide and mainly starting material. The mixture was taken up in a fresh solution of lithium bromide in acetone and refluxed for 2 weeks. After the same work-up as above, the residue

was distilled. The mesityl oxide came over first and no 4-*t*-butylcyclohexene was found. The bromide fraction was dissolved in pentane and chromatographed over alumina to remove acetone condensation products. The material so obtained still contained traces of ketone. It consisted of a mixture of *cis*- and *trans*-4-*t*-butylcyclohexyl bromide as well as the third bromide. The infrared spectrum of the material looked very much like that of the product obtained by boiling 4-*t*-butylcyclohexanol with hydrobromic acid.

Debromination of 3,4-dibromo-t-butylcyclohexane. With potassium iodide. 3,4-Dibromo-*t*-butylcyclohexane (27.2 g.), as obtained in the reaction of commercial 4-*t*-butylcyclohexanol with phosphorus pentabromide, and 37 g. potassium iodide were dissolved in 350 ml. 90% ethanol and refluxed for 6 hr. The alcoholic solution was poured into water and extracted repeatedly with pentane. The organic layer was washed with sodium thiosulfate solution, 20% calcium chloride soln., sodium bicarbonate soln., and brine. After drying over sodium sulfate the pentane was evaporated. The infrared spectrum of the residue showed that part of the dibromide had been converted to 4-*t*-butylcyclohexene and that the dibromide with C—Br 14.7 bands at 14.13 and 14.7μ had been enriched at the expense of the dibromide having C—Br bands at 14.85 and 15.5μ.

The crude residue was taken up in another solution of 20 g. potassium iodide in 300 ml. 90% ethanol and refluxed for 12 hr. after which the mixture was left standing at room temperature for 7 days. It was worked up as above. The infrared spectrum showed a further enrichment but the axial C—Br bands at 14.85 and 15.5μ were still present.

3,4-Dibromo-*t*-butylcyclohexane (14.4 g.), rich in the diequatorial isomer, was treated with a solution of 20 g. potassium iodide in 200 ml. 90% ethanol. The mixture was refluxed for 3 days. It was poured into water to which a slight excess of sodium thiosulfate had been added. The mixture was worked up as before and the residue distilled. Pure 4-*t*-butylcyclohexene (5.2 g.) was obtained. Later 1.5 g. of unreacted dibromide with a trace of olefin distilled over. The infrared spectrum showed the diequatorial dibromide to be the main component but the diaxial isomer was still present.

With zinc and acetic acid. A similar 3,4-dibromo-*t*-butylcyclohexane mixture as above (12.7 g.), was dissolved in 60 ml. acetic acid and small amounts of zinc powder were added in portions over a period of three hours. After that time a white precipitate was observed and the reaction was stopped by pouring the mixture into water. The mixture was extracted with pentane and worked up in the usual manner. The residue was distilled *in vacuo*. 4-*t*-Butylcyclohexene (2.3 g.) contaminated by its two position isomers was obtained. After that 3.0 g. of unreacted dibromide distilled over. It was enriched in the diequatorial isomer at least to the same extent as the product obtained by the potassium iodide reaction. The low yield of the olefin might be accounted for by its low boiling point and some of it might have been lost while evaporating the pentane.

With sodium thiophenolate. To a solution of 3.0 g. (0.01 mole) of 3,4-dibromo-*t*-butylcyclohexane, rich in the presumed diequatorial isomer, in 10 ml. 87% ethanol was added 2.75 g. (0.025 mole) of thiophenol and 20 ml. (0.022 mole) of a 1.1 N solution of base obtained by dissolving sodium in 87% ethanol. After four days at room temperature, a copious, beautifully crystalline precipitate had formed. This was collected and identified as diphenyl disulfide, m.p. 59.5–60.8° (lit. 61°), undepressed by admixture with authentic material, and weighed 1.6 g. (73%). The filtrate was poured into water, extracted with ether-petroleum ether and the extract washed with aqueous potassium hydroxide, water, aq. calcium chloride and dried over calcium chloride. The residue, after concentration, contained very little residual dibromide, according to infrared spectrum. Upon chromatography, most of the material was eluted with petroleum ether and the infrared spectrum did not change. Distillation of this material gave 4-*t*-butylcyclohexene, b.p. 68°/22 mm. (lit. 65–66°/20 mm.),[1b] identified by infrared spectrum, and further amounts of diphenyl disulfide.

Elimination of bromine from the diequatorial dibromide probably does not involve prior equilibration with the diaxial isomer since a control experiment showed that the diaxial isomer was unaffected by standing with 87% ethanol for four days.

Addition of bromine to 4-t-butylcyclohexene. Pure, freshly prepared,[32] 4-*t*-butylcyclohexene (5.2 g.) was dissolved in 20 ml. of chloroform and cooled to 0°. A solution of 6 g. bromine in 10 ml. of chloroform was slowly added with stirring. The solution turned cloudy. A preliminary experiment had shown that the addition does not stop after the calculated amount had been added so that no attempt was made to add bromine till the color of bromine persisted.

The organic solution was washed with water, bicarbonate, and brine. It was dried over potassium carbonate and stripped. The residue (10 g.) was distilled at 12 mm. Four fractions were collected.

Fraction 1 (few drops) contained unreacted olefin and traces of ketone. Fractions 2 and 3 contained the desired dibromide. This was a mixture of the two dibromides encountered before, with the diaxial predominating. Fraction 4 turned pink on distillation and its infrared spectrum had some extraneous bands; it probably contains more highly brominated material.

Hydrogenation of t-butylcyclohexene. The olefin mixture obtained from the reaction of pure *cis*-4-*t*-butylcyclohexanol with phosphorus pentabromide (3.7 g.) was hydrogenated over platinum oxide in alcohol. This olefin mixture contained mainly 4-*t*-butylcyclohexene but the infrared spectrum had shown extraneous bands at 13.85μ (3-*t*-butylcyclohexene); 12.50, 11.90, 9.62, 7.85μ (1-*t*-butylcyclohexene) and 13.10, 11.60, 11.25, and 8.80μ (both these isomers).

One mole of hydrogen was taken up. The catalyst was filtered off, the alcoholic solution poured into water and extracted with pentane. The pentane solution was washed with 20% calcium chloride solution, dried and stripped. The residue was distilled in a bulb-tube (70° air bath temp.; 13 mm. pressure) yielding 2.75 g. of a product of $n_D^{20.2}$ 1.4489. The infrared spectrum was compared with API spectrum 55° (*t*-butylcyclohexane n_D^{20} 1.4464). Extraneous bands were found at 7.83, 8.80, 10.50, 10.88, 11.61, 12.30, 13.1, and 14.33μ. All these could be assigned to 1-*t*-butylcyclohexene which must have escaped hydrogenation because of steric hindrance.

In another experiment, olefin mixtures obtained from the reaction of commercial 4-*t*-butylcyclohexanol and phosphorus pentabromide were hydrogenated as above. The olefin had strong extraneous bands at 13.08 and 14.32μ. After hydrogenation these extraneous bands persisted. The mass spectrum of this sample showed among others an extraneous peak at parent minus six. The infrared spectrum of *t*-butylbenzene was then consulted and indeed its strongest bands were at 13.08 and 14.32μ.

Hydrogenolysis of bromide mixtures. Ten g. of a mixture of *t*-butylcyclohexyl bromides as obtained from the reaction of 4-*t*-butylcyclohexanol and hydrobromic acid was treated with Raney nickel (one teaspoon) in 100 ml. 8% ethanolic potassium hydroxide and hydrogen (50 p.s.i) for 6 hr. The product was left standing in this solution for 2 weeks at room temperature and then worked up in the usual manner and distilled. The first and main fraction (65°/15 mm.) consisted of a mixture of *t*-butylcyclohexane and 4-*t*-butylcyclohexene. Only one band (9.0μ) could not be assigned to these compounds and probably represents a C—O band. The second, very minor, fraction was unreacted bromide. The *trans*-4-*t*-butylcyclohexyl bromide was preferably used up.

This reaction was repeated except that after the six hours hydrogenolysis the product was isolated immediately

(32) On standing hydroxyperoxides are formed quite rapidly leading to undesired oxygen-containing impurities.

and rehydrogenated with platinum oxide as catalyst. The infrared spectrum (0.02 mm. neat film) of the product ($n_D^{20.2}$ 1.4479) was identical to *t*-butylcyclohexane except for an extraneous band at 9.0μ. An infrared spectrum in a 0.2 mm. cell revealed however also extraneous bands at 9.4, 13.1, and 14.3μ. These bands can be assigned to *t*-butylbenzene.

Reaction of a Mixture of 3-trans-4-cis- and 3-cis-4-trans-dibromo-t-butylcyclohexane with sodium hydroxide. The dibromide mixture obtained from the reaction of commercial 4-*t*-butylcyclohexanol and phosphorus pentabromide (24.1 g.), was treated with 50% of the calculated amount of sodium hydroxide in 200 ml. 85% ethanol. It was left standing at room temperature for 2 weeks. The alcoholic solution was then poured into water and extracted with pentane. The pentane solution was washed dried and stripped. Twenty g. of residue were obtained. The infrared spectrum of the crude residue showed that appreciable amounts of the diaxial isomer were still present. The crude residue was then boiled with a solution of 3 g. sodium hydroxide in 200 ml. ethanol for 3 hr. It was worked up as before and 15 g. of crude residue was obtained. The material was distilled at 15 mm.

Fraction 1, b.p. 64–80°; fraction 2, b.p. 90–99°; fraction 3, residue. Fraction 1 was an olefinic mixture with bands in the 9μ region and characteristic bands at 12.9, 13.1, 13.6, 14.9, and 15.4μ.

Fraction 2 was a different olefinic mixture with characteristic bands at 12.8, 13.8, and 15.03μ.

Fraction 3 (residue) was mainly diequatorial dibromide with some diaxial isomer and at least one further product, probably an ether. No further attempts were made to separate this complex mixture.

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NOTRE DAME, IND.

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

Conformational Analysis. VI. The Hunsdiecker Reaction with *cis*- and *trans*-4-*t*-Butylcyclohexanecarboxylic Acid[1]

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Reaction of the silver salts of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid with bromine in boiling carbon tetrachloride gave identical mixtures of 4-*t*-butylcyclohexyl bromides containing 65 ± 3% of the *trans* isomer. Neither the *cis* acid nor the *cis*-bromide is appreciably epimerized under the conditions of the reaction.

The reaction of the silver salt of an organic acid with bromine to give an alkyl bromide, carbon dioxide, and silver bromide: $RCOOAg + Br_2 \rightarrow RBr + CO_2 + AgBr$ is generally known as the Hunsdiecker Reaction.[2] The likely mechanism of this reaction has been discussed extensively[2b-d-4] and it appears that a mechanism involving free radicals as intermediates best fits most of the known facts.[5]

Among the evidence favoring a free radical mechanism are optical studies in systems where the group R is asymmetric at its point of attachment to the carboxylate group.[3,6-10] In all but two[6,7] of these cases an active acid RCOOH gave rise to a racemic bromide R—Br, as is to be expected if the reaction proceeds *via* the radical R·.[11] Of the two remaining cases,[6,7] one,[6] the conversion of silver hydratropate $C_6H_5CH(CH_3)COOAg$ to α-phenethyl bromide, $C_6H_5CHBrCH_3$, is beclouded by the fact that at least three investigators[3,7,12] could not repeat the reaction even with racemic starting material, and that the active bromide, if obtained, should have racemized extensively under the conditions of the reaction.[6,13] In the other instance,[7] the activity of the product was so slight that a small amount of asymmetric induction may be responsible for it.

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(12) J. Cason, M. J. Kalm, and R. H. Mills, *J. Org. Chem.*, 18, 1670 (1953).

(13) C. L. Arcus and G. V. Boyd, *J. Chem. Soc.*, 1580 (1951).

Studies involving optically active bromides as products are complicated by the fact that these bromides are apt to racemize quite rapidly under the conditions of the Hunsdiecker reaction[3,6,13] and that it is therefore often difficult to decide whether the obtention of racemic bromide really reflects on the mechanism of the Hunsdiecker reaction, or whether the bromide was racemized after the event. Another, minor, drawback of such studies is that the DL-bromide is both the product of greatest stability and the product of random attack on the radical. These difficulties might be avoided by the use of geometric instead of optical isomers. Four such studies are known. In one,[14] it was shown that both *cis*- and *trans*- cinnamic acid give rise to *trans*-β-bromostyrene in the Hunsdiecker reaction. It was not shown whether *cis*-β-bromostyrene is stable under the conditions of the reaction; demonstration of this point would have been complicated by the unavoidable addition of bromine to the β-bromostyrene. The cinnamic acid case is not strictly comparable with other instances of the Hunsdiecker reaction, since it involves an unsaturated group with sp^2 hybridization at the reaction center. Other pertinent cases are those of the *cis*- and *trans*- cyclohexane-1,2-dicarboxylic acids[15] and the corresponding cyclobutanedicarboxylic acids.[16] These acids gave, exclusively, *trans*-1,2-dibromocyclohexane and -cyclobutane, respectively. In the case of the cyclobutanedicarboxylic acid, the optically active *trans* isomer gave rise to an active *trans*-dibromide. This latter observation[16] precludes a symmetrical intermediate in the reaction—such as an olefin or a symmetrically bridged radical. The significance of the former finding (exclusive formation of *trans*-dibromides from both *cis*- and *trans*-diacids) is not clear. The difference in free energy between the *cis*- and *trans*-dibromides is not known,[17] and therefore one cannot tell to what extent this difference reflects itself in the difference in activation energy for the formation of the two dibromides in the Hunsdiecker reaction. There seems to be little doubt, however, that the diastereoisomeric homogeneity of the product in the reaction of the 1,2-dicarboxylic acids involves some sort of neighboring group effect[19] and therefore does not necessarily bear on the mechanism of the Hunsdiecker reaction in general. Finally, it has been claimed that *cis*- and *trans*-3-methylcyclohexanecarboxylic acids yield the corresponding bromides in the Hunsdiecker reaction with 70% and 95% retention of configuration, respectively.[20] Since the configurational assignments of the bromides used are probably uncertain,[1] and since other work pertaining to the acids[20] was later shown to be in error,[21] this claim should probably be viewed with much reserve.

Having available, in our laboratory, in connection with other problems, pure *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acids[22] as well as the corresponding bromides,[18] we felt that a study of the Hunsdiecker reaction in this system would be of interest. Equilibrium between the bromides in this system, corresponding to *ca.* 77% *trans* and 23% *cis* isomer at 25°,[18,23] is neither random (50-50) nor all the way on one side. Moreover control experiments (see Experimental) indicated that the *cis* acid is configurationally stable under the conditions of the Hunsdiecker reaction and that a *cis*-rich bromide is epimerized only to a negligible extent by either silver bromide alone or silver bromide-bromine in carbon tetrachloride, the reaction solvent.[24]

Treatment of the dry silver salts of either *cis*- or *trans*-4-*t*-butylcyclohexanecarboxylic acid with an equivalent amount of bromine in boiling carbon tetrachloride gave a mixture of *cis*- and *trans*-4-*t*-butylcyclohexyl bromides contaminated with an ester (probably the "Simonini ester" 4-*t*-butylcyclohexyl 4-*t*-butylcyclohexanecarboxylate) which was removed by distillation or chromatography. The infrared spectra of the purified bromide frac-

(14) C. C. Price and J. D. Berman, *J. Org. Chem.*, **23**, 102 (1958).

(15) P. I. Abell, *J. Org. Chem.*, 22, 769 (1957).

(16) D. E. Applequist and A. S. Fox, *J. Org. Chem.*, 22, 1751 (1957); see also footnote 2 in that communication.

(17) However, at least in the case of the 1,2-dibromocyclohexane, it would not appear that equilibrium lies all the way on the side of the *trans* compound. The *trans* compound is an equilibrium mixture of about equal amounts of the diequatorial and diaxial isomer [P. Bender, D. L. Flowers, and H. L. Goering, *J. Am. Chem. Soc.*, **77**, 3465 (1955)] and other references there cited—and the *cis* form is an equilibrium mixture of equal amounts of the two enantiomeric equatorial-axial isomers. Hence the geometric isomers differ by only one axial bromide (assuming perfect chair shapes throughout), which difference should not amount to more than about 0.7 kcal./mole.[18]

(18) E. L. Eliel and R. G. Haber, *Chem. & Ind. (London)*, 264 (1958); *J. Am. Chem. Soc.*, in press.

(19) For a similar effect in radical addition to olefins, *cf.* H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, 77, 3465 (1955).

(20) M. Mousseron and R. Jacquier, *Bull. soc. chim. France*, 80C(1951). To the best of our knowledge, experimental details supporting this claim have not been published up to now.

(21) H. L. Goering and F. H. McCarron, *J. Am. Chem. Soc.*, **80**, 2287 (1958).

(22) R. D. Stolow, Ph.D. dissertation, University of Illinois, Urbana, 1956; *cf. Dissertation Abstr.* **17**, 751 (1957). We are grateful to Professor David Y. Curtin for communicating the details of preparation of these acids to us well ahead of publication. We have also employed a modified method of preparation developed and kindly communicated by Professor Harold Hart, Michigan State University.

(23) This equilibrium measurement refers to 87% ethanol as a solvent. However, P. Klaeboe, J. L. Lothe, and K. Lunde, *Acta Chem. Scand.*, **10**, 1465 (1956) report that the relative intensity of the infrared absorption bands due to equatorial and axial bromine in cyclohexyl bromide does not vary when the solvent is changed from cyclohexane to nitromethane and is therefore independent of solvent polarity. Hence it may be assumed that the equilibrium composition is not much different in carbon tetrachloride.

(24) The *cis* isomers were chosen for the control experiments because they are the less stable of each pair.

tion from a number of runs employing *cis* or *trans* acid, or mixtures of the two as starting materials were virtually identical. Infrared analysis, employing the intensity of the 12.24μ, 11.4μ and 8.6μ bands as measure of the concentration of the *trans* isomer and the 11.7μ and 8.0μ bands for the *cis* isomer[1] indicated a composition of 65 ± 3% *trans* isomer for the products.

The fact that both diastereoisomeric silver salts generate the same mixture of bromides would seem to demand a common reaction intermediate from both starting materials. Concerted mechanisms involving rearward attack (whether heterolytic or homolytic) are ruled out, as they should have led to predominant inversion in the configuration of the product. Similarly, internal mechanisms involving frontal attack (similar to the S_Ni mechanism[25]) should have led to predominant retention of configuraion and are therefore inadmissible. A carbonium ion intermediate for the reaction, already ruled out on other grounds,[3,26] is also inconsistent with the present results, as it should have given rise to 3- as well as 4-*t*-butylcyclohexyl bromide.[1] An anion intermediate is unlikely, since there is no obvious reason why a cyclohexanecarboxylate anion should have lost carbon dioxide under the conditions of the Hunsdiecker reaction.[27] We therefore, in agreement with a number of other investigators and reviewers,[2b-d,3] favor a free radical intermediate for the Hunsdiecker reaction in the system and under the conditions of the present study. This does not mean that a different mechanism could not contribute, or even take over, in a different system or under different experimental conditions.

Our product composition (65% *trans:* 35% *cis*) differs from a random mixture (50:50) on the side of the equilibrium composition(77:23 at a slightly lower temperature and in a different solvent).[23] We take this to mean that the product-determining step in the reaction (*i.e.*, the reaction of the intermediate radical R· with bromine from an unspecified source) has an appreciable activation energy, so that the free energy difference of the products can reflect itself in the corresponding transition states to a considerable extent.[28] A radical chain mechanism of the type generally favored for the Hunsdiecker reaction[2b-d] would fulfill this condition.[29]

Careful scrutiny of the data for the one-hour runs in Table I suggests that possibly a little more *trans*-bromide resulted from the *cis* acid than did from the *trans* acid. This was also suggested by a visual inspection of the infrared spectra of the products. We therefore carried out[30] a kinetic analysis of the bromide mixture, using their reaction with thiophenolate in 87% ethanol. The rates of this reaction for the pure *cis*- and *trans*-bromides had been previously determined and differ by the substantial factor of 62.[18] The analysis indicated 57% *trans*-bromide in the product from the *trans* acid and 62% *trans*-bromide in the product from the *cis* acid. While the absolute accuracy of these figures is not so high as that of the infrared analysis, the *difference* between the two products is brought out more clearly by the kinetic analysis. Even so, it cannot be claimed that the trend (which is based on two single experiments) is of unequivocal significance. If real, it may show that in addition to the process involving a common intermediate, there may be a *very minor* contributing mechanism involving inversion of configuration, as claimed by Kenyon *et al.*[6]

TABLE I

SUMMARY OF HUNSDIECKER PRODUCTS

Starting Acid	Reaction Time, Hr.	Yield, %	*trans* Isomer in Product, % (A)[a]	(B)[a]	(C)[a]
cis	1	21.5	66–67	65	68
trans	1	23.9	65–66	60	65
cis	5	25.4	64–65	68	..
trans	5	24.1	68	69	..
Mixed	5	41.2	62–63	..	..
Mixed[b]	5	50.1	67	..	..

[a] 12.42μ and 11.7μ bands used for analysis; (B) based on 11.4μ and 11.7μ bands; (C) based on 8.6μ and 8.0μ bands. [b] Run carried out by Dr. Ralph G. Haber.

(25) Ref. 11, pp. 79–83.

(26) W. T. Smith and R. L. Hull, *J. Am. Chem. Soc.*, **72**, 3309 (1950).

(27) *Cf.* J. Berman and C. C. Price, *J. Am. Chem. Soc.*, **79**, 5474 (1957).

(28) It is possible though unlikely that predominant formation of the more stable product may be fortuitous—in other words, that the activation energy of the product-forming step may not be related to the free energy of the products but be controlled in some other way. We feel that in cases where the more stable product is obtained predominantly, a causal connection between the activation energy of the product-controlling step and the free energy of the products may be presumed to exist unless there is compelling evidence to the contrary. In this connection, see G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(29) Professor Harold Hart, Michigan State University, has kindly informed us that the decomposition of *cis*- and *trans*-4-*t*-butylcyclohexanecarbonyl peroxides in tetrabromoethane at 50° gives, among other products, identical mixtures of *cis*- and *trans*-4-*t*-butylcyclohexyl bromides containing 52–55% of the *trans* isomer. Infrared comparison indicates the *trans* isomer content of this mixture to be slightly but significantly smaller than that of the Hunsdiecker product. This may be due to the differing nature of the product-forming step. In the reaction studied by H. Hart and H. Lau, this is reaction of the 4-*t*-butylcyclohexyl radical with tetrabromoethane at 50°. The nature of the product-determining step in the Hunsdiecker reaction is not known. It has been suggested to be reaction of the alkyl radical with bromine[2b,d] or with acyl hypobromite.[2c] It is not clear why either of these reactions should be more selective than the reaction of the radical with tetrabromoethane, since the Br—Br and O—Br bonds are weaker than C—Br.

(30) This part of the work was performed by E. L. E. at Harvard University while on a National Science Foundation Senior Postdoctoral Fellowship.

EXPERIMENTAL

Melting and boiling points are uncorrected. Infrared analyses were performed on a Baird double-beam instrument.

4-t-Butylcyclohexanecarboxylic Acids.[22] The *cis* acid melted at 116°, the *trans* acid at 174°. These melting points are in agreement with those reported by other investigators[22] and the infrared spectra of the acids were identical with spectra kindly provided by Professor Harold Hart. The mixed (*cis-trans*) acid employed in some experiments was obtained by catalytic reduction of 4-*t*-butylbenzoic acid over ruthenium oxide catalyst at 100° using a hydrogen pressure of 1000–1800 p.s.i.

Hunsdiecker reaction. Twenty g. (0.11 mole) of 4-*t*-butylcyclohexanecarboxylic acid was added slowly to a hot solution of 5 g. (0.12 mole) of sodium hydroxide in 50 ml. water and the mixture boiled until solution was complete. The solution was filtered, nitric acid was added dropwise to incipient turbidity, and a few drops of sodium hydroxide solution were then added just to clear up the solution again. Slow addition of a solution of 19 g. (0.11 mole) silver nitrate in 30 ml. water, with stirring, produced a copious precipitate of the silver salt which was collected, washed with water, and carefully dried in a vacuum desiccator. The yield of silver salt was quantitative.

To an ice-cooled suspension of 30 g. (0.10 mole) of the dry silver salt in 100 ml. of dry carbon tetrachloride in a three necked flask equipped with a reflux condenser, addition funnel, and efficient stirrer was added 5.4 ml. (15.8 g., 0.10 mole) of bromine dissolved in 20 ml. of carbon tetrachloride. The suspension was heated to boiling and stirred for periods ranging from 1 to 10 hr. It was then cooled and filtered, the silver bromide in the filter being washed with a fresh portion of carbon tetrachloride. The carbon tetrachloride layer was washed with sodium thiosulfate, sodium hydroxide, water, and brine, dried over sodium sulfate, and concentrated. The residue (12.5 g.) was distilled in a small Claisen flask and the product collected in three fractions, b.p. 82–86°/4.5 mm. (1.5 g.), 86–88°/4.5 mm. (7.8 g.), and 100–102°/4.5 mm. (2.0 g.). Fractions 1 and 2 were identical in infrared spectrum and were combined, yield 9.3 g. (41%). The combined fraction was subjected to infrared analysis (see below). In some instances, this fraction contained traces of ester (carbonyl band in infrared), in which case it was dissolved in petroleum ether, percolated through a small alumina column, recovered by concentration, and subjected to analysis.

The high-boiling fraction appeared to be mainly ester, as evidenced by the intensity of its carbonyl band in the infrared.

The above experiment is typical of a number which were carried out with different starting materials (*cis*, *trans*, and mixed) and for different lengths of time. Highest yields of bromide were obtained with the shortest reaction time (1 hr.). In the 10-hr. runs, and, to a much lesser extent, in the 5-hr. runs, the presence of extraneous products [probably 3-*t*-butylcyclohexyl bromide(s)[1]] manifested itself. For this reason, the products of the 10-hr. runs were not analyzed. The various runs are summarized in Table I above.

Infrared analyses. The bromide (0.100 g.) was dissolved in 0.50 ml. carbon disulfide and the infrared spectrum was recorded in a 0.1 mm. cell (using a similar cell filled with carbon disulfide for a blank). Calibration spectra were recorded in a similar way for synthetic mixtures ranging from 25% to 95% *trans* isomer. Compositions were calculated by interpolating the ratio of the intensity of two bands, one characteristic of the *trans* isomer, the other of the *cis* for the unknowns between the corresponding ratios for known mixtures. Combinations used were (A) 12.24μ (*trans*) and 11.7μ (*cis*), (B) 11.4μ (*trans*) and 11.7μ (*cis*), and (C) 8.6μ (*trans*) and 8.0μ (*cis*). The last combination could not be used in the 5-hr. runs, because of interference of the impurities present in these runs. The accuracy of the analysis was estimated as ±3% from the scatter of the data.

Kinetic analysis. Sodium was dissolved in 87% ethanol and the solution titrated against standard acid. Twenty-five ml. of this solution (0.57*N*) were pipetted into a 50-ml. volumetric flask and an excess of thiophenol (1.8 g.) was added. The solution was thermostatted at 25.1°, a weighed amount of the bromide sample was added, and the solution made up to the mark with 87% ethanol at 25.1° and thoroughly mixed. A 5-ml. sample was immediately withdrawn at time zero, quenched into excess standard (*ca.* 0.1*N*) hydrochloric acid, and titrated with standard (*ca.* 0.1*N*) base. The bulk of the solution was blanketed with nitrogen and placed in the thermostat. At appropriate intervals, 5-ml. samples were withdrawn from the flask and quenched and titrated as above, the time of quenching being recorded. The bulk of the solution was blanketed with nitrogen after each such withdrawal. Table II gives the pertinent data for the bromide from the *trans* acid and Table III for the bromide from the *cis* acid.

TABLE II

KINETIC ANALYSIS OF BROMIDE FROM *trans*-ACID

3.276 Millimoles Bromide and 14.25 Millimoles Base in 50 ml.					
Time (min.)	0	1101	2460	4257	6069
% Reaction	0	36.1	44.0	46.8	51.3

TABLE III

KINETIC ANALYSIS OF BROMIDE FROM *cis*-ACID

3.892 Millimoles Bromide and 14.19 Millimoles Base in 50 ml.							
Time (min.)	0	225	509	836	1423.5	1874.5	3287
% Reaction	0	11.9	22.9	29.8	35.7	37.5	41.0

Using k_{cis} 5.7 × 10^{-3} l. $mole^{-1}$ $min.^{-1}$ and k_{trans} 0.09^{-3} l. $mole^{-1}$ $min.^{-1}$, the data in Table I are best fitted by a composition of 57% *trans*-bromide and those in Table III by 62% *trans*-bromide (remainder *cis*-bromide). The fit was obtained by calculating, empirically, the per cent reaction to be expected for different initial concentrations of *cis*- and *trans*-bromide, corresponding to different compositions of the weighed amount of sample taken. The calculation was performed by means of the integrated form of the second-order rate equation, $\log \frac{a - x}{b - x} = \frac{k(a - b)t}{2.303} - \log \frac{b}{a}$. It was assumed that the two reactions are independent. This is not quite true (since both reactions consume base), but does not introduce a large error in the early stages of the reaction, since the contribution of the *trans* isomer to the total extent of reaction is so small, and since the base was in over 3:1 excess.

Control experiments. (a) The Hunsdiecker reaction was carried out as above, using the silver salt of the *cis* acid as starting material, but employing only half the theoretical amount of bromine. The mixed silver salts, filtered after 1 hr. reflux time, were dried and warmed with dilute hydrochloric acid. The resulting suspension was extracted with petroleum ether and the petroleum ether layer dried over sodium sulfate and evaporated. The residual acid melted at 114–115°, as compared with a melting point of 115–117° for the original *cis* acid. The infrared spectrum of the recovered acid was identical with that of the *cis* acid and did not show the characteristic bands corresponding to the *trans* acid.

(b) A suspension of 0.85 g. of dry silver acetate in 15 ml. of carbon tetrachloride was treated with 0.8 ml. bromine in 10 ml. carbon tetrachloride and stirred for 30 min. at room temperature followed by 30 min. at reflux. To the resulting suspension of silver bromide was added 1 g. of a 4-*t*-butylcyclohexyl bromide mixture very rich in the *cis* isomer.

Stirring was continued at reflux for 5 hr. and the bromide was then recovered in the usual way. The recovered bromide showed a slight increase in the amount of *trans* isomer, as evidenced by the diagnostic infrared bands of the latter, but was still very predominantly *cis*.

(c) The above experiment was repeated, expect that pure *cis*-bromide was used and the bromide was added to the silver acetate suspension one minute *before* bromine addition commenced. In this way, the *cis*-bromide was exposed to *both* bromine *and* silver bromide under the reaction conditions, rather than to silver bromide only. After 1 hr. boiling at reflux with stirring, the mixture was worked up as previously described. The product showed a marked ester band in the infrared at 5.77μ and very weak bands ascribable to the *trans* isomer, the one at 11.4μ being the most prominent (about six scale divisions). However, the recovered material was still very largely *cis*-bromide.

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NOTRE DAME, IND.

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

The Substituent Constant of the 3,4-Benzo Group

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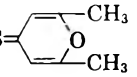
The effect of the 3,4-benzo substituent in different reactions has been examined by analyzing literature data, supplemented by further kinetic studies on the benzoylation of 2-naphthylamine, the alkaline hydrolysis of ethyl 2-naphthylacetate and of 2-naphthoic esters, and the acid-catalyzed esterification of 2-naphthoic acid. The substituent constant ($\sigma_{3,4\text{-benzo}}$) varies systematically with reaction type and it is possible to distinguish σ^-, σ and σ^+ values. The σ^- values display an unexpected anomaly, which is discernible also in the comparable data for the *p*-nitro substituent.

Hammett[1] calculated a value of 0.170 for the substituent constant of the 3,4-benzo substituent, using the dissociation constant of the 2-naphthylammonium ion. In testing this $\sigma_{3,4\text{-benzo}}$ value in nine other reactions he found a probable error of 0.102, one of the largest listed by him. Now for a number of reactions, plots of log k *vs.* σ show that the 3,4-benzo substituent is well removed from the best straight line and that a lower $\sigma_{3,4\text{-benzo}}$ value would provide a better fit. Examples of such reactions are (*a*) R-C_6H_4COOEt + OH^- in dioxane/water (Ref. 2, reaction 47L) (*b*) dissociation of R-$C_6H_4B(OH)_2$ in ethanol/water (Ref. 2, reaction 13) (*c*) R-$C_6H_4COCH_2Br$ +  in benzene (Ref. 2, reaction 105a) (*d*) dissociation of R-$C_5H_4NH^+$ in water (Ref. 14). For reaction (*a*) Jaffe[2] has already noted the marked deviation, from the linear plot, of this substituent.

Although a few independent determinations of $\sigma_{3,4\text{-benzo}}$ have been made, Hammett's value is still generally taken as the standard for reference. But if it be assumed that the benzo substituent has the ability to withdraw electrons by the conjugative mechanism (−T), then the substituent constant obtained by Hammett is likely to be a σ^- value. For reactions other than those of phenol or amine derivatives a normal σ value should apply although, with its weak conjugative withdrawal of electrons, this substituent is likely to have σ^- and σ values not greatly different in magnitude. However, it is clearly of interest to know whether such distinct values may be assigned to the 3,4-benzo group and also to learn whether, with its ability to donate electrons conjugatively (+T mechanism) in suitable circumstances, the group requires also a σ^+ value under these conditions. From the literature, data of sufficient accuracy have now been found for the calculation of over 20 sigma values for this substituent. In addition, in order to extend these values, and in one case to confirm a value derived from published data, further kinetic studies have been made.

EXPERIMENTAL

Benzoylation of naphthylamines. The reaction rates of many substituted anilines were measured at 25° by Stubbs and Hinshelwood,[3] and a smaller number of measurements were made by these workers at 40°. The data for 25° fit a Hammett plot exceptionally well in most cases but two amines, of which 2-naphthylamine is one, do not lie on the linear plot. Calculation gives the apparent $\sigma_{3,4\text{-benzo}}$ value as 0.06 (cf. Hammett's value of 0.17) and, to obtain confirmation of this value, the kinetics of reaction of 2-naphthylamine were re-examined using the same technique. Measurements were made over the temperature range 10–45°; the 1-naphthylamine reaction was similarly examined for general comparative purposes. Results are given in Tables I and II, and it will be seen that results at 25° agree well with those of the previous study.

Alkaline hydrolysis of ethyl naphthylacetates (in 87.83% ethanol/water). The only previous work is recorded by

(1) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, Ch. 7.

(2) H. H. Jaffé, *Chem. Revs.*, **53**, 237 (1953).

(3) F. J. Stubbs and C. N. Hinshelwood, J. Chem. Soc., 152, S.71 (1949).

TABLE I

BENZOYLATION OF AMINES

Amine	Rate Constants k × 10² (l. mole⁻¹ sec.⁻¹) 10°	25°[a]	35°	45°	Arrhenius Data E(kcal. mole⁻¹)	$Log_{10}A$
1-Naphthylamine	0.430	1.02	1.71	2.71	9.50 ± 0.05	4.96 ± 0.03
	0.437	0.978	1.70	2.73		
	0.438	0.967	1.66	2.79		
		0.986	1.69	2.75		
		1.02	1.76	2.72		
		1.01	1.76			
		0.974	1.75			
			1.72			
2-Naphthylamine	2.31	4.57	7.48	11.4	7.96 ± 0.05	4.51 ± 0.04
	2.46	4.58	7.44	11.2		
	2.50	4.73	7.38	11.1		
	2.30	4.61	7.54	11.3		
	2.34	4.46	7.44	11.7		
	2.44	4.74	7.48	10.9		
	2.33	4.61	7.38	11.3		
	2.41	4.78		10.8		

[a] *cf.* Stubbs and Hinshelwood[3] $k \times 10^2$ = 1.04 (1-naphthylamine)
= 5.12 (2-naphthylamine)

TABLE II

DERIVED DATA FOR BENZOYLATION REACTIONS

Amine	$k_{25°} \times 10^2$ (l. mole⁻¹ sec.⁻¹)	E (kcal. mole⁻¹)	$Log_{10}A$	$\Delta\Delta H^{\ddagger}$ (kcal. mole⁻¹)	$T\Delta\Delta S^{\ddagger}_{25°}$ (kcal. mole⁻¹)
Aniline[a]	7.40	7.60	4.44	(0.00)	(0.00)
1-Naphthylamine	1.01	9.50	4.96	2.09	0.90
2-Naphthylamine	4.78	7.96	4.51	0.54	0.27

[a] Stubbs and Hinshelwood.[3]

TABLE III

ALKALINE HYDROLYSIS OF SUBSTITUTED ETHYL ACETATES

Ethyl Ester	Rate Constants k × 10³ (l. mole⁻¹ sec.⁻¹) 20°	30°	35°	40°	50°	E (kcal. mole⁻¹)	$Log_{10}A$
Phenylacetate	5.50	12.3[a]	19.4		55.4	14.67 ± 0.12	8.66 ± 0.09
	5.33	12.1[a]	19.3		55.3		
	5.37		17.4[b]				
	5.26		17.7[b]				
1-Naphthylacetate	2.22[b]	5.56		12.4	25.4	15.43 ± 0.09	8.85 ± 0.07
	2.23[b]	5.64		12.5	25.8		
	2.23[b]	5.71			27.4		
	2.17[b]	5.55			26.2		
		5.58					
2-Naphthylacetate	6.98	14.9	23.2	32.0	69.2	14.58 ± 0.11	8.69 ± 0.08
	6.90	14.7	23.3	32.7	70.7		
		15.0	22.4[b]	34.6			
		15.1	22.5[b]	33.9			

[a] *Cf.* Kindler's value of 10.6. [b] Obtained with reactants in unequal concentrations.

Kindler,[4] who examined several substituted phenylacetic esters at 30°. The ethyl naphthylacetates were not included. These have now been studied, over the temperature range 20°–50°, and under similar conditions to those of Kindler. Ethyl phenylacetate was also included in our work and checked with the previous study. Hence a value for $\sigma_{3,4\text{-benzo}}$ may be derived from our results used in conjunction with those of Kindler. Results are given in Tables III and IV.

Alkaline hydrolysis of ethyl and methyl 2-naphthoates (in 60% acetone/water). The experimental procedure was that of Tommila and Hinshelwood.[5] We included kinetic results on 1-naphthoates in an earlier communication[6] in which compatibility between our conditions and those of Tommila and Hinshelwood was demonstrated by agreement on ethyl benzoate. Present results are given in Table V.

Acid-catalyzed esterification, in methanol, of 2-naphthoic acid. This also is an extension of work reported earlier,[6]

(4) K. Kindler, *Ann.*, **452**, 90 (1927).

(5) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

(6) J. Packer, J. Vaughan, and E. Wong, *J. Org. Chem.*, **23**, 1373 (1958).

TABLE IV

DERIVED DATA FOR REACTIONS IN TABLE III

Ethyl Ester	$k_{30°} \times 10^3$ (l. mole^{-1} sec.$^{-1}$)	E (kcal. mole^{-1})	$Log_{10}A$	$\Delta\Delta H^{\ddagger}$ (kcal. mole^{-1})	$T\Delta\Delta S_{30°}^{\ddagger}$ (kcal. mole^{-1})
Phenylacetate	12.3	14.7	8.66	(0.00)	(0.00)
1-Naphthylacetate	5.44	15.4	8.85	0.76	0.27
2-Naphthylacetate	18.1	14.6	8.69	−0.09	0.03

TABLE V

HYDROLYSIS AND FORMATION OF 2-NAPHTHOIC ESTERS

Ester Hydrolyzed or Acid Esterified	Rate Constant k × 10^4 (l. mole^{-1} sec.$^{-1}$)					Arrhenius Data	
	15°	25°	40°	50°	60°	E (kcal. mole^{-1})	$Log_{10}A$
Ethyl 2-naphthoate	15.66	36.0	119.2	247.1		14.62 ± 0.03	8.29 ± 0.02
	15.69	36.3	120.9	248.5			
Methyl 2-naphthoate	51.4	121.2	387	767		14.34 ± 0.05	8.59 ± 0.03
	51.7	121.3	390	783			
2-Naphthoic acid		2.05	6.85	14.52	28.94	14.95 ± 0.03	7.27 ± 0.02
				14.39	29.28		

in which a method similar to that of Hartman and Borders[7] was used, and in which compatibility of results between the two sets of workers was demonstrated. Results are included in Table V. Unfortunately, the σ values from this reaction prove subject to large errors. Using reaction constant (ρ) values from Jaffé,[2] σ values for the 3,4-benzo substituent are $\sigma_{25°} = 0.054$; $\sigma_{40°} = 0.066$; $\sigma_{50°} = 0.075$; $\sigma_{60°} = 0.079$. But the values for the correlation coefficients ($r \approx 0.4$) and the standard deviations ($s \approx 0.14$) calculated by Jaffé for these reaction series indicate that they fit the Hammett equation very poorly. Thus substituent constants obtained from these esterification experiments were not used in compiling Table VI.

DISCUSSION

In Table VI are listed the substituent constant values for the 3,4-benzo substituent, calculated from reactions for which rate or equilibrium data for 2-naphthyl derivatives are available. For many of the reactions Jaffé[2] has already calculated the reaction constant ρ. Where rate data for 2-naphthyl derivatives were available, Jaffé used appropriate log k values together with Hammett's $\sigma_{3,4\text{-benzo}}$ value of 0.170 in determining the corresponding ρ values. In such cases, therefore, ρ values have now been recalculated without using the rate data for this substituent. Application of the log $k_{3,4\text{-benzo}}$ values to these newly calculated figures for ρ then gave $\sigma_{3,4\text{-benzo}}$ values. Also listed in the table are values for ρ, the correlation coefficient r, and standard deviation s of the best straight line through the points, and n, the number of substituents for which data were available. In the last column, where references are given to sources of rate data for 2-naphthyl derivatives, the absence of a reference number indicates that such rate data were obtained from direct references given in Jaffé's review.[2] Principles guiding selection of material for Table VI were: (i) in calculating ρ values, only σ constants given by Jaffé were included, the restriction being imposed because many σ values reported more recently have yet to be tested in other reactions. (ii) Only those reaction series with a correlation coefficient >0.95 were listed. This restriction follows Jaffé, but in the present calculations it resulted in the elimination of only one or two possible sources of $\sigma_{3,4\text{-benzo}}$ values. (iii) In certain reactions $\sigma_{3,4\text{-benzo}}$ values could be calculated for more than one temperature. In order that no particular reaction should be overweighted in the calculation of mean σ values (see later), σ in such a reaction was calculated only for the temperature at which data for the greatest number of substituents were available. This restriction also is far from severe, because σ shows little change with temperature. On the other hand, solvent variation appears to have an appreciable effect and $\sigma_{3,4\text{-benzo}}$ values, determined for the same reaction in different solvents, have been included. Reactions 1–9 are reactions of anilines, phenols, or their derivatives; reactions 10–13 cover carbinyl chloride solvolyses; reactions not entering either of the first two categories are those numbered 14–26. It is clear that reactions 14–26 are those which should require normal σ values; reactions 10–13 presumably demand σ^+ values, and to reactions 1–9 σ^- values should apply. The calculated σ values do indeed group themselves accordingly, although the substituent constants for phenol and amine reactions (1–9) are less internally consistent (see later, however).

Reactions other than aniline, phenol and solvolysis reactions. The mean value of σ from reactions 14–26 is 0.042 ± 0.030. Two comments may be made concerning the small error on this mean value. First, no reaction with a negative ρ value is included in this set of reactions and it appears that such data are neither available nor readily obtainable. However, the range of positive ρ values

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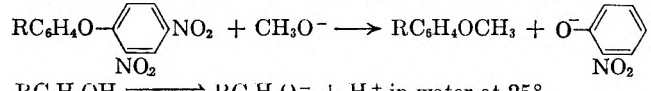
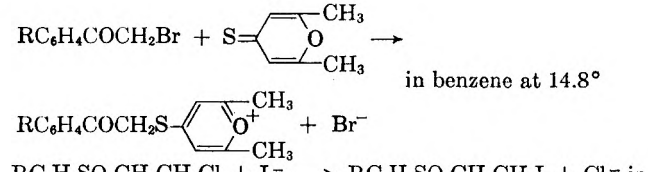
TABLE VI

SUBSTITUENT CONSTANT VALUES FOR THE 3,4-BENZO GROUP

Reaction	$\sigma_{3,4\text{-benzo}}$	ρ	r	s	n	Reference	Description
1	0.120	2.798	0.999	0.046	13		$RC_6H_4NH_3^+ \rightleftharpoons RC_6H_4NH_2 + H^+$ in water at 25°
2	0.153	−0.947	0.993	0.062	9		$RC_6H_4O^- + \overline{CH_2CH_2O} \longrightarrow RC_6H_4OCH_2CH_2O^-$ in 98% ethanol/water at 70.4°
3	0.184	−0.770	0.987	0.068	9		$RC_6H_4O^- + CH_3\overline{CHCH_2O} \longrightarrow RC_6H_4OCH(CH_3)CH_2O^-$ in 98% ethanol/water at 70.4°
4	0.219	0.598	0.987	0.053	14		$RC_6H_4OSO_2OH + H^+ \longrightarrow RC_6H_4OH + SO_2OH^+$ in water at 48.7°
5	0.154	1.450	0.999	0.020	4		 in methanol at 20°
6	0.046	2.099	0.991	0.077	17	8	$RC_6H_4OH \rightleftharpoons RC_6H_4O^- + H^+$ in water at 25°
7	0.070	−1.245	0.997	0.026	8		$RC_6H_4OH + HCOOH \longrightarrow RC_6H_4NHCHO + H_2O$ in 67% pyridine/water at 100°
8	0.066	−3.220	0.999	0.051	10	Present work	$RC_6H_4NH_2 + C_6H_5COCl \longrightarrow RC_6H_4NHCOC_6H_5 + HCl$ in benzene at 25°
9	0.053	−1.545	0.983	0.104	18		(*trans*) $R'C_6H_4N{=}NC_6H_4R'' + C_6H_5COOOH \longrightarrow$ (*trans*) $R'C_6H_4N(O){=}NC_6H_4R'' + C_6H_5COOH$ in benzene at 15°
10	−0.132	−4.639	1.000	0.07	18	9	$RC_6H_4C(CH_3)_2Cl + H_2O \longrightarrow RC_6H_4C(CH_3)_2OH + HCl$ in 90% acetone/water at 25°
11	−0.188	−4.376	0.997	0.14	12	10	$RC_6H_4CH(C_6H_5)Cl + C_2H_5OH \longrightarrow RC_6H_4CH(C_6H_5)OC_2H_5 + HCl$ in ethanol at 25°
12	−0.147	−2.606	0.994	0.11	7	11	$RC_6H_4C(C_6H_5)_2Cl + C_2H_5OH \longrightarrow RC_6H_4C(C_6H_5)_2OC_2H_5 + HCl$ in ethanol/ether (40/60) at 0°
13	−0.113	−4.669	0.993	0.06	5		$RC_6H_4CH(C_6H_5)Cl + (CH_3)_2CHOH \longrightarrow RC_6H_4CH(C_6H_5)OCH(CH_3)_2 + HCl$ in isopropyl alcohol at 25°
14	0.042	1.000				12	$RC_6H_4COOH \rightleftharpoons RC_6H_4COO^- + H^+$ in water at 25°
15	0.084	0.483	0.981	0.033	14	13	$RC_6H_4CH_2COOH \rightleftharpoons RC_6H_4CH_2COO^- + H^+$ in water at 25°
16	0.045	2.137	0.996	0.062	13		$RC_6H_4B(OH)_2 \rightleftharpoons RC_6H_4B(OH)O^- + H^+$ in 25% ethanol/water at 25°
17	0.032	0.879	0.956	0.104	11		$RC_6H_4AsO_3OH^- \rightleftharpoons RC_6H_4AsO_2O^{2-} + H^+$ in water at 22°
18	0.084	0.961	0.970	0.077	14		$RC_6H_4SeOOH \rightleftharpoons RC_6H_4SeOO^- + H^+$ in water at 25°
19	0.022	5.685	0.995	0.147	10	14	$RC_6H_4NH^+ \rightleftharpoons RC_6H_4N + H^+$ in water at 23°–25°
20	0.079	2.537	0.998	0.067	12	15	$RC_6H_4COOC_2H_5 + OH^- \longrightarrow RC_6H_4COO^- + C_2H_5OH$ in 85% ethanol water at 25°
21	0.031	2.310	0.999	0.026	3		$RC_6H_4COOC_2H_5 + OH^- \longrightarrow RC_6H_4COO^- + C_2H_5OH$ in 70% dioxan/water at 25°
22	0.036	2.265	0.984	0.141	25	Present work	$RC_6H_4COOC_2H_5 + OH^- \longrightarrow RC_6H_4COO^- + C_2H_5OH$ in 60% acetone/water at 25°
23	0.042	2.229	0.995	0.106	11	Present work	$RC_6H_4COOCH_3 + OH^- \longrightarrow RC_6H_4COO^- + CH_3OH$ in 60% acetone/water at 25°
24	0.000	0.824	0.974	0.105	6	Present work	$RC_6H_4CH_2COOC_2H_5 + OH^- \longrightarrow RC_6H_4CH_2COO^- + C_2H_5OH$ in 87.83% ethanol/water at 30°
25	−0.005	0.862	0.982	0.064	9		 in benzene at 14.8°
26	0.060	0.618	0.980	0.050	4		$RC_6H_4SO_2CH_2CH_2Cl + I^- \longrightarrow RC_6H_4SO_2CH_2CH_2I + Cl^-$ in acetone at 75°

covered is from 0.483 to 5.685. Within this range no trend in σ is observed and there seems to be no reason to expect a variation if the range were extended to negative reaction constants. Second, in certain of the reactions (i.e. reactions 14, 16–18, 20–23) weak resonance interaction between a −T side-chain and a +T *para* substituent should be possible. In each case, however, there is cross-conjugation in the side-chain itself and it is evident that in these cases any side-chain-substituent resonance has a negligible effect on the substituent constant.

Carbinyl chloride solvolyses. The mean $\sigma^+_{3,4\text{-benzo}}$ value from reactions 10–13 is -0.145 ± 0.028. It is true that the four reactions listed are similar in type and that it would be desirable to obtain data for the 3,4-benzo substituent on reactions of different types which still require σ^+ values. However, Okamoto and Brown[9] have shown that σ^+ for other +T substituents (*e.g.* *p*-OCH_3) have a remarkably wide applicability.

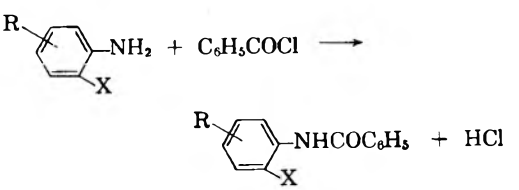
Reactions of anilines, phenols and their derivatives. Reactions 1–9 are those which appear to require σ^- values. Of the listed reactions the highest substituent constants are those for reactions 1–5. These are presumably uncomplicated $\sigma^-_{3,4\text{-benzo}}$ values, the mean of which is 0.166 ± 0.033. In support of this assumption, other −T substituents such as the well studied *p*-nitro group also require their accepted σ^- values in these reactions. For reactions 6–9, however, the substituent constants are significantly lower and distinction between the two sets appears to be real. In only one earlier investigation have unexpectedly low σ^- values been particularly noted and that was by Bordwell and his coworkers,[16,17] who measured pK_a values for certain phenols and thiophenols. The substituents concerned were the *p*-NO_2 and *p*-CH_3SO_2 groups. This work, and Bordwell's suggested explanation, indicate that large differences in the abilities of side-chains to enter into conjugation with a given substituent result in a variation in the σ^- value. In the present case, however, we cannot even suggest a single explanation, of low σ^- figures, which would cover the three "amine" reactions 7–9. As far as these reactions are concerned, the results appear reliable and for reaction 8, for example, the substituent constant obtained in the present work confirms that derived from the study of Stubbs and Hinshelwood.[3] Furthermore, these "low σ^-" values for the 3,4-benzo substituent run parallel to similar low σ^- values for the *p*-nitro group (the only other −T substituent for which satisfactory rate data are available) in these and other amine reactions. This is demonstrated in Table VII. The comparative substituent constants given by Hammett are: $\sigma^-_{3,4\text{-benzo}} = 0.170$; $\sigma^-_{p\text{-nitro}} = 1.270$, and data are drawn from references in Jaffé's review with the exception of reactions 8 and 8a (present work).

TABLE VII

SUBSTITUENT CONSTANTS IN AMINE REACTIONS

Reaction	Apparent $\sigma^-_{3,4\text{-benzo}}$	Apparent $\sigma^-_{p\text{-nitro}}$	ρ	r	s	n
7	0.070	...	−1.245	0.997	0.03	8
8	0.066	1.022	−3.220	0.999	0.05	10
8a[a]	0.064	0.975	−3.167	0.995	0.03	3
9	0.053	1.043	−1.545	0.983	0.10	18
9a[b]	0.054	1.056	−1.488	0.982	0.10	18
27[c]	...	1.022	−3.192	0.997	0.09	6
28[c]	...	0.980	−3.398	1.000	0.01	4

[a] Reaction 8a is reaction 8 at 40°. [b] Reaction 9a is reaction 9 at 15°. [c] Reactions 27 and 28:



in benzene at 25°.

For reaction 27, X = CH_3.
For reaction 28, X = OCH_3.

The differences between the apparent σ^- figures and the normally accepted figures originally derived by Hammett appear to be appreciable and, for example, when Hammett plots are made for reactions 7, 8, and 28 there are significant and striking deviations of these two substituents from otherwise accurately linear plots when the Hammett σ^- values are used.

It is evident that further information is desirable about the "accepted" σ^- values for −T substituents in amine reactions (reaction 1 is the sole example) and about "low σ^-" values for such substituents in phenol reactions (reaction 6 is the sole example). Without such information it can only be stated that in reactions 1–5 the difference in resonance interaction (involving substituent and side-chain) between reactant and product (or transition state) appears to be markedly greater than this difference for reactions 6–9.

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[Contribution from the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture]

Reactions of Unsaturated Fatty Alcohols. IV. Oxidative Degradation of Lauryl Isopropyl Ether[1]

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Lauryl isopropyl ether containing catalytic amounts of cobalt naphthenate was degraded with oxygen at 150°. Degradation products were separated by distillation, solvent extraction, and chromatography.

Isolated oxidation products indicate attack at both carbon atoms adjacent to the ether oxygen. Degradation products isolated were lauric acid, acetone, isopropyl laurate, lower fatty acids from C_2 to C_{11} and their esters, carbon dioxide, isopropyl alcohol, and polymerized acidic products.

Lauric acid and isopropyl laurate were oxidized under the same conditions as lauryl isopropyl ether. Lauric acid gave small amounts of lower acids in the homologous series as degradation products. Isopropyl laurate was oxidized to fatty acids from C_2 to C_{12} in about one third the quantities found from lauryl isopropyl ether.

Previously,[3] we reported the polymerization and film properties of some unsaturated fatty vinyl ethers. During evaluation work it was observed that certain of these films dissolved rapidly in 5% aqueous alkali. This result was unexpected because an ether linkage should be resistant to alkali. Further work demonstrated that the vinyl ether polymer films were being degraded by oxygen during the baking process or while standing in air for several days. Infrared spectroscopic studies on the oxidized films indicated hydroxyl, carbonyl, and ester groups. Chemical data on the alkali-soluble products from the oxidized films that were baked showed that C_{18} acids corresponding to the alkyl group in the vinyl ethers were present.

Since oxidation of stearyl vinyl ether polymer would not be complicated by double bonds in the fatty side chains, this polymer was oxidized under the same conditions as those used for the unsaturated vinyl ethers. Stearic acid was identified as an oxidation product, thus establishing oxidative attack at the alpha carbon atom of the fatty side chain. No oxidation products derived from the vinyl chain of the polymer could be identified. To obtain a clearer picture of the nature of this oxidation, we selected lauryl isopropyl ether because it contained the same carbon skeleton about the ether oxygen as found in the vinyl ether polymers.

Oxidation of ethers by oxygen to form "peroxides" has been known for many years. More recent work[4,5] has shown that oxygen initially attacks a carbon atom adjacent to the ether oxygen to form a hydroperoxide (A). Metallic ions, such as cobalt, are known to catalyze oxidations of this type as well as to promote subsequent decomposition of the hydroperoxide into other radicals and end products.[6,7] Equations shown in Fig. 1

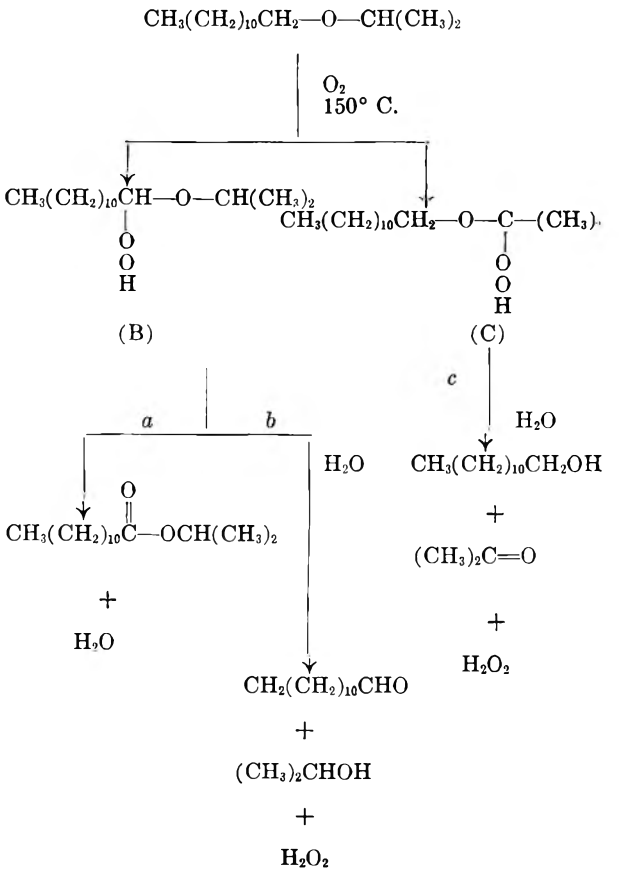
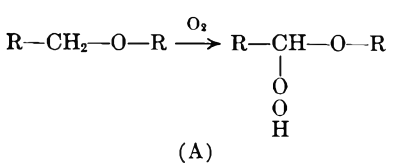


Fig. 1. Formation of oxidation products from lauryl isopropyl ether



(1) Presented at the fall meeting of American Oil Chemists' Society, Cincinnati, Ohio, Sept. 30–Oct. 2, 1957.

(2) Present address: Knox College, Galesburg, Ill.

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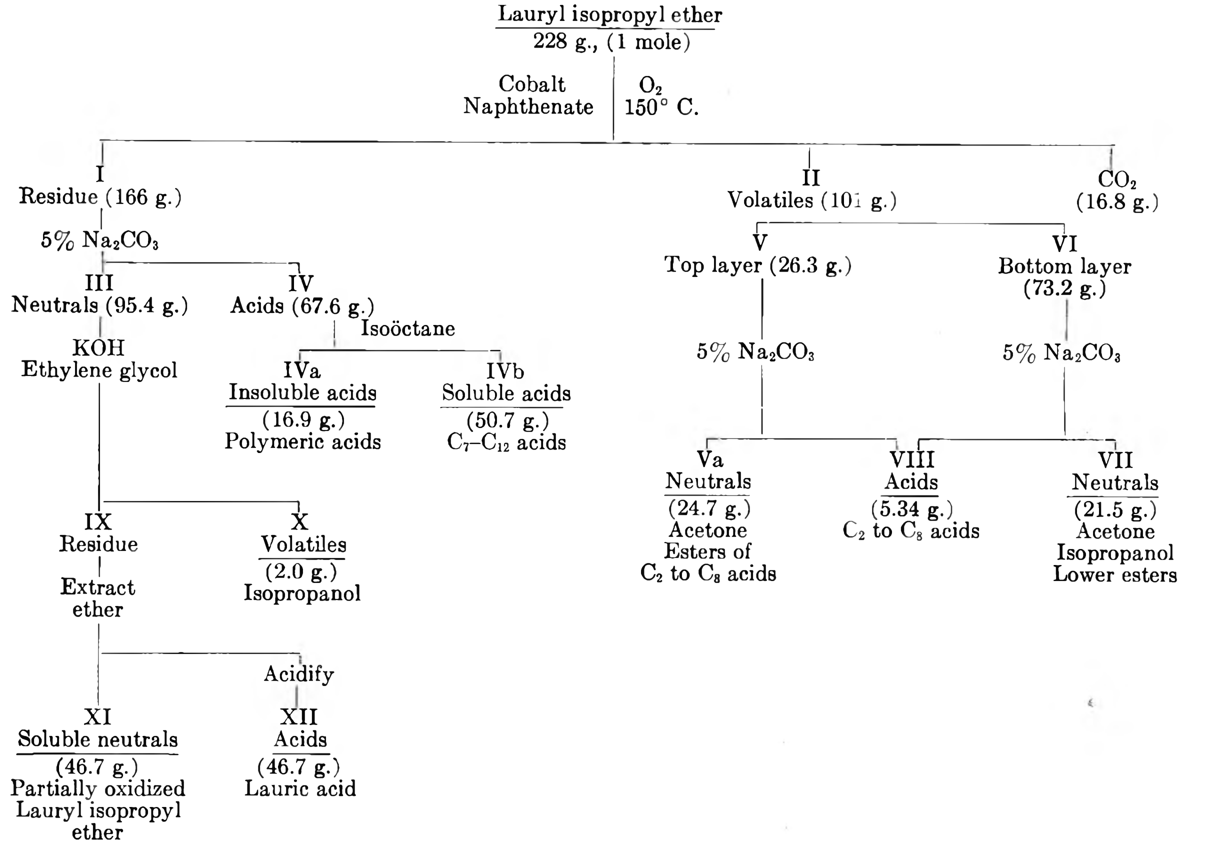

Fig. 2. Fractionation of oxidized lauryl isopropyl ether

present a simplified route to formation of the more important oxidation products from lauryl isopropyl ether. Carbonyl compounds, alcohols, acids, and esters are products known to be formed from hydroperoxide decompositions.[5,7] According to the scheme shown in Fig. 1, either carbon adjacent to the oxygen could be oxidized, but the tertiary carbon in the isopropyl group is probably most susceptible to attack.[8] Decomposition of hydroperoxide (B) by route *a* would produce isopropyl laurate and water, whereas route *b* would yield lauryl aldehyde and isopropyl alcohol. The water necessary for reaction *b* is supplied from reaction *a*.

Hydroperoxide (C), formed by attack at the tertiary carbon atom of isopropyl group, could decompose into lauryl alcohol and acetone by route *c*, a process similar to that indicated by route *b*.[5] (C) could not decompose by route *a* because there is no hydrogen left on the α-carbon atom.

The products actually isolated as shown in Fig. 2 strongly support the series of equations postulated in Fig. 1.

Lauryl aldehyde was not isolated as a degradation product since it is relatively nonvolatile and would remain in the reactor to be oxidized to lauric acid and its lower homologs as shown later. Isopropyl alcohol, volatile under conditions of the reaction, was isolated from fractions V and VII, of Fig. 2 as the 3,5-dinitrobenzoate. Some acetone could be derived from this material by oxidation. Isopropyl laurate was identified in fraction III by saponifying the ester component and characterizing the lauric acid and isopropyl alcohol formed. The acetone formed was found in fractions V and VII, whereas the lauryl alcohol remaining in the oxidation mixture would presumably be converted to lauryl aldehyde, lauric acid, and other products formed by their degradation.

Isopropyl laurate, formed by route *a*, is partially oxidized through the hydroperoxide to lauric acid. This oxidation could proceed by attack at the tertiary hydrogen of the isopropyl group to form hydroperoxide (D) which would decompose into acetone and lauric acid as follows:

$$CH_3(CH_2)_{10}COOCH(CH_3)_2 \xrightarrow{O_2} CH_3(CH_2)_{10}COOC(OOH)(CH_3)_2 \quad \text{D}$$

$$\xrightarrow{H_2O} CH_3(CH_2)_{10}COOH + (CH_3)_2C{=}O + H_2O_2$$

Decomposition of (B) by route *a* or *b* and of (C) by route c leads to products that can eventually be oxidized to lauric acid, lower acids in the homologous series, and carbon dioxide as shown in Table I. A possible mechanism for this oxidation will be discussed later.

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TABLE I

ACIDS FROM OXIDATION OF ISOPROPYL LAURYL ETHER

Fatty Acid	Threshold Vol. (Ml.)[a] Known	Unknown[b]	Percentage of Total Acids Mole	Weight
C_{12}	19	19[b]	30.7	41.3
C_{11}	22	21	11.3	14.1
C_{10}	25	25	6.8	7.9
C_9	30	29	5.3	5.6
C_8	37	38[b]	5.9	5.7
C_7	47	51	5.8	5.1
C_6	62	64	6.1	4.8
C_5	81	86	6.5	4.5
C_4	107	112	8.6	5.1
C_3	163	167[b]	8.3	4.1
C_2	300	305	4.7	1.9

[a] These values are reported for a 2 × 8 cm. column bed containing approximately 7.5 g. of silicic acid. [b] Identity verified by production of a single band when rechromatographed with the appropriate known acid.

On a molar basis, lauric acid was formed in 3 to 5 times the amount of any other acids. Acids from C_5 to C_{10} were formed in roughly equal amounts. These data indicate that lauric acid was formed more rapidly than it was destroyed and accumulated in the degradation mixture.

Data in Table I suggest that C_3 and C_4 acids are more resistant to oxidation than the other acids; however, the higher yields of C_3 and C_4 acids may merely reflect the conditions under which oxidation was carried out. These acids were partially distilled from the reaction mixture into the trap because their boiling points are near or below the temperature of oxidation (150°). Thus, being protected from further oxidation, they tend to accumulate more than the less volatile acids. This phenomenon also accounts for the smaller quantity of acetic acid found among the products. Formic acid would not be an expected oxidation product because it contains an aldehyde, as well as an acid group, and it is easily oxidized to unstable carbonic acid.

Oxidation of lauryl isopropyl ether is difficult to interpret on a quantitative basis because all oxidation routes lead to intermediates that can be converted, at least in part, to identical products. According to the reactions proposed in Fig. 1, the moles of isopropyl laurate, acetone, isopropyl alcohol, and unreacted lauryl isopropyl ether present in the oxidation mixture should total one mole. The amount of each product isolated along with the unreacted lauryl isopropyl ether is shown in Table II. Approximately 86% of the starting ether is accounted for.

TABLE II

MOLE OF DEGRADATION PRODUCTS ISOLATED FROM ONE MOLE OF LAURYL ISOPROPYL ETHER

Compound	Mole
Isopropyl laurate	0.23
Acetone	0.22
Isopropanol	0.20
Unreacted lauryl isopropyl ether	0.21
	0.86

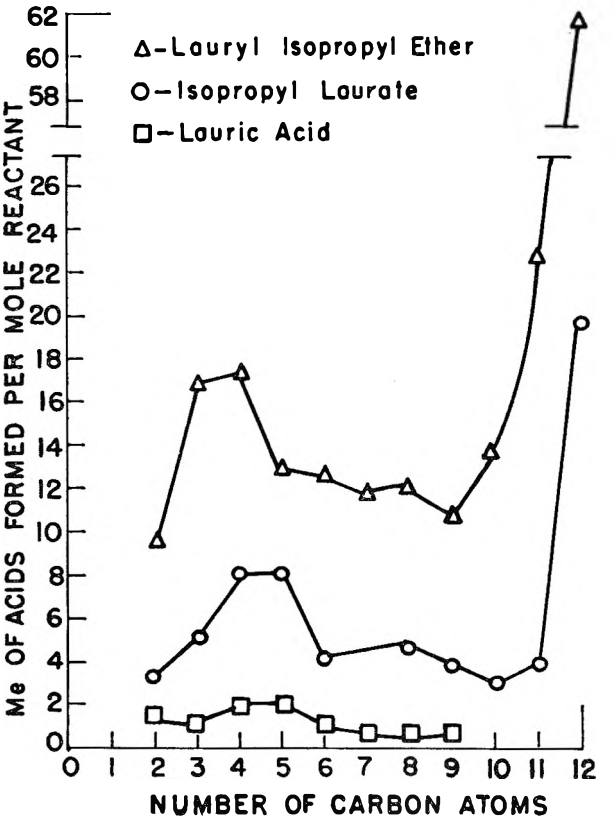

Fig. 3. Acids from the oxidation of lauryl isopropyl ether, isopropyl laurate, and lauric acid

Fig. 3 shows that under identical conditions of oxidation, isopropyl lauryl ether produces more lauric acid and lower acid homologs than isopropyl laurate and is more readily oxidized than lauric acid. Apparently the 12-carbon chain in isopropyl lauryl ether is more easily oxidized to lower acid homologs than the 12-carbon chain in lauric acid. This behavior may be due to differences in the oxidation processes of these substances. Any proposed reaction sequence for the formation of lower acids from these materials must account for the products isolated. Random attack at all possible positions along the 12-carbon chain appears to be a minor reaction since dibasic acids would be expected as products along with the lower monobasic acids. No dibasic acids were isolated from the reaction mixture. Reaction exclusively at the alpha position in lauric acid is unlikely because this center is considered somewhat deactivated toward radicals that seek points of high electron density, *e.g.*, oxygen and chlorine. In addition an alpha attack mechanism would produce some hydroxy and keto acid intermediates of short chain length that would distill from the reaction mixture into the trap. No products of this type were isolated. A possible reaction sequence for isopropyl lauryl ether that accounts for the acidic products formed and seems

reasonable in view of current thinking on oxidation can be illustrated as follows: Hydroperoxides formed from lauryl isopropyl ether decompose into free radicals of various types. For example, hydroperoxides decompose at elevated temperatures:[7]

$$ROOH \rightleftharpoons RO\cdot + \cdot OH$$

Lauryl aldehyde formed from ether cleavage (see Figure 1) is susceptible to attack by hydroxy or alkoxy radicals yielding a carbonyl radical as shown by reaction 1.

$$RCH_2CHO + \cdot OH \longrightarrow RCH_2\dot{C}{=}O + H_2O \quad (1)$$

$$RCH_2\dot{C}{=}O \longrightarrow RCH_2\cdot + CO \quad (2)$$

$$RCH_2\dot{C}{=}O + O_2 \longrightarrow RCH_2COOO\cdot \quad (3)$$

$$RCH_2COOO\cdot + RCH_2CHO \longrightarrow RCH_2COOOH + RCH_2\dot{C}{=}O \quad (4)$$

Chain decomposition can occur by decarbonylation as shown by reaction 2[9] or oxidation can occur to yield ultimately a peracid shown by reactions 3 and 4.[10] Peracids have been observed to decompose at elevated temperatures to yield an alcohol and carbon dioxide[11] thus producing additional chain degradation. The alcohol produced in reaction 5

$$RCH_2COOOH \xrightarrow{\Delta} [RCH_2COO\cdot + \cdot OH] \longrightarrow RCH_2OH + CO_2 \quad (5)$$

may be converted to the corresponding aldehyde by a Fenton-type oxidation involving cobalt instead of iron.[12] Although reaction 6 shows the

$$Co^{++} + H_2O_2 \longrightarrow Co^{+++} + \cdot OH + OH^- \quad (6)$$

$$R'CH_2OH + \cdot OH \longrightarrow R'\dot{C}HOH + H_2O \quad (7)$$

$$R'\dot{C}HOH + Co^{+++} \longrightarrow R'CHO + H^+ + Co^{++} \quad (8)$$

decomposition of hydrogen peroxide to a hydroxy radical, an alkyl hydroperoxide would serve as well in this reaction sequence. The aldehyde produced by reaction 8 enters into reactions 1, 2, and 3 to be degraded further.

The alkyl radical produced in reaction 2 would combine with more oxygen by a series of reactions discussed by Vaughan *et al.*[13] to produce a mole of aldehyde and alcohol by reactions 9, 10, and 11.

$$RCH_2\cdot + O_2 \longrightarrow RCH_2OO\cdot \quad (9)$$

$$2RCH_2OO\cdot \longrightarrow 2RCH_2O\cdot + O_2 \quad (10)$$

$$2RCH_2O\cdot \longrightarrow RCHO + RCH_2OH \quad (11)$$

The aldehyde from reaction 11 can enter into a series of reactions shown by reactions 1, 2, and 3 to produce more chain degradation. The alcohol can be oxidized back to an aldehyde by reactions 7 and 8.

Lower acids isolated in this work could be produced by the decomposition of peracids.[11]

$$RCOOOH \xrightarrow{\Delta} RCOOH + 1/2\ O_2 \quad (12)$$

This reaction would compete with reaction 5.

With the oxidation of isopropyl laurate, hydrogen peroxide formed along with lauric acid from the decomposition of product D can produce some perlauric acid as illustrated in reaction 13.[14]

$$H_2O_2 + RCOOH \rightleftharpoons RCOOOH + H_2O \quad (13)$$

Degradation of the carbon chain of the peracid may proceed by reaction 5. Thus, reaction 13 appears to be the major reaction leading to the formation of degradation products from isopropyl laurate. Presumably alkyl hydroperoxides could serve as well as hydrogen peroxide in this reaction. The low yield of acidic products from the ester (see Fig. 3) probably results from the lack of an easily oxidized intermediate, *e.g.*, lauryl aldehyde, to initiate oxidative degradation. Fig. 3 also shows that the oxidation of free lauric acid is curtailed probably by a lack of a good radical source. Random oxidative attack along the 12-carbon chain, however, could produce some hydroperoxy, hydroxy, and alkoxy radicals which would lead to ultimate formation of small amounts of hydrogen peroxide and perlauric acid. Degradation could then proceed as illustrated by reactions previously described. Small amounts of volatile acids (approximately 1%) have been observed as oxidation products of synthetic long chain fatty acids.[15]

EXPERIMENTAL

Lauryl iodide. A mixture of 223 g. (1.2 moles) of 95% lauryl alcohol (Dytol L-79, Rohm & Haas Co.[16]), 12.0 g. (0.384 mole) of red phosphorus, and 160.8 g. (1.32 moles) of iodine were placed in a three-necked, round-bottomed flask fitted with a stirrer and condenser. After the initial exothermic reaction, the mixture was heated by an oil bath at 150° for 5 hr. After cooling, the mixture was taken up in ether and the phosphorus removed by filtration. The products were washed with 5% sodium hydroxide, then with water until free of alkali, and dried over calcium chloride. Ether was stripped off and 327 g. (92% yield) of light amber product remained; n_D^{30}, 1.4800. The crude iodide was distilled using a short Vigreux column to yield 270 g. (82.5% yield) of purified product, b.p. 93–95°/0.2 mm.; n_D^{30}, 1.4801.

Anal. Calcd. for $C_{12}H_{25}I$: C, 48.70; H, 8.51; I, 42.85. Found: C, 48.63; H, 8.46; I, 43.20.

Lauryl isopropyl ether. In a three-necked, round-bottomed flask fitted with a stirrer and dropping funnel were placed 25.3 g. (1.1 moles) of sodium and 330 g. (5.5 moles) of puri-

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(15) A. Davanhov and D. Fedotova, *Organic Chem. Ind.* (U.S.S.R.), 2, 85 (1936).

(16) Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

fied isopropyl alcohol. After the rapid initial reaction was completed, the flask was gently heated with stirring until all the sodium had dissolved. To the sodium isopropoxide formed was added dropwise 327 g. (1.1 moles) of lauryl iodide. The mixture was heated at reflux for an additional 2 hr. The solution was filtered to remove sodium iodide, washed with water, and dried over calcium chloride to yield 206.6 g. of product. Distillation of the product gave 78.2 g. of impure dodecene, b.p. 95–96°/10 mm.; n_D^{30}, 1.4240; I.V., 113, and 108.4 g. of lauryl isopropyl ether, b.p. 137–141°/10 mm.; n_D^{30}, 1.4250.

Anal. Calcd. for $C_{15}H_{32}O$: C, 78.80; H, 14.13. Found: C, 78.45; H, 13.93.

Lauric acid. This material was obtained from Distillation Products Industries (White Label grade) and used as received.

Isopropyl laurate. In a round-bottomed flask fitted with a condenser were placed 40 g. (0.2 mole) of lauric acid, 240 g. (4 moles) of isopropyl alcohol, and 1.4 g. of *p*-toluenesulfonic acid. This mixture was heated on a steam bath for 10 hr. After neutralizing the catalyst with sodium carbonate, excess isopropyl alcohol was distilled, and the crude ester was washed until neutral with distilled water and then dried. The product was distilled to yield 41.2 g. (85% yield) of purified ester, b.p. 91°/0.12 mm.; n_D^{30}, 1.4258; acid value, 0.23.

Anal. Calcd. for $C_{15}H_{30}O_2$: C, 74.50; H, 12.51; Sap. equiv., 242.4. Found: C, 74.42; H, 12.44; Sap. equiv., 250.

Oxidative degradation of lauryl isopropyl ether. A mixture of 228 g. (1 mole) of lauryl isopropyl ether and 3.2 g. of a 6% solution of cobalt naphthenate was placed in a flask and heated to 150° for 4 hr. while oxygen was introduced through a fritted-glass tube. The oxidation apparatus was connected to a trap surrounded by a bath of acetone and solid carbon dioxide. The outlet from the trap was connected to an Ascarite tube to absorb any carbon dioxide formed. After 4 hr., 166 g. of material remained in the reactor, 101 g. had collected in the trap as two layers, and 16.8 g. of carbon dioxide (0.38 mole CO_2 per mole ether) were absorbed in the Ascarite tube. A total of 283.8 g. of oxidation products was obtained, representing a pick-up of 55.8 g. of oxygen or 3.49 atoms of oxygen per mole of lauryl isopropyl ether. A flow sheet for the fractionation of the oxidized samples is shown in Fig. 2.

Acidic products. The acids from the oxidative degradation were isolated in fractions IV and VIII (Fig. 2), were separated by partition chromatography on a silicic acid column according to the procedure of Ramsey and Patterson,[17] and were tentatively identified by their threshold volumes. Acid bands containing 2 to 20 mg. of material were easily observed on the column; however, a more reliable method of detecting small amounts of acidic materials was to titrate small portions (1 to 3 ml.) of the eluting solvent with 0.02*N* sodium methoxide. Trace amounts of acids were easily detected by this technique. Threshold volumes were determined from the sharp rise in the titration curves.

Chromatography of fraction VIII showed the presence of lower fatty acids (C_2 to C_6); fraction IV contained the less volatile acids (C_6 to C_{12}). Information obtained on both fractions is combined and summarized in Table I.

Approximately 25% of the acidic material in fraction IV was insoluble in iso-octane and could not be placed on the chromatographic column. The insoluble material was a dark brown viscous oil; neutral equivalent, 372; carbonyl oxygen, 1.76%; sap. equiv., 185. Insolubility in iso-octane suggests a dibasic acid; however, the neutral equivalent was too high. This material appears to be a polymeric acid containing enough polar groups, *e.g.*, carbonyl and carboxyl, to render it insoluble in iso-octane. Infrared spectra on the acidic material show associated hydroxyl, carbonyl, carboxyl, and possibly ester groups in the molecule. The chemical data as shown confirm the presence of these groups.

Volatile neutral products. Neutral compounds were isolated from material in the cold trap. The top layer (fraction V) amounted to 26.3 g. and was extracted with sodium carbonate to remove 1.6 g. (6%) of acidic materials. Fraction VII was obtained as an insoluble oil by saturating fraction VI with sodium carbonate. Qualitative tests on these fractions indicated esters, alcohols, and carbonyl compounds. Fraction VII contained most of the alcohols as evidenced by infrared spectra.

Quantitative analyses gave the following results:

	Fraction V	Fraction VII
I.V.	11.1	10.0
Neut. equiv.	870	—
Sap. equiv.	232[a]	529
Carbonyl oxygen	7.1%	6.7%

[a] Corrected for acids.

Small samples (0.15 g. each) of fractions V and VII were combined and treated with an alcoholic solution of 2,4-dinitrophenylhydrazine.[18] After heating 15 min. on a steam bath, the 2,4-dinitrophenylhydrazone was filtered and dried (0.18 g.), m.p. 115–118°. The product was recrystallized from 95% ethanol to yield 0.11 g. of orange-yellow crystals, m.p. 120–121°. A small amount of these crystals was placed on a 2 × 20-cm. chromatographic column packed with Celite-Bentonite.[19] This column was developed with alcohol-chloroform (1:20) to yield a main band followed by three trace bands. The main band was eluted and recovered from the solvent as 2,4-dinitrophenylhydrazone melting at 123°. A mixed melting point obtained with an authentic sample of acetone-2,4-dinitrophenylhydrazone showed no depression. X-ray diffraction patterns were identical for 2,4-dinitrophenylhydrazone and for acetone-2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_9H_{10}N_4O_4$: C, 45.40; H, 4.25; N, 23.50. Found: C, 45.76; H, 4.16; N, 23.35.

If all of the carbonyl oxygen content of fractions V and VII is due to acetone, 12.8 g. of acetone was obtained from 228 g. of lauryl isopropyl ether or 0.22 mole of acetone per mole of ether.

Since fraction V had a saponification equivalent of 232, considerable ester was indicated. Data on acid components of the ester were obtained by refluxing fraction V with alcoholic potassium hydroxide for 4 hr. A small amount of the recovered acids (74 mg.) was dissolved in iso-octane and chromatographed on a silicic acid column.[12] Results are shown in Table III. The average molecular weight of the acids was 101.5. If isopropyl alcohol is assumed to be the alcoholic component of these esters (isopropyl alcohol was the only alcohol found in the volatile fractions), the mixture would have a saponification equivalent of 143.5. Comparison of this value with an observed saponification equivalent of 232 indicates fraction V was 62% ester. Carbonyl content of fraction V indicated 26% acetone, and extraction of this fraction with sodium carbonate gave 6% acids. It can be assumed that esters accounted for the remaining 68%. This value is in fair agreement with the value of 62% obtained from determining the acid content of the esters. The ester content of fraction V represents 0.113 mole of esters formed per mole of ether oxidized.

Since the infrared spectra of fraction VII showed the presence of considerable alcohol, 0.3 g. of this alcoholic material was treated with 1 g. of 3,5-dinitrobenzoyl chloride,

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TABLE III

ACIDS OBTAINED FROM SAPONIFICATION OF FRACTION V[a]

Acid	Threshold Vol. (Ml.)[b]		Percentage of Total Acids	
	Known	Unknown	Mole	Weight
C_8	37	39	3.97	5.86
C_7	47	46	8.64	11.52
C_6	62	59	14.15	16.84
C_5	81	81	21.25	22.17
C_4	107	108	32.14	29.32
C_3	163	156	14.38	10.91
C_2	300	311	5.45	3.35

[a] Volatile neutral fraction from the oxidation of lauryl isopropyl ether. [b] These values are reported for a 2 × 8 cm. column bed containing approximately 7.5 g. of silicic acid.

and the mixture was heated on a steam bath for 5 to 10 min. The resultant product was washed with water, 2% sodium carbonate solution, and finally with water to yield 0.24 g. of crystals, m.p. 110–115°. The product was recrystallized from 95% ethanol to yield 0.10 g., m.p. 117–118°. A mixed melting point of this material with an authentic sample of isopropyl 3,5-dinitrobenzoate (m.p. 122°) melted at 118–119°.

Anal. Calcd. for $C_{10}H_{10}O_6N_2$: C, 47.3; H, 3.98; N, 11.0. Found: C, 47.1; H, 3.80; N, 10.9.

Fraction VII and pure isopropyl alcohol were examined in the infrared at 3570 cm.$^{-1}$ Comparison of the hydroxyl bands showed that fraction VII contained approximately 55% isopropyl alcohol by weight, if no other hydroxyl compounds were present. Since fraction VII amounted to 21.5 g., it contains 11.8 g. of isopropyl alcohol or 0.197 mole of isopropyl alcohol formed per mole of lauryl isopropyl ether.

Summarizing these data, fraction VII was found to contain 55% isopropyl alcohol and 24% acetone (by carbonyl analysis). Assuming the remaining material (21%) to be esters and correcting the saponification equivalent of 529 for this amount of ester, a new saponification equivalent of 111 is obtained. Since the esters in fraction VII amounted to 4.52 g. and had an average molecular weight of 111, 0.041 mole of esters was produced per mole of lauryl isopropyl ether oxidized.

Nonvolatile neutrals. Extraction of residue I with sodium carbonate solution gave a neutral fraction III and the previously investigated acidic fraction IV (Figure 2). Functional group analyses on fraction III showed the presence of carbonyl compounds (0.7% carbonyl oxygen) and esters, [sap. equiv., 259 (corrected for acids)]. The infrared spectrum showed bands corresponding to ester and to unreacted lauryl isopropyl ether. A comparison of the spectrum of the unknown with that of an authentic sample of isopropyl laurate gave an estimate of 70–75% ester in fraction III (calculated as isopropyl laurate).

Information on the acidic and alcoholic materials making up the ester in fraction III was obtained as follows: 9.8 g. of sample were treated with 10 g. of ethylene glycol containing 6.6% potassium hydroxide in a test tube fitted with a nitrogen inlet tube and a side arm leading to a receiver cooled by ice. The test tube was heated by an oil bath at 150° for 1.5 hr. as a gentle stream of nitrogen was allowed to flow through the apparatus. Two fractions were obtained as shown in Fig. 2: a residue (IX) and a small amount of volatile material (X). The neutral products were removed from fraction IX by diluting the residue with 2 volumes of distilled water and extracting 5 times with ethyl ether. The ether layers were combined and washed free of alkali with water. The combined ether layer was evaporated to yield 4.1 g. of an odorless yellow oil (XI). *Anal.* Found: C, 75.8; H, 13.55. Empirical formula: $C_{9.3}H_{20}O$. Mol. weight, 240.

The empirical formula shows that XI may be a 9 to 10 carbon atom alcohol or ether. However, the molecular weight corresponds to a partially oxidized isopropyl lauryl ether. The infrared spectra of XI is almost identical with isopropyl lauryl ether except for the hydroxyl adsorption at 3330 cm.$^{-1}$ The alkaline layer from fraction XI was acidified with hydrochloric acid, ether was added, and the layers were separated. The ether layer was washed free of mineral acid, and the ether was evaporated to yield 4.1 g. of acids (XII), neut. equiv., 236.

Fraction X (0.2 g.) was treated with 0.5 g. 3,5-dinitrobenzoyl chloride as described previously to yield 0.15 g. of crystalline ester, m.p. 112–115°. The product was recrystallized from alcohol to yield 0.10 g. a 3,5-dinitrobenzoate, m.p. 118°. A mixed melting point of this material with an authentic sample of isopropyl 3,5-dinitrobenzoate showed no depression.

Purification of fraction XII by partition chromatography on a silicic acid column (2 × 20 cm.) according to the method of Ramsey and Patterson[12] gave only one acid band having the threshold volume of lauric acid. The acid band was recovered and treated with thionyl chloride and ammonia to yield a crystalline amide, m.p. 98°. A mixed melting point determination with authentic lauramide showed no depression; hence, the ester in fraction XII was isopropyl laurate. Since the moles of isopropyl laurate in fraction III would be equivalent to the moles of lauric acid found in fraction XII, 0.23 mole of isopropyl laurate was formed per mole of lauryl isopropyl ether.

Oxidation of lauric acid and isopropyl laurate. Lauric acid and isopropyl laurate were found to be degradation products from lauryl isopropyl ether. Since these compounds are relatively nonvolatile, they were subjected to an oxidative environment during the experiment. In order to obtain data on the type of products formed from their degradation, lauric acid and isopropyl laurate were oxidized for 4 hr. at 150° with oxygen in the presence of cobalt naphthenate. The apparatus was the same as that used to oxidize lauryl isopropyl ether. The acids produced during this treatment were determined by partition chromatography on silicic acid[13] and results are shown in Fig. 3 along with similar data obtained on lauryl isopropyl ether.

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Benzene-Alcohol-Soluble Extractives of Sitka Spruce

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Extraction of mature Sitka spruce woodmeal with benzene-alcohol (2:1) dissolved 2.0% of the wood. After precipitation of an ether-insoluble lignin-like fraction (0.2% of the wood), the extractives were separated into neutral, acidic, and phenolic portions by conventional methods. The phenolic fraction (0.36%) consisted of acetovanillone (0.144%), vanillin (0.144%), and vanillyl alcohol (0.072%). Tropolones were absent. The acidic fraction (0.27%) apparently contained no volatile or fatty acids but contained a lignin-like acid (methoxyl = 11%, neut. equiv. = 750). The cyclohexylamine salts of the acid fraction precipitated as an oil or solid from which a low melting acid fraction (m.p., *ca.* 50° neut. equiv. = *ca.* 300) could be regenerated.

Neutral compounds amounted to about 65% of the ether soluble extractives (1.17% of the wood) and consisted of volatiles (0.18%): a conjugated monoterpene diene, possibly caradiene, and an unsaturated alcohol; and nonvolatiles (0.97%): β-sitosterol (.09%) and l-2-octyl-β-sitosterol phthalate (0.90%). Phthalates have apparently been isolated from only one other plant source in trace amounts. The fact that one has been obtained here as one-half of the ether-soluble extractives emphasizes the marked chemical differences between extractives of Sitka spruce and those of more thoroughly investigated species.

The extractive components which occur in mature woody tissue have considerable interest in organic chemistry, in plant taxonomy and in the wood-based industries. Although they sometimes affect the course of pulping processes and the durability of the wood, some of the commercial woods of North America have not been investigated thoroughly,[1-3] among them Sitka spruce (*Picea Sitchensis*, Carr.). Previous reports on the extractive content of this species appear to be restricted to values of the content of total extractives (2.61%[4] or 2.3%[5]), to a portion of an investigation by Erdtman on the presence or absence of conidendrin in conifers,[6] and to a portion of an investigation of components of leaf oils of conifers by Lehman and Lynn.[7] Erdtman found no conidendrin present in Sitka spruce woodmeal, and the latter authors found in its leaf oils β-pinene, β-phellandrene, camphor, borneal, terpineol, and nonylic and butyric acids. Terpenes are reported to constitute over 40% of the steam volatile oil.[8]

The present investigation was carried out upon a sample of extractives obtained from mature Sitka spruce logs. The alcohol-benzene extract contained extractives amounting to 2% of the wood weight. The solution was concentrated on a cyclone separator and separated by conventional methods into four fractions, an ether-insoluble material and acidic, phenolic, and neutral ether-soluble materials (Fig. 1). The ether-insoluble fraction had the appearance of a native lignin fraction and was not investigated in detail.

A number of separate experiments were run on the acid fraction. The bicarbonate-soluble material was steam-distilled after acidification and no volatile acids were found to be present. However, when the residue from the steam distillation was extracted into ether a small amount of ether-insoluble acid was obtained. This amounted to five or six per cent of the original sodium bicarbonate-soluble material. It was a brown amorphous solid melting from 175 to 195° with a neutral equivalent of 771 to 773 and a methoxyl content of 11.2%. The ultraviolet absorption spectrum showed a minimum at 258 to 260 mμ and a maximum at 283 to 284 mμ. This is reminiscent of an ether-insoluble lactonic acid reported previously to be isolated after steam distillation of wood extractive acids[9,10] but appeared more ligninlike in character.

Separation of fatty and resin acids was attempted by several procedures. The resin acids were precipitated by cyclohexylamine from acetone solutions of the bicarbonate-soluble material, (acids), the alkali-soluble material (phenols and acids), and also the total ether-soluble material. From both the bicarbonate-soluble and alkali-soluble products only viscous oils were obtained. On precipitating cyclohexylamine salts from the total ether-soluble material, a light colored precipitate corresponding to 15% of the total was obtained. This is essentially the same quantity of acids as was obtained by bicarbonate extraction. The total acid fraction was therefore apparently precipitable by cyclohexylamine. The cyclohexylamine salt on acidification with boric acid yielded a yellow light

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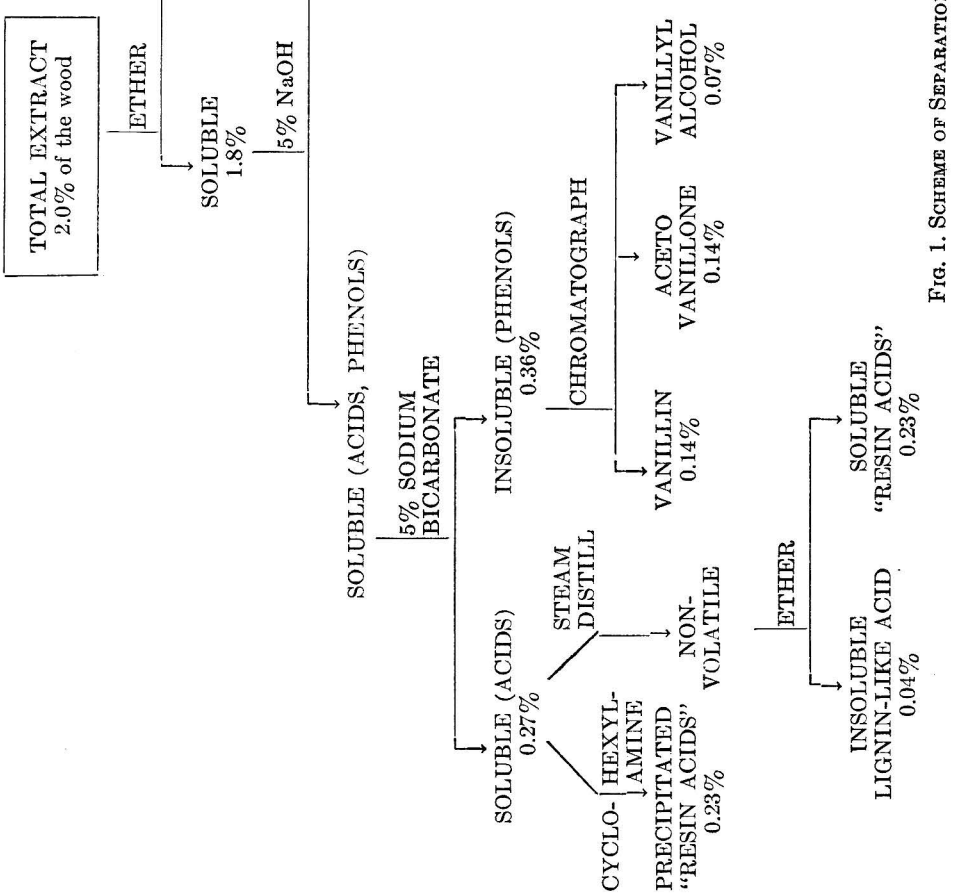

FIG. 1. SCHEME OF SEPARATION

colored solid with a melting range of 50–55° and with a neutral equivalent of 300. The melting point range appeared unusually low even for a gross mixture of resin acids. The product had an ultraviolet absorption spectrum showing several maxima. However, the product obtained on standard precipitations with diamylamine had litte absorption in the ultraviolet and when the total acid mixture was treated in a similar fashion with diethylamine to obtain neoabietic acid only a trace of precipitate was obtained. These and similar results probably indicate that the products decomposed on manipulation but new resin acids may be present. Several standard methods for obtaining urea inclusion compounds failed to separate any aliphatic acids. All the acids in Sitka spruce therefore appear to behave like resin acids except for the observed melting range. No volatile or aliphatic acids were found.

The phenolic fraction, which was bicarbonate-insoluble and alkali-soluble, was separated readily on alumina. The phenols were developed with chloroform and three distinct yellow bands appeared. The most strongly adsorbed top band, representing 40% of the mixture, was acetovanillone, the middle band, 20%, was vanillyl alcohol, and the lower band, 40%, vanillin. Identification was by means of qualitative tests, mixed melting points, and derivatives.

The neutral compounds amounted to 65% of the ether-soluble extractives. Steam distillation separated about one sixth of the neutral materials as a volatile fraction. The volatile fraction distilled into two fractions of almost equal size boiling at 35–38° and 55–60° at 1 mm. The first fraction, redistilled at 74 to 77°, 10–mm. pressure, was a light yellow oil which formed fine needle-like crystals at about 10°. The oil had a refractive index of 1.4945 and a density of 0.79 at 25°, was unsaturated to bromine and permanganate, and gave a negative test for alcohol and for carbonyl. The ultraviolet absorption spectrum had a peak at 265 mμ with an absorption coefficient of approximately 70. This material was hydrogenated under a slight pressure using platinum on charcoal as catalyst and absorbed 1.96 moles of hydrogen per 10 carbon atoms. On filtration of the hydrogenated solution and evaporation of ethanol, a yellow solid which had a menthol-like odor was obtained in insufficient quantities for other tests.

These results can be interpreted in the following manner: The boiling point and density are in a range suitable for a monoterpene but low for a sesquiterpene. Quantitative hydrogenation indicates two double bonds per C_{10} unit. The absorption coefficient and wave length of maximum absorption are typical of a conjugated diene, with both double bonds in a single cyclohexane ring since acyclic conjugated dienes or those with double bonds not in the same ring absorb between 217 and 250 mμ (Woodward's rules).[11] The molecular refraction for acyclic, monocyclic, and bicyclic monoterpene conjugated dienes are 47.46, 45.26, and 43.77. The values obtained from the experimental refractive index and density (for the corresponding assumed molecular weights of 138, 136, and 134) are 46.19, 45.52, and 44.85. The best agreement is therefore for the monocyclic diene; however, a 2% or 3% increase in our semimicro determination of density, the value of which appeared to be low, would make the bicyclic dienes a possibility as well. Known monocyclic dienes such as α-terpinene and the phellandrenes having conjugated double bonds do not have similar physical properties and the corresponding saturated hydrocarbons are liquids. However, some saturated bicyclic monoterpenes such as camphane and isocamphane are fragrant solids. The four adjacent carbon atoms of the diene system must not include a bridgehead carbon atom (Bredt's rule). If the unknown is bicyclic, only two adjacent carbon atoms can be common to both rings. Therefore, of the seven principal bicyclic monoterpene skeletons only that of carane has a suitable structure. This reasoning leads to the conclusion that the diene most probably is the unknown caradiene. However, carane prepared previously by the hydrogenation of carene and by other methods is a liquid. This is in conflict with our supposition but Simonsen suggests that the caranes obtained are probably mixtures of stereoisomers.[12]

The higher boiling fraction of the steam-volatile neutrals was an unsaturated alcohol, described in the Experimental section. It was obtained in rather small quantity and not completely identified.

The nonvolatile neutral fraction comprised the largest portion of the extractives of Sitka spruce and amounted in fact to about 55% of the ether-solubles. The nonvolatile material gave a negative ceric nitrate alcohol test and a negative dinitrophenylhydrazine carbonyl test. Permanganate and bromine tests for unsaturation were inconclusive. The Lieberman-Burchard test for sterols was positive but the material was clearly a mixture from its behavior on crystallization.

Nine grams of the nonvolatile neutral fraction was treated with digitonin and approximately seven tenths of a gram of the free sterol precipitated as the digitonide. This accounted for about 7% of the total neutral fraction or 4.5% of the total extractives. The remaining nonvolatile neutral compound was isolated by distilling off under vacuum the alcohol from which the digitonide had been precipitated. Two grams of this material was dissolved in petroleum ether and chromatographed on alumina. On development with ben-

(11) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 72 (1942).

(12) J. L. Simonsen, *The Terpenes*, Vol. II, Cambridge University Press 1949, p. 61 *ff.*

zene one sharp yellow-brown band appeared which was eluted to yield 1.9 grams or 95% as a yellow semisolid material. This material had a saponification equivalent ranging from 269 to 272 and was titrated and shown to have no detectable acidity. By ether extraction of the alkaline solution a solid alcohol was recovered. This, as well as the free sterol, was identified as β-sitosterol by precipitation with digitonin, the Leiberman-Burchard sterol test, ultraviolet absorption spectrum in 97% sulfuric acid, and agreement between the melting points for the purified β-sitosterol and its acetate and benzoate with the literature values. No evidence was found for the presence of any other sterol than β-sitosterol in the ester or as free sterol.

From the saponification of the nonvolatile neutral material with potassium hydroxide in 95% ethanol there was also obtained a potassium salt which precipitated from the cold basic solution and which amounted to 10% of the fraction. The potassium salt was acidified and yielded an acid melting at 205–207° which had a neutral equivalent of 81 to 81.5. The product of reaction with thionyl chloride proved to be an anhydride melting at 130°. The acid also formed a *p*-bromophenacyl ester melting at 153° and a mixed melting point of the unknown with phthalic acid was undepressed. The ultraviolet absorption spectrum of the isolated acid was essentially identical with that of phthalic acid. Ultraviolet absorption and saponification also established the expected amount of the phthalic acid in the purified ester.

When the alkaline solution from the saponification of one gram of pure ester was distilled a water-white, water-immiscible liquid was also obtained weighing approximately one tenth of a gram. It boiled between 180 and 185°, had a density of 0.820, a refractive index of 1.4244, a melting point of approximately −30°, a specific rotation of −60°. Oily 3,5-dinitrobenzoates and phenylurethanes were formed and a solid hydrogen phthalate melting at 74 to 75°. The corresponding properties of 2-octanol[13] are: b.p., 179–180°, d^{25} 0.817, n^{25} 1.4244, m.p., −31.6°, m.p. of derivative 75°. The specific rotations, $[\alpha]_D^{25}$, have been variously reported from ±8 to ±9°. The nonvolatile neutral compounds present in Sitka spruce are therefore essentially a mixture of a small amount of β-sitosterol and l-2-octyl-β-sitosterol phthalate.

There are several substantial differences between the extractives of Sitka spruce and other related wood species. The carboxylic acid fraction amounts to only 15–20% of the total ether-soluble fraction which is much less than is usually reported for soft woods. Resin and fatty acid fractions often account for around 70% of the extractives from other spruce species. The phenolic fraction on the other hand is considerably greater than is usually found in related species. The three phenolic compounds isolated constitute 15 to 20% of the total ether-soluble extractives.

The neutral fraction of this species is most unusual. The most remarkable fact is that so large a percentage of the extractive fraction should be a phthalate ester. Neither phthalic acid nor any phthalic ester seems to have been found in nature except for a single report of trace amounts of dibutyl phthalate found in Zinfandel grapes by Haagen-Smit and co-workers.[14] This appears also to be the first report of l-2-octanol as well although other naturally occurring octanols have been found. It will be interesting to learn whether the postulated presence of caradiene proves correct. These results once more emphasize the remarkable differences found between the extractive fractions of closely related species.

EXPERIMENTAL

Preparation of extract. The Sitka spruce logs were supplied by the Columbia Cellulose Co., Ltd., of Prince Rupert, B. C. They came from trees approximately 75 years old from an upland stand of 700 feet elevation where they occurred in mixture with Hemlock, near Terrace, B.C.

The whole logs were split, chipped, and hammer-milled to a coarse meal. Eighty-five pounds of the meal in 10-pound batches was extracted twice by immersion for 24 hr., with occasional stirring, in 15 gal. of alcohol-benzene (1:2) at room temperature. The solvent was drawn off and concentrated in a steam-jacketed vacuum flash evaporation apparatus (Scientific Glass Co., Inc., Cat. J-52, #J-1563), at the rate of just under 2 gal. per hr.

A total of approximately 700 g. of alcohol-benzene–soluble extraneous components was thus obtained, in the form of a 30% concentrate in alcohol-benzene. This total extractive concentrate, a dark brown slurry, was freed from solvent by vacuum distillation to yield the free extractives as a viscous semisolid mass. This was stirred with five to ten times its weight of ethyl ether, in order to separate the ether-soluble material. The precipitated ether-insoluble material constituted 8 to 10% of the total benzene-alcohol extract and resembled a native lignin fraction. It had a methoxyl content of 14.3% (analysis by Dr. K. Ritter, Basel, Switzerland) and the ultraviolet absorption spectrum showed a maximum at 282 mμ. The maxima reported for softwood lignins fall in a range of 280 to 284 mμ.

The ether-soluble fraction constituted approximately 90% of the total extract or 1.8% of the air-dried weight of the wood.

Separation of alkali-soluble, bicarbonate-soluble, and neutral fractions. In a typical separation, 30.5 g. of the total ether-soluble extractives was dissolved in 150 ml. of ethyl ether and shaken three times in a separatory funnel with 100-ml. portions of 5% sodium hydroxide solution. The sodium hydroxide solutions were combined and acidified to *p*H 4 to 5 with sodium dihydrogen phosphate, then extracted with 250-ml. portions of ethyl ether. The ether solutions were combined, dried over magnesium sulfate, and the ether evaporated to yield 14.2 g. (46.5%) of total acidic material, including phenolics. Under slightly different conditions, 65% of the extractives were recovered as brown viscous neutral material not extracted by 5% alkali from the original ether extract.

(13) G. L. Dorough, H. B. Glass, T. L. Gresham, G. B. Malone, and E. E. Reid, *J. Am. Chem. Soc.*, **63**, 3100 (1941).

(14) A. J. Haagen-Smit, F. N. Hirosawa, and T. H. Wang, *Food Research*, **14**, 472 (1949).

Repeated separations of phenols and acids were carried out as follows: Thirty g. of the sodium hydroxide–soluble material was dissolved in 300 ml. of ether and extracted in a separatory funnel with three 250-ml. portions of 5% sodium bicarbonate. The sodium bicarbonate solutions were combined and acidified to a *p*H of 4 to 5 with sodium dihydrogen phosphate, then extracted with three 250-ml. portions of ether. The ether solutions were combined and dried over magnesium sulfate, and the ether evaporated off to yield approximately 12 to 13 g. of sodium bicarbonate-soluble material.

The carboxylic acids. (*1*) *The resin acids.* In the first trials, portions of the total ether-soluble material were dissolved in five times their weight of boiling acetone, about 5% (of the total weight) of cyclohexylamine was added and the resulting solution was allowed to cool overnight at 0°. A pale yellow-brown precipitate was filtered off which amounted to 15% of the total ether-soluble material, calculated as free resin acids, or roughly the same as the bicarbonate-soluble fraction. The precipitated salts were taken up in saturated boric acid solutions and shaken with ethyl ether. The ether layers were separated, dried over magnesium sulfate, and the ether evaporated off to yield a yellow-brown solid with a melting range of 50–55°. This had a neutral equivalent of 300.

The ultraviolet absorption spectrum of this material showed maxima at 244, 248, 254, and 260 mμ, with absorption coefficients (α) ($\alpha = \frac{D}{C}$, D is optical density, C is concentration in g./l.) of 37.5, 47.5, 52.5, and 32, respectively, and an inflection point at 238 mμ with an absorption coefficient of 29.

The acid fraction obtained from the cyclohexylamine precipitation was dissolved in boiling acetone and an equimolar amount of diamylamine added. On cooling the solution overnight at 0°, a yellow precipitate was obtained. This was recrystallized from acetone to a constant melting point of 50–52°, then shaken as before with ether and saturated boric acid solution. Upon evaporation of the ether, a solid amounting to 16% of the total acid fraction was obtained and was recrystallized from ethanol to a constant melting point of 58°. An ultraviolet absorption spectrum of the material showed negligible absorption.

When the total "resin acid" mixture was treated in a similar fashion with diethylamine, a specific precipitant for neoabietic acid, only a trace of precipitate was obtained.

When the alkali-soluble or the bicarbonate-soluble fraction was dissolved in boiling acetone and treated as before with cyclohexylamine, only gummy, viscous oils were obtained upon cooling. These could not be induced to crystallize either by supercooling in Dry Ice–acetone or by trituration with nonsolvents such as petroleum ether or ethyl ether.

(*2*) *The fatty and volatile acids.* In several separate trials, 1 g. of the sodium hydroxide–soluble or sodium bicarbonate–soluble material, as obtained above, was added to 30 ml. of hot methanol containing 5 g. of urea or 20 ml. containing 3 g. of urea. When this solution was cooled, no solid appeared.

Two g. of the sodium hydroxide–soluble or sodium bicarbonate–soluble material was ground for 2 hr. with 10 g. of urea moistened with methanol, then extracted with petroleum ether to remove uncomplexed material. Examination of the residual urea crystals showed no evidence of complex. The crystals were dissolved in dilute hydrochloric acid to destroy any complex, if present, and the acidic solution extracted with petroleum ether. The petroleum ether solution was dried over $MgSO_4$ and evaporated to leave negligible material.

The sodium bicarbonate–soluble material was steam-distilled, in portions of 20 to 30 g., for 5 hr. or more until approximately one l. of distillate was collected. This was extracted with three 250-ml. portions of ether, the ether solutions combined and dried over magnesium sulfate. No acidic product was obtained. When the nonsteam-volatile acids were extracted with ether, a small amount of ether-insoluble acid was obtained. This amounted to 5 to 6% of the original sodium bicarbonate–soluble material. It was a brown amorphous solid which melted from 175–195°, and had a neutral equivalent of 771 to 773. The ultraviolet absorption spectrum of this material showed a minimum at 258 to 260 mμ, α of 14, and a maximum at 283 to 284 mμ, with an α of 22. Analysis showed a methoxyl content of 11.20, 11.12% (analysis of Dr. K. Ritter, Bazel, Switzerland). Its appearance was similar to that of a lignin fraction.

Phenolic constituents. Ether extraction of sodium bicarbonate suspensions of the sodium hydroxide–soluble material, as outlined in the separation of the carboxylic acid fraction, served to separate the phenolic material, amounting to 50 to 60% of the sodium hydroxide–soluble portion.

In appearance, the phenolic material was an amorphous yellow solid having an odor reminiscent of vanillin. It melted over the range of 70° to 80°. A ferric chloride test was positive, producing a pinkish coloration.[15] Reaction with 2,4-dinitrophenylhydrazine indicated the presence of a carbonyl fraction.[15]

One g. of the phenolic mixture was dissolved in the minimum volume of chloroform necessary for solution, (*ca.* 5 ml.) and added to a chromatographic grade, neutralized alumina column, measuring approximately 3 × 50 cm. Upon development with a large volume of chloroform three distinct yellow bands appeared. The column was extruded, the bands were cut out and each extracted with ethanol. The alcohol extracts were evaporated to yield 0.4 g. (40% of the mixture) from the top, 0.2 g. from the middle somewhat diffuse band, and 0.4 g. from the bottom band.

The material constituting the bottom band of the chromatogram melted in the range of 75–80°, had a vanillin-like odor and gave a positive Tollen's aldehyde test,[15] and a pink color characteristic of vanillin when treated with resorcinol and hydrochloric acid.[16] (The materials constituting both the top and middle bands gave negative Tollen's tests.)

When the unknown was dissolved in 50% aqueous ethanol and heated with potassium cyanide ammonium carbonate, a hydantoin which melted at 275–276° with decomposition, was obtained. (Vanillin hydantoin 276°.) The unknown formed a *p*-nitrobenzoate of m.p. 123–124°. Vanillin *p*-nitrobenzoate melts at 124.5°. A mixed melting point of the purified unknown, m.p. 80–81°, with vanillin, m.p. 81°, showed no depression.

The material forming the middle band of the chromatogram melted in a crude state at 95–105°. After repeated recrystallizations from aqueous ethanol it had a constant melting point of 113–114° and showed no depression with vanillyl alcohol. Its identity was confirmed by preparation of a benzoate,[15] recrystallized from aqueous alcohol, m.p. of 120–121° and an acetate recrystallized from aqueous alcohol, m.p. 47–48°.

The product from the top band of the chromatogram gave a positive carbonyl test with 2,4-dinitrophenylhydrazine, but negative Schiff's and Tollen's aldehyde tests.[15] When repeatedly recrystallized from aqueous ethanol, the melting point rose slightly to a constant value of 113–115°. No depression was shown in a mixed melting point of the unknown phenol with acetovanillone, melting at 113–114°. The substance also reacted with aqueous copper acetate to form a yellow-green complex, as reported by Mulliken[17] for acetovanillone. Its identity with acetovanillone was confirmed by the preparation of a benzoate[15] m.p. of 105–106° and an acetate[15] m.p. 57–58°.

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(15) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, Thomas V. Crowell Co., New York, 1947.

(16) Official and Tentative Methods of Analysis, Assoc. of Official Agric. Chemists, 320.

(17) S. P. Mulliken, *A Method for the Identification of Pure Organic Compounds*, Vol. I, John Wiley, New York, 1904, p. 95.

The neutral compounds. (1) *Steam distillation.* Ten g. of the total neutral material was distilled with steam for 8 hr. The distillate was extracted three times with 100-ml. portions of ether, the ether solutions combined and dried over magnesium sulfate. Upon evaporation of the ether 1.5 g. of a pungent-smelling yellow oil, about 10% of the total ether-soluble extractives, was obtained. Vacuum distillation of the oil in a Todd column gave two fractions of almost equal size: (1) a fraction boiling at 35–38° at 1-mm. pressure, (2) a fraction boiling at 55–60° at 1 mm.

A. The first fraction, redistilled at 74–77°, 10-mm. pressure, was a light yellow oil, more than half of which formed fine needle-like crystals at about 10°. The oil had a refractive index, n_D^{25}, of 1.4945 and a density of 0.790 (25°). Bromine and permanganate tests for unsaturation[15] were positive, a ceric nitrate test for alcohols was negative. Tollen's aldehyde and 2,4-dinitrophenylhydrazone tests were also negative. The ultraviolet absorption spectrum had a peak at 265 mμ with an absorption coefficient, α, of approximately 70, both indicating a conjugated diene.

This material (51.38 mg.) was hydrogenated under a slight pressure of hydrogen using 10 mg. of 5% platinum on charcoal catalyst in a system similar to that described by Vandenheuvel.[18] Sixteen and two-tenths ml. of hydrogen at standard temperature and pressure was consumed in 3 hr. Therefore, 70.3 g. of the sample was equivalent to 1 mole of hydrogen or 1.96 double bonds per ten carbon atoms. On filtration of the hydrogenated solution and evaporation of the ethanol, a yellow solid which had a menthol-like odor was obtained in insufficient quantity for other tests.

B. The higher boiling fraction of the steam volatile compounds gave a positive permanganate unsaturation test and also a positive ceric nitrate alcohol test.[15] On reaction with phenyl isocyanate a solid was formed which seemed to be a mixture of two compounds, one melting around 190°, the other about 240°. This oil had a refractive index, n_D^{25}, of 1.4473, and a density of 0.845 at 25°.

(2) *The nonsteam volatiles.* The residue after steam distillation above was extracted with ether (250 ml.) three times, the ether dried over magnesium sulfate and evaporated at the water pump to yield *ca.* 8 g. of viscous brown material, about 55% of the total ether-soluble alcohol-benzene–extracted compounds. This material was soluble in ether, petroleum ether, benzene, ethanol, and chloroform, sparingly soluble in methanol, and insoluble in water. It gave a negative ceric nitrate alcohol test and a negative dinitrophenylhydrazine carbonyl test.[15] Permanganate and bromine tests for unsaturation were inconclusive.[15] A Lieberman-Burchard color test for sterols[19] was positive.

Three grams of the total nonvolatile neutral compounds was saponified by the method of Jamieson[20] for 3 hr. Upon cooling fine needle-like crystals were formed in the aqueous ethanol and filtered off. The alkaline solution was extracted three times with 50 ml. of ether, the ether solutions combined, dried over magnesium sulfate and the ether evaporated to yield 2.7 g. of unsaponifiable material.

The crystals previously filtered off were recrystallized from 95% ethanol to fluffy white needles which did not melt at temperatures up to 250°, but gave a positive flame test for potassium.[19] It was acidified with 10% hydrochloric acid and extracted with ether. The ether extract on evaporation and recrystallization from water yielded an acid of m.p. 208–210° and neut. equiv. 81.5. The acid on reaction with excess thionyl chloride and ice cold excess concentrated ammonium hydroxide failed to form the amide.[21] A light tan nitrogen-free solid was formed, melting at 130–131° and corresponding to phthalic anhydride m.p. 131°.

A solid *p*-bromophenacyl ester was obtained from the acid which had a constant melting point of 153–154°. The ultraviolet absorption spectra of phthalic acid and the acid isolated from saponification were essentially identical and a mixed melting point was undepressed.

The unsaponifiable fraction, a viscous brown oil, gave a positive Lieberman-Burchard sterol test. Accordingly, it was treated with digitonin, a specific precipitant for sterols, as described by Hibbert and Phillips.[9] The digitonide was decomposed by heating with excess pyridine, the pyridine was stripped off under vacuum and the residue was extracted with ether, leaving behind the insoluble digitonin.[9] On evaporation of the ether, the crude sterol was obtained melting over the range 112–125°.

The acetate of the sterol was formed in very poor yield by heating the dry digitonide in 5 ml. of acetic anhydride until complete dissolution, cooling and adding 30 ml. of 60% aqueous ethanol to the cold solution. The acetate thus precipitated had a constant melting point of 118–119° after repeated recrystallizations from 95% ethanol. The benzoate, after repeated recrystallizations from 95% ethanol, had constant m.p. 139–140°. The sterol itself was recrystallized from methanol to constant m.p. 134–135°. The corresponding melting points for β-sitosterol are 118–119° for the acetate, 141–142° for the benzoate, and 135.5–136° for the free sterol.[22] The ultraviolet absorption spectrum of the sterol in 97% H_2SO_4[23] corresponded closely to that of β-sitosterol reported by Bernstein and Lenhard.[23]

When 0.9 g. of the total nonvolatile neutral material was treated with digitonin before saponification, approximately 0.7 g. of β-sitosterol was isolated and identified as before. This corresponds to about 5% of the total extractives as free sterol.

The remaining nonvolatile neutral compounds were obtained by distilling off under vacuum the alcohol from the solution from which the digitonide had been precipitated. A 2-g. sample of this material was dissolved in approximately 20 ml. of petroleum ether and chromatographed on a 3.5 × 40 cm. column packed with alumina. On development with benzene a sharp yellow-brown band appeared and was eluted. The benzene was evaporated from this eluate fraction to yield 1.9 g. or 95% of a yellow semisolid material. This material had saponification equivalents ranging from 269 to 272, indicating a molecular weight of 540 or greater, depending on the purity of the chromatographic fraction which could not be recrystallized.

An ultraviolet absorption spectrum was taken of the purified phthalate ester. The extinction coefficient for the ester at the wave length 282 mμ was that to be expected of a phthalate ester of about 650 molecular weight approximately corresponding to one sterol unit per phthalic acid residue. However, when the sample was titrated it was shown to have no detectable acidity and therefore was not a half ester of phthalic acid.

When the pure ester was saponified with alcoholic potassium hydroxide followed by ether extraction of the alkaline solution, a solid alcohol was recovered. From one gram of ester approximately 0.6 g. of a yellow-white solid alcohol was obtained with a m.p. range 110–120°. It gave a positive Lieberman-Burchard color test[19] and showed the same absorption spectrum, in 97% sulfuric acid, as the β-sitosterol obtained as the free sterol, and from saponification of the total nonvolatiles.

When the alkaline solution from the saponification of 1 g. of ester was distilled, a water-white, water-immiscible liquid was obtained, approximately 0.1 g. It boiled between 180 and 185° and had a density, at 25° of 0.820. The refractive

(18) F. A. Vandenheuvel, *Anal. Chem.*, 24, 847 (1952).

(19) O. Gisvold and C. H. Rogers, *The Chemistry of Plant Constituents*, p. 139 Burgess Publ. Co., Minneapolis, 1943.

(20) G. S. Jamieson, *Vegetable Fats and Oils*, 2nd Ed., p. 390 Reinhold Publ. Corp., New York, 1943.

(21) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 2nd Ed., John Wiley, New York, 1940.

(22) L. E. Wise and S. T. Moore, *J. Org. Chem.*, 10, 516 (1945).

(23) S. Bernstein and R. H. Lenhard, *J. Org. Chem.*, 18, 1146 (1953).

index, n_D^{25}, was 1.4244. When frozen in Dry Ice–acetone, the melting point was approximately −30°. The optical rotation of this alcohol, $[\alpha]_D^{25}$, was −6.0°, c = 4.56 in alcohol. Attempted preparations of the 3,5-dinitrobenzoate and phenylurethane of the alcohol led only to uncrystallizable oils. The hydrogen phthalate[24] melted at 74–75°. l-2-Octyl hydrogen phthalate melts at 75°.[21]

(24) J. F. Goggans, Jr. and J. E. Copenhaver, *J. Am. Chem. Soc.*, 61, 2909 (1939).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, MCGILL UNIVERSITY]

Ring D Steroid Oximes and the Beckmann Rearrangement

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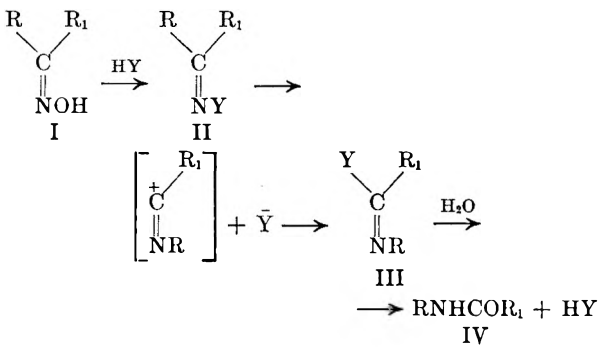
Whereas simple ring D and ring A steroid oximes yield the corresponding oxime acetates on subjection to mild acetylating conditions, 3β-hydroxyandrostan-16,17-dione 16-oxime gives a pure crystalline compound which was characterized by its chemical properties and behavior as an intermediate in a Beckmann Rearrangement. Rearrangement could be completed under appropriate, though equally mild, conditions. Reasons for the unexpected rearrangement under such mild conditions are advanced.

The mechanism of the Beckmann Rearrangement still stimulates considerable experimental investigation despite the ninety years that have elapsed since the original discovery of the reaction. Mesenheimer, Kuhara, and Chapman have laid the foundations of our knowledge and outlined the generalizations for understanding this reaction.[3] As stated by various authors,[4,5] Beckmann Rearrangement with a variety of acid reagents essentially involves ester formation between an oxime (I) and the reagent HY. By means of ionization a process of *trans* interchange then takes place yielding an imidoyl ester (III) from the oxime ester (II). The amide (IV), the end-product of the reaction, arises from (III) by ill-defined steps, one of which undoubtedly is hydrolytic, and the acid reagent is regenerated.



A recent paper by Stephen and Staskun[6] departs from the classical formulations of this reaction and proposes a new mechanism for amide formation under entirely anhydrous conditions. Our contribution in this field arose during the course of investigations on the structure of Heard's lactone.[7] These investigations involved an attempt to prepare 3β-acetoxy-16-acetoximinoandrostan-17-one (VI) from 3β-hydroxyandrostan-16,17-dione 16-oxime (V) by allowing the latter to stand overnight in a mixture of acetic anhydride and pyridine at room temperature. We have acetylated the oximes of cholestanone, testosterone, and epiandrosterone under these same conditions. However, while many stable acetates of alpha oximino ketones have been prepared,[8] the product obtained from V was not VI, as expected, but has been formulated as having the structure VII.

After recrystallization from anhydrous ether VII was obtained as colorless feathery needles. While stable in the dark, it gradually turns yellow on exposure to light. It has an absorption peak in the ultraviolet at 223 mμ as compared with the peak at 240 mμ exhibited by V. This hypsochromic shift of 17 mμ could not be explained by mere acetylation of the oxime hydroxyl—as in VI—, especially since we observed that similar acetylation of testosterone oxime causes a bathochromic displacement of the absorption maximum of 5 mμ. (Table I). When dissolved in alcohol the absorption

(1) (a) Deceased September 1957. (b) Abstracted from a thesis submitted by Michael T. Ryan to the School of Graduate Studies, McGill University, in April 1955 in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (c) Present address: Department of Biochemistry, University of Ottawa Medical School, Ottawa, Ont.; to which enquiries concerning this paper should be addressed.

(2) Present address: Du Pont of Canada, Ltd., Montreal.

(3) See, for example, B. Jones, *Chem. Revs.*, **35**, 335 (1944).

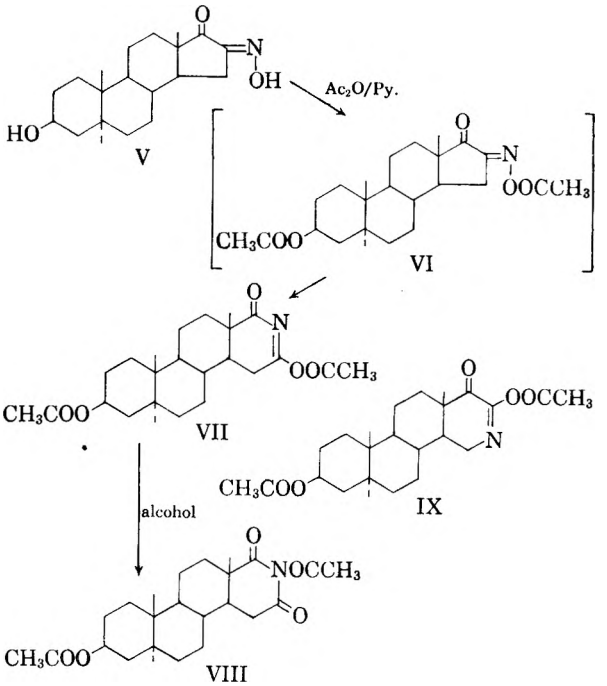
(4) D. E. Pearson and F. Ball, *J. Org. Chem.*, **14**, 118 (1949).

(5) C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, 20, 1482 (1955); also (3) and (4).

(6) H. Stephen and B. Staskun, *J. Chem. Soc.*, 980 (1956).

(7) R. D. H. Heard, *J. Am. Chem. Soc.*, **60**, 493 (1938).

(8) A. H. Blatt, and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934); **57**, 1331 (1935); **58**, 1903 (1936).



band at 223 mμ fades gradually at a rate which, as measured spectrophotometrically, is dependent on the temperature and on the presence and concentration of added hydrochloric acid (Table II and Fig. I).

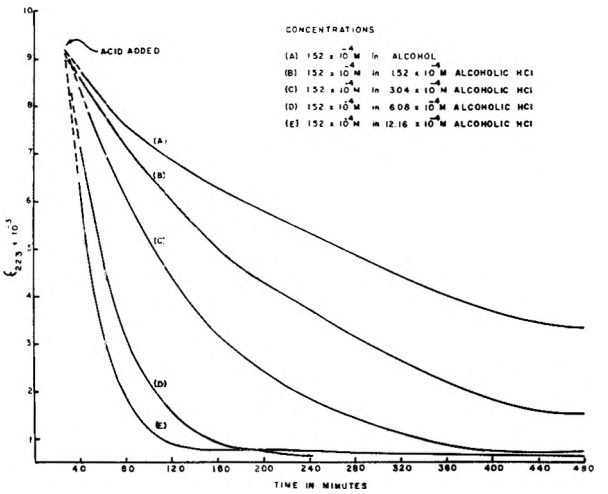
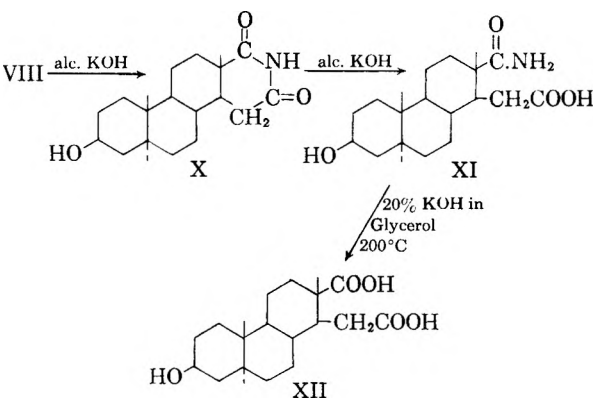


Fig. 1. Rearrangement of VII at room temperature in alcohol and alcoholic hydrochloric acid. The rearrangement was followed at 223 mμ in a Beckmann DU Quartz Spectrophotometer with photomultiplier attachment. Zero Time is the time of addition of the alcohol to VII. Aqueous hydrochloric acid was subsequently added at the time indicated to give the stated concentrations

The structure VII corresponds to that of an intermediate in the Beckmann Rearrangement of the alpha oximino ketone (V)—or, more exactly, of its diacetate (VI)—and presupposes that the starting oxime consists of a single geometric isomer. The alternate isomeric orientation of the oxime hydroxyl should yield a compound of structure IX which does not correspond to the chemical behavior of the material isolated. That such ring D oximes consist of single isomers is indicated by the work of Regan and Hayes[9] on the behavior of estrone oxime 3-methyl ether and 3β-acetoxy-5-androsten-16,17-dione 16-oxime in a formal Beckmann Rearrangement. This preferred orientation of the oxime hydroxyl is to be expected in this region of the molecule and is further indicated in a comparison of the melting points of the acetates of ring D and ring A oximes (Table I). In the case of testosterone and cholestanone oximes acetylation yields a mixture of the oxime acetate isomers, as indicated by the wide range of melting points of the products. The 3β - acetoxy - 17 - acetoximino - androstane, on the other hand, has a very sharp melting point and must consist of a single isomer.

The proof of the structure of VII rests on its easy rearrangement in alcohol, especially under the influence of heat and acid conditions, as compared to its stability in anhydrous ether from which it could be crystallized. The oily neutral product, formulated as VIII, obtained by refluxing VII in alcohol, could be converted by stepwise alkaline hydrolysis into 3β-hydroxy-16,17-*seco*-androstan-16,17-imide (X), 3β-hydroxy-16,17-*seco*-androstan-16,17-dioic acid 17-amide (XI), and the known 3β-hydroxy - 16,17 - *seco* - androstan - 16,17 - dioic acid (XII). The tertiary nature of the semi-amide XI is borne out by its resistance to alkaline hydrolysis, which could only be effected by heating to 200° in a solution of 20% potassium hydroxide in glycerol, as well as its failure to react with cold nitrous acid. This inertness is well known to be characteristic of C_{17} carboxyl derivatives.[9]



Much controversy has existed as to the actual occurrence of the imidoyl ester type of structure, such as VII, during the course of Beckmann Rearrangement. Such a formulation was given by Kuhara[10] in the rearrangement of *O*-benzenesulfonylbenzophenone oxime but was later disputed by Chapman.[11] Over the years, however, indirect

(9) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, **78**, 639 (1956).

(10) M. Kuhara, K. Matsumiya, and N. Matsunami, *Mem. Coll. Sci. Kyoto*, **1**, 25 (1914).

(11) A. W. Chapman and C. C. Howis, *J. Chem. Soc.*, 808 (1933).

TABLE I[a]

SOME STEROID OXIMES AND THEIR ACETATES

Oxime	Acetate
17-Oximino-3β-acetoxy-androstane	17-Acetoximino-3β-acetoxy-androstane
M.p. 184–186°	M.p. 180–180.5°
Calcd. for $C_{21}H_{33}O_3N$: C, 72.59; H, 9.51; N, 4.03.	Calcd. for $C_{23}H_{35}O_4N$: C, 70.95; H, 8.99; N, 3.59.
Found: C, 72.66, 72.50; H, 9.78, 9.83; N, 4.16	Found: C, 70.93, 71.04; H, 9.31, 9.11; N, 3.71
Cholestanone oxime	3-Acetoximino cholestane
M.p. 200–201° (Kofler)	M.p. 124–138° (Kofler)
Reported[18] m.p. 196°	Calcd. for $C_{29}H_{49}O_2N$: C, 78.55; H, 11.06; N, 3.13.
	Found: C, 78.41, 78.36; H, 11.08, 11.00; N, 3.21.
Testosterone Oxime	17β-Acetoxy-3-acetoximino-4-androstene
M.p. 222–223° (Kofler)	M.p. 113–131° (Kofler)
Reported[19] m.p. 221–222.5°.	Calcd. for $C_{23}H_{33}O_4N$: C, 71.32; H, 8.52; N, 3.61.
	Found: C, 71.01, 71.21; H, 8.75, 8.80; N, 3.68.
λ_{max}. 241 mμ (ε 19,520)	λ_{max}. 246 mμ (ε 23,976)

[a] Spectra were done in alcohol at a concentration of $2 \times 10^{-5} M$.

evidence has accumulated for the occurrence of such imidoyl esters as intermediates[12] and Coleman and Pyle[13] have isolated in imidoyl chloride in the rearrangement of benzophenone oxime by phosphorus pentachloride. The isolation of a pure crystalline imidoyl acetate in these studies, together with the associated shift in the absorption maximum, is further unequivocal evidence as to the structural changes taking place during the course of the Beckmann Rearrangement. In addition, the properties of the final product of the overall rearrangement—the oil obtained by refluxing VII in 95% alcohol—suggest that it is the *N*-acetyl imide rather than the free imide (X). In fact the free imide is only produced after prolonged hydrolysis of the oil.

The occurrence here of the Beckmann Rearrangement under conditions so mild that they should properly yield only the oxime acetate (VI) is attributed, partly at least, to the strained nature of ring D of the steroid nucleus and to the steric hindrance prevailing in this region of the molecule. In this context it is known, for example, that hindered ketones often yield rearranged products on attempted oximation.[14] It should be emphasized, however, that the acetate of a simple ring D oxime (epiandrosterone oxime) was isolated under those same conditions which led to rearrangement in the case of the ring D alpha oximino ketone (V). It is presumed that rearrangement under such mild conditions is an inherent property of the alpha oximino ketone grouping when present in a strained ring system Further work would be necessary to establish this.

(12) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1514 (1948); B. B. Lampert and F. G. Bordwell, *J. Am. Chem. Soc.*, **73**, 2369 (1951); C. W. Kenner, A. R. Todd, and R. F. Webb, *J. Chem. Soc.*, 1231 (1956).

(13) G. H. Coleman and R. E. Pyle, *J. Am. Chem. Soc.*, **68**, 2007 (1946).

(14) F. Greer and Pearson, D. E. *J. Am. Chem. Soc.*, **77**, 6649 (1955).

EXPERIMENTAL[15]

3β-Hydroxyandrostan-16,17-dione 16-oxime (V) was prepared in a manner similar to that of Huffman.[16] It was purified, however, by dissolving 2.95 g. of crude product in a mixture of 40 ml. methanol and 10 ml. water and refluxing in the presence of charcoal. After removal of the charcoal the hot filtrate was concentrated by evaporation and then allowed to crystallize. This furnished pure material in 70% over-all yield. M.p. 220° (Kofler). Reported[16] m.p. 218–219.5°. Ultraviolet spectrum in ethanol; λ_{max}. 240 mμ (ε 9570).

Acetylation of (V) One hundred milligrams of V was dissolved in a mixture of 1 ml. of pyridine (freshly distilled from barium oxide) and 1 ml. of acetic anhydride (twice distilled from fused sodium acetate; b.p. 137–138°) and allowed to stand overnight. The solution was then poured with stirring into 50 ml. of 3*N* hydrochloric acid. After filtration the white precipitate was washed with dilute hydrochloric acid and water. It was then dried on suction and in a vacuum desiccator over calcium chloride. This yielded 102 mg. of colorless powdery material, m.p. 161.5–163°. Recrystallization from hot anhydrous ether (Merck) gave 82 mg. of VII as long feathery crystals, m.p. 163–165°. Ultraviolet spectrum in ethanol; λ_{max}. 223 mμ (ε 9431).

Anal.[17] Calcd. for $C_{23}H_{33}O_5N$: C, 68.48; H, 8.18; N, 3.47. Found: C, 68.49, 68.39; H, 8.38, 8.23; N, 3.38.

Crystallization from Merck Reagent ether yielded material in much lower yield, m.p. 154–164°. The compound (VII) is quite stable in the dark (unchanged after 1.5 years) but turns yellow within one week when exposed to light. It is particularly unstable in solution in alcohol where the absorption peak at 223 mμ gradually disappears—especially in the presence of acid or on heating (Fig. 1 and Table II).

Preparation and acetylation of other oximes. Oximes were prepared in the usual manner by refluxing in alcohol for 2 hr. in the presence of excess hydroxylamine hydrochloride and sodium acetate. Acetylating conditions identical to those used in the preparation of VII were employed and the

(15) Unless otherwise stated all melting points were carried out on the Fisher-Johns apparatus and are uncorrected.

(16) M. N. Huffman and M. H. Lott, *J. Biol Chem.*, **207**, 431 (1954).

(17) Microanalyses were performed by E. Thommen, Thannerstrasse 45, Basel, Switzerland.

(18) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264, (1935).

(19) D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.*, 67 (1952).

authenticity of the acetates was established by alkaline hydrolysis to the starting oximes.

Conversion of VII to VIII. Five hundred milligrams of VII was dissolved in 50 ml. of 95% alcohol and refluxed. Samples were taken at one-hour intervals and after appropriate dilution measured in the spectrophotometer at 223 mμ. As can be seen from Table II the absorption peak disappears within 3 hr. After 6 hr. the solvent was evaporated yielding a pale yellow oil which could not be crystallized. The oil was insoluble in aqueous sodium carbonate and could not be extracted out of an ether solution with alkali.

TABLE II

REARRANGEMENT OF VII IN BOILING ALCOHOL

Time, hours	ϵ_{223}
0	9,400
1	1,410
3	427
4	427

Alkaline hydrolysis of VIII. To 500 mg. of the oil dissolved in 50 ml. of 95% alcohol 2.5 g. of potassium hydroxide was added and the solution refluxed for 20 hr. On cooling, the solution was evaporated *in vacuo* and the residue dissolved in 50 ml. of water. Ether extraction removed 60 mg. of yellow oil. Addition of concentrated hydrochloric acid to the clear aqueous phase precipitated a mixture of X and XI.

Isolation of 3β-hydroxy-16,17-seco-16,17-dioic acid 17-amide (XI). To the acidified aqueous suspension 60 ml. of chloroform was added and the whole shaken in a separatory funnel during which X passed into the chloroform phase. After separation, the aqueous suspension was filtered and the precipitate washed thoroughly with water and dried. This yielded 220 mg. of material, m.p. 214–218°. After 6 recrystallizations from methanol followed by drying *in vacuo* over phosphorous pentoxide at 120° needle crystals melting at 218.5–220.5° were obtained. The compound was completely insoluble in chloroform, benzene, ether, and ethyl acetate but was soluble in dilute aqueous sodium carbonate. Titration indicated that it was a monobasic acid. When dissolved in cold acetic acid and treated with a cold solution of sodium nitrite, no evolution of nitrogen was evident which confirmed the tertiary nature of the amide grouping.

Anal. Calcd. for $C_{19}H_{31}O_4N$: C, 67.65; H, 9.46; N, 4.16. Found: C, 67.67, 67.61; H, 9.36, 9.40; N, 4.25.

Isolation of 3β-hydroxy-16,17-seco-androstan-16,17-imide (X). The chloroform solution obtained in the isolation of XI was washed free of acid and dried over sodium sulfate. Evaporation of the chloroform solution *in vacuo* yielded 136 mg. of a yellowish flaky solid which melted at 100–110°. This was dissolved in 4 ml. methanol and a few drops of water added which removed the yellow impurity. The solution was then centrifuged and the supernatant removed. The concentration of the methanol solution was then adjusted by boiling and adding water so that on cooling the material crystallized out as fine colorless needles. After drying *in vacuo* at 120° over phosphorus pentoxide for 1.5 hr. 113 mg. of X melting at 180–182.5° was obtained. It was readily soluble in dilute aqueous sodium carbonate. On refluxing a sample in 10% aqueous potassium hydroxide for 24 hr. it was converted into XI.

Anal. Calcd. for $C_{19}H_{29}O_3N$: C, 71.48; H, 9.09; N, 4.38. Found: C, 71.55, 71.92; H, 8.97, 9.16; N, 4.72.

Conversion of XI to 3β-hydroxy-16,17-seco-androstan-16,17-dioic acid (VII). Forty milligrams of the pure semi-amide (XI) was added to 5 ml. of a solution of 20% potassium hydroxide in glycerol. The flask was placed in an oil bath and the temperature gradually raised to 200° whereupon a copious evolution of bubbles of a basic gas took place. After 2.5 hours heating was stopped. The material came out of solution on cooling but on dilution with water a clear, slightly yellow, solution was obtained. This was acidified and after standing for 2 hr. it was filtered and washed well with water. It was dried on suction and finally *in vacuo* over phosphorus pentoxide at 120°. This yielded 20 mg. of material which melted at 234–237° with previous softening at 225°. After one recrystallization from methanol the melting point was 237.5–238.5°. It titrated as a dibasic acid and sodium fusion indicated the absence of nitrogen. On admixture with an authentic sample of XII there was no depression in the melting point.

OTTAWA, CANADA

[CONTRIBUTION FROM U. S. DEPARTMENT OF AGRICULTURE]

Separation of Aliphatic Disulfides and Trisulfides by Gas-Liquid Partition Chromatography

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The polar stationary phases, Carbowax and Reoplex, and a nonpolar phase, Apiezon M, have been compared in the separation of aliphatic disulfides and trisulfides by gas-liquid partition chromatography. Mixtures of disulfides and trisulfides can be separated at 150° without decomposition. The polar phases are particularly useful for separating unsaturated disulfides from the corresponding saturated compounds.

This paper reports the application of gas-liquid partition chromatography to the separation and isolation of some simple aliphatic disulfides and trisulfides in connection with a study of the volatile components of onions.[1] A number of investigators have studied the separation of thiols and sulfides. Sunner, Karrman, and Sunden[2] reported quantitative separation of a number of thiols by gas-liquid partition chromatography, and Ryce and Bryce[3]

(1) Presented at the Joint Symposium of Analytical and Petroleum Chemistry, American Chemical Society meeting, New York, September 1957.

(2) S. Sunner, K. J. Karrman, and V. Sunden, *Mikrochim. Acta*, 1144 (1956).

(3) S. A. Ryce and W. A. Bryce, *Anal. Chem.*, 29, 925 (1957).

separated mixtures of low-boiling mercaptans and sulfides and one disulfide, dimethyl disulfide. Amberg[4] has reported relative retention times for 8 thiols, 5 sulfides, and 11 thiophenes, and recently Coleman,[5] Thompson, Ward, and Rall have separated and identified a number of low-boiling mercaptans and sulfides in crude oil by gas-liquid partition chromatography. However, little has been reported on the separation of disulfides and trisulfides.

The separation of disulfides and trisulfides by distillation, especially in the presence of mercaptans, is difficult. Ionic displacement by mercaptide ion may produce new disulfides and mercaptans as artifacts as in

$$RS^- + R'SSR' \rightleftharpoons RSSR' + R'S^-$$
$$\Big\| \; RS^-$$
$$RSSR + R'S^-$$

Fava, Iliceto, and Camera[6] have shown the importance of this displacement even under mild conditions. The production of artifacts by free radical decomposition of disulfides and trisulfides is particularly facile as demonstrated by Birch.[7] A third type of decomposition applicable to allylic disulfides is thermal decomposition in the presence of metals as zinc to yield the allylic monosulfides, metallic sulfide, and polymeric material.[8] Conditions have been found for the separation of a number of disulfides and trisulfides by gas-liquid partition chromatography without appreciable decomposition. In particular, unsaturated disulfides may be separated from the corresponding saturated compounds.

In this study, the aim has been to separate these compounds in quantities sufficient for identification by infrared methods. In some cases, by chromatographing several times, sufficient material could be isolated for identification by the formation of crystalline derivatives.[9]

EXPERIMENTAL

Apparatus. The gas-liquid partition chromatography apparatus was of the coiled tube type patterned after Dimick and Corse.[10] The columns were of stainless steel, 1/4 in. O.D. and 5 to 7 ft. in length coiled to fit into a 1 gal. stainless-steel Dewar vessel containing heating liquid, mechanical stirrer, and thermometer. The katharometer was a stainless-steel block, immersed in the heating bath, with two Gow-Mac filaments[11] operated at 175 ma. Electrical imbalance was measured on a recording potentiometer with a 2- or 4-mv. full scale deflection. The bath temperature was generally maintained with a maximum variation of ±0.5°. Helium temperature at the inlet injection chamber was maintained at approximately 20° higher than the column operating temperature. Samples were injected as liquid with a microsyringe. The stationary phases consisted of firebrick (C-22, Johns Manville) ground to 40–60 mesh, acid washed, and then heated to 400° and impregnated with the appropriate organic phase (dissolved in acetone or hexane) in the ratios of firebrick to liquid phase of 4:1 (by weight).

For larger scale separations a helical stainless-steel column, 1/2 in. O.D. and 5.5 ft. in length was used. The stationary phase consisted of 1 part of organic liquid to 2 parts of firebrick. This column could handle approximately 6 times the quantities used with the smaller columns. Although resolution was not so good as with the corresponding 1/4 in. column, partial purification could be obtained, and the fractions were then later purified on the smaller columns.

Preparation of compounds. All of the disulfides with the exception of methyl-*n*-propyl disulfide, di-*iso*propyl and *n*-propyl-*iso*propyl disulfides and allyl-*n*-propyl and diallyl disulfides were Eastman Chemicals. The trisulfides were synthesized as described.

Allyl propyl disulfide. The preparation of the compound is described in detail, since it has not been heretofore described in the literature. Allyl mercaptan was prepared by alkaline hydrolysis of allyl isothiourea hydrobromide and the oily product resulting on acidification was used immediately without purification. A mixture of crude allyl mercaptan, 16 g., 0.22 mole, and *n*-propyl mercaptan, 12 g., 0.16 mole, was dissolved in a cold solution of 20 g. of sodium hydroxide in 200 cc. of water. A solution of 122 g., 0.37 equiv., of potassium ferricyanide in 400 cc. of water was added in 10-cc. portions over a 2-hr. period with mechanical stirring and cooling in an ice bath, and stirring was continued for 2 hr. longer. The resulting yellow milky emulsion was extracted with ether, the ether extract was dried with calcium chloride, and after removal of ether *in vacuo*, the resulting liquid was distilled at 5 mm. Hg from a water bath at 62°–70° to yield 19.8 g. (*ca.* 70%) of pale yellow distillate. The disulfide mixture was separated into dipropyl, allyl propyl, and diallyl disulfides by passage through a gas-liquid partition column of coiled stainless steel, 1/2 in. O.D. and 5.5 ft. in length, packed with a stationary phase consisting of 1 part of Carbowax 1540 on 2 parts of 40–60 mesh firebrick. Quantities of 160–180 μl. of crude disulfide mixture were injected with a helium flow rate of 180 cc./min. and a column temperature of 140°. The collected fractions were further purified by chromatography on a 1/4 in. O.D. column with the same packing. Measurement of peak areas indicated the composition of the disulfide mixture to be approximately diallyl, 32%, allyl propyl disulfide, 41%, and dipropyl disulfide, 23%, with approximately 4% of low-boiling material (partly diallyl sulfide). For the preparation of allylic disulfides, the ferricyanide oxidation procedure was found to be superior to the usual iodine oxidation which often led to excessive tar formation.

Methyl-n-propyl disulfide was prepared by alkaline ferricyanide oxidation of a mixture of 0.375 mole of methyl mercaptan and 0.21 mole of *n*-propyl mercaptan. The disulfide was isolated from the crude distillate by gas-liquid partition chromatography under conditions similar to those used with the mixed allyl propyl disulfides. Peak areas indicated the composition of the distilled disulfide mixture to be dimethyl, 9.2%; methylpropyldisulfide, 38.5%, and dipropyldisulfide, 52.3%.

(4) C. H. Amberg, *Can. J. Chem.*, **36**, 590 (1958).

(5) H. J. Coleman, C. J. Thompson, C. C. Ward, and H. J. Rall, *Anal. Chem.* **30**, 1592 (1958).

(6) A. Fava, A. Iliceto, and E. Camera, *J. Am. Chem. Soc.*, **79**, 833 (1957).

(7) S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petroleum*, **39**, 206 (1953).

(8) F. Challenger and D. Greenwood, *J. Chem. Soc.*, 26 (1950).

(9) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **22**, 1725 (1957).

(10) K. P. Dimick and J. Corse, *Food Technol.*, **10**, 360 (1956).

(11) Gow-Mac Co., 100 Kings Road, Madison, N. J. Mention of commercial names does not imply endorsement by the Department of Agriculture.

Di-isopropyl disulfide and isopropyl-n-propyl disulfide were similarly prepared from an equimolar mixture of isopropyl and *n*-propyl mercaptans. Yields of the three disulfides were di-isopropyl disulfide, 18.3%; isopropyl-*n*-propyl disulfide, 45.8% and di-*n*-propyl disulfide, 35.8%.

Methyl-n-propyl trisulfide and di-n-propyl trisulfide. These compounds were prepared by an adaptation of the procedure of Westlake, Laquer, and Smyth.[12] A mixture of dimethyl disulfide, 12 g. (0.13 mole), di-*n*-propyl disulfide, 10 g. (0.067 mole), sulfur, 7 g. (0.22 g. atom), and 0.5 ml. of di-*n*-butylamine were heated in an oil bath at 130–135° for 5 hr. An ethereal solution of the brown reaction solution was washed with dilute hydrochloric acid and water, dried over calcium sulfate and concentrated *in vacuo* to yield 25 cc. of a brown oil. Distillation *in vacuo* (1 mm.) (bath temp. 50–125°) yielded 20 ml. of yellow liquid distillate. Gas-liquid chromatography on a 1/2 in. O.D. column of Carbowax 1540 at 140° and 180 cc./min. of helium yielded 5 separate peaks corresponding to dimethyl disulfide, methyl-*n*-propyl disulfide, dimethyl trisulfide and di-*n*-propyl disulfide (not separated), methyl-*n*-propyl trisulfide, and di-*n*-propyl trisulfide. The unresolved peak containing dimethyl trisulfide and dipropyl disulfide was separated into the two components with an Apiezon column. Methyl-*n*-propyl trisulfide and di-*n*-propyl trisulfide were collected and purified by rechromatography on a 1/4-in. Carbowax column.

Dimethyl trisulfide was isolated as a by-product from the previous preparation and was also prepared by the procedure of Gorin and Dougherty.[13]

Diethyl trisulfide was prepared from diethyl disulfide, sulfur, and di-*n*-butylamine by the procedure of Westlake, Laquer, and Smyth.[12]

DISCUSSION

Mixtures of aliphatic disulfides and trisulfides up to and including di-*n*-butyl disulfide and di-*n*-propyl trisulfide can be separated by gas-liquid partition chromatography at 150° without serious decomposition. No exchange reactions occurred between mercaptans, disulfides, and trisulfides as demonstrated by the fact that mixtures of unsymmetrical disulfides and trisulfides in the presence of mercaptans could be chromatographed without the formation of any symmetrical disulfides or trisulfides and, similarly, chromatography of mixtures of the symmetrical compounds yields no corresponding unsymmetrical disulfide or trisulfide. Allylic disulfides could be separated without the formation of monosulfides. Absence of decomposition during chromatographic separation was confirmed by infrared analysis of collected fractions. Decomposition was observed, however, with one stationary phase, U.S.P. solid white petrolatum. Diallyldisulfide decomposed when injected into a petrolatum-firebrick column at temperatures of 130–150° as evidenced by a peak for diallyl sulfide and a long plateau between this peak and the disulfide peak. Collected fractions were yellow although the original disulfide was colorless. This behavior has not been observed with any of the other stationary phases tested.

TABLE I

RETENTION TIMES OF DISULFIDES AND TRISULFIDES

Compound	Retention Times (Corr. for Dead Space)[a] Carbowax 1540,[b] 1/4" O.D., 6' × 5" length	Reoplex 400,[c] 1/4" O.D., 5' × 10" length	Apiezon M,[d] 1/4" O.D., 5' × 10" length
$(CH_3)_2S_2$	3.85 min.	3.20 min.	2.90 min.
$(C_2H_5)_2S_2$	7.30	5.90	8.00
CH_3S_2-*n*-C_3H_7	7.65	6.40	8.30
(*i*-$C_3H_7)_2S_2$	8.50	6.95	14.2
(*n*-C_3H_7)S_2-*i*-C_3H_7	11.2	9.05	18.6
(*t*-$C_4H_9)_2S_2$	11.8	9.30	23.6
(*n*-$C_3H_7)_2S_2$	14.3	11.8	22.3
CH_2=CH—$CH_2S_2CH_2CH_2CH_3$	17.7	14.9	20.3
$(CH_2$=CH—$CH_2)_2S_2$	21.7	18.3	18.4
(*i*-$C_4H_9)_2S_2$	18.1	15.1	38.0
(*n*-$C_4H_9)_2S_2$	31.8	25.6	65.4
(*i*-$C_5H_{11})_2S_2$	44.3	36.6	>110
$(CH_3)_2S_3$	15.9	12.8	12.3
$(C_2H_5)_2S_3$	25.1	20.8	30.4
CH_3S_3-*n*-C_3H_7	28.0	23.3	32.9
(*n*-$C_3H_7)_2S_3$	48.8	41.6	82.4
Air	0.75	0.70	0.60
Column efficiency[e] for (*n*-$C_3H_7)_2S_2$	806	905	680

[a] Retention times in minutes = time from air peak to peak maximum, column temp. = 150 ± 0.5°, helium flow rate 45 cc./min., recorder sensitivity 2 mv. or 4 mv. full scale, filament current = 175 ma. [b] One part of Carbowax 1540 to 4 parts firebrick (by weight), weight of stationary phase 28.0 g. [c] One part Reoplex 400 to 4 parts firebrick, weight of stationary phase = 22.2 g. [d] One part Apiezon M to 4 parts firebrick, weight of stationary phase = 21 g. [e] Given in number of theoretical plates for 3 μl. sample calculated by the formula:

$$n = \frac{16\,D^2}{W^2}$$ where D = distance from air peak to peak maximum and W = width of peak at the base measured between tangents to the peak inflection points [H. W. Johnson and F. H. Stross; *Anal. Chem.*, **30**, 1586 (1958)].

Table I lists retention times for a number of disulfides and trisulfides at 150° for three different substrates, two highly polar phases, Carbowax 1540[14] and Reoplex 400[15] and one extreme nonpolar phase Apiezon M.[16] Peaks were sufficiently sharp that a difference of 5–10% in retention times of two components gave two observable peaks for a mixture of the two components in equal proportions but without complete separation.[17] Thus, mixtures of diethyl disulfide and

(12) H. E. Westlake, Jr., H. L. Laquer, and C. P. Smyth, *J. Am. Chem. Soc.* **72**, 436 (1950).

(13) G. Gorin and G. Dougherty, *J. Org. Chem.*, **21**, 241 (1956).

(14) Union Carbide Chemicals Co., 30 East 42nd St., New York 17, N. Y.

(15) Geigy Pharmaceutical Division, Geigy Chemical Corp., Ardsley, N. Y.

(16) Metropolitan-Vickers Electrical Co., Ltd., London, England.

(17) Although complete separation cannot be attained in these cases, relative retention times are sufficiently reliable to constitute presumptive evidence for the identity of the compounds, particularly if determined with several substrates.

methyl-*n*-propyl disulfide could not be separated on Carbowax or Reoplex columns although two peaks were observable, and similarly mixtures of di-*n*-propyl, allyl propyl, and diallyl disulfide on Apiezon showed three distinct peaks without separation. A difference of 15% or more in retention times between components allowed complete separation (return of recorder pen to base line between peaks). Percentage variation in retention time for a given compound was less than 2% except for the slowest disulfides and trisulfides with retention times greater than 40 min. where reproducibility was within 4%. Table II records retention times relative to cyclohexanone as a standard (retention time/retention time of cyclohexanone) for the disulfides and trisulfides shown in Table I. These ratios are independent of small variations in temperature and flow rate but are quite variable if the column is overloaded. Relative retention times were substantially constant for quantities varying from 0.1 μl. to 3 μl. For quantities greater than 5 μl., the higher disulfides and trisulfides have delayed retention times, due to peak asymmetry, resulting in increased ratios.

TABLE II

RELATIVE RETENTION TIMES OF DISULFIDES AND TRISULFIDES (RELATIVE TO CYCLOHEXANONE)

Compound	Retention Time/Ret. Time of Cyclohexanone (Corr. for Dead Space)		
	Carbowax 1540, 1/4" O.D., 6' × 5" length	Reoplex 400, 1/4" O.D., 5' × 10" length	Apiezon M, 1/4" O.D., 5' × 10" length
Cyclohexanone	1.00	1.00	1.00
$(CH_3)_2S_2$	0.333	0.308	0.349
$(C_2H_5)_2S_2$	0.629	0.567	0.964
CH_3S_2-*n*-C_3H_7	0.660	0.615	1.00
$(i\text{-}C_3H_7)_2S_2$	0.733	0.668	1.71
$i\text{-}C_3H_7S_2\text{-}n\text{-}C_3H_7$	0.961	0.870	2.24
$(t\text{-}C_4H_9)_2S_2$	1.02	0.894	2.84
$(n\text{-}C_3H_7)_2S_2$	1.23	1.13	2.69
$CH_2{=}CH{-}CH_2S_2\text{-}n\text{-}C_3H_7$	1.53	1.43	2.45
$(CH_2{=}CH{-}CH_2)_2S_2$	1.87	1.76	2.22
$(i\text{-}C_4H_9)_2S_2$	1.56	1.45	4.58
$(n\text{-}C_4H_9)_2S_2$	2.74	2.46	7.88
$(i\text{-}C_5H_{11})_2S_2$	3.82	3.52	>13.00
$(CH_3)_2S_3$	1.37	1.23	1.48
$(C_2H_5)_2S_3$	2.16	2.00	3.66
$CH_3S_3\text{-}n\text{-}C_3H_7$	2.42	2.34	3.96
$(n\text{-}C_3H_7)_2S_3$	4.20	4.00	9.93

Disulfide and trisulfide peaks were generally symmetrical for quantities less than 5 μl. Larger quantities, particularly of the 6 carbon (or higher) disulfides or of the trisulfides showed highly skewed peaks with long fronts and sharp tails. This was more pronounced with the polar substrates than with Apiezon. A possible cause of this asymmetry is incomplete volatilization in the injection chamber with large samples, particularly since the temperature of the helium flowing through the injection chamber is lower than the boiling point of many of the compounds. Asymmetry of this type, long front and sharp tail, has been attributed to a type of nonlinear behavior where the partition coefficient (concentration of solute in stationary phase/concentration in gas phase) increases with increasing concentration of solute.[18]

The polar substrates, Carbowax and Reoplex, are particularly useful in that allylic disulfides can be separated from the corresponding saturated compounds. As expected from the known behavior of these materials, with other unsaturated compounds, allyl propyl disulfide and diallyl disulfide are retarded by these substrates and can be separated from each other and from di-*n*-propyl disulfide. Fig. 1 shows a separation of these disulfides with a

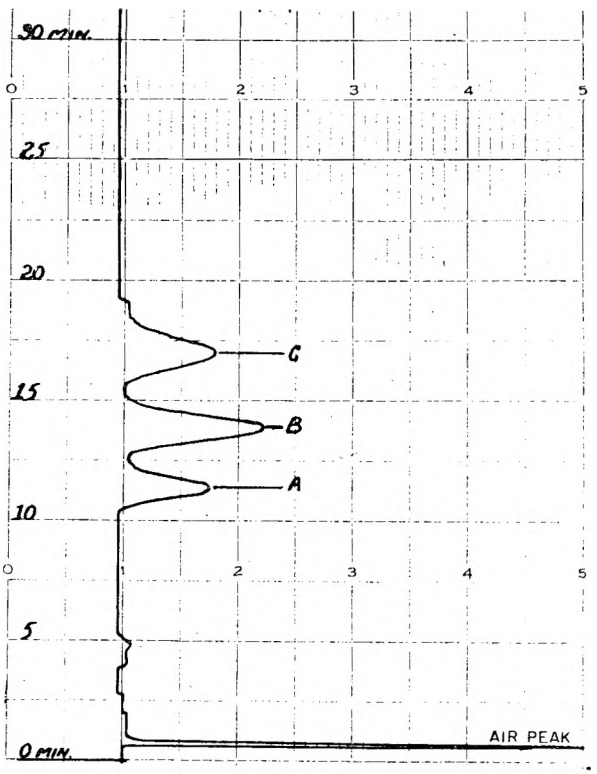

Fig. 1. Separation of mixed allyl and *n*-propyldisulfides. Reoplex 400 column at 150°; 45 ml. He/min.; filament current, 175 ma.; 4-mv. full scale deflection. Sample volume = 3/μl. A = Di-*n*-propyldisulfide; B = allyl-*n*-propyldisulfide; C = diallyldisulfide

1/4-in. Reoplex column. These particular substrates are also faster than the paraffinic types and the higher boiling disulfides and trisulfides can be eluted in a reasonable time. Similar behavior was experienced with other polyglycols. Octyl phenoxypolyethylene glycol (O.P.E. 30)[19] was

(18) P. E. Porter, C. H. Deal, and F. H. Stross, *J. Am Chem. Soc.*, 78, 2999 (1956).

(19) Rohm and Haas Co., Washington Square, Philadelphia 5, Pa.

found to be very close to the polyethylene glycols in separating ability and retention time, but a sample of polypropylene glycol[14] was somewhat inferior in separating unsaturates. A silicone column (General Electric SF96-40) was found to be intermediate in retention time and separating ability between the polyglycol type and the paraffin type.

With Apiezon M, retention times generally followed boiling points, and the order of emergence of the allylic disulfides was reversed from that of the polar phases and separation was not complete. This stationary phase also had the disadvantage that higher disulfides and trisulfides had unusually long retention times. However, certain combinations not completely resolvable with the polar phases can be completely separated with Apiezon. Inspection of Table I or Table II shows that of the 16 disulfides and trisulfides listed, 9 pairs would probably not be completely separated on the polar substrates because the retention times are too close (< 15%). With the exception of the straight chain isomers, methyl-*n*-propyl disulfide and diethyl disulfide and the pair of corresponding trisulfides each of these pairs should be completely separable on Apiezon. This has been confirmed experimentally for several cases. In particular, the pairs dimethyl trisulfide and di-*n*-propyl disulfide, di-*i*-butyl disulfide and allyl-*n*-propyl disulfide, methyl-*n*-propyl trisulfide and di-*n*-butyl disulfide, and di-*i*-propyl disulfide and diethyl disulfide (or methyl-*n*-propyl disulfide) were incompletely resolved on Carbowax but were easily separated with Apiezon. This is merely one more example of the advantage of using two or more different stationary phases and in this case with a wide variation in polar character.

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Synthesis in the 5-Hydroxyindole Series. *N*-Acetyl-5-hydroxytryptophan and Related Compounds

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A number of pharmacologically interesting 5-hydroxyindole derivatives, including *N*-acetyl-5-hydroxytryptophan (X), 5-hydroxyindole-3-acetamide (XVI) and 5-hydroxytryptophol (XIX) were synthesized. An improved process for the large scale preparation of 5-hydroxytryptophan was reported.

The importance of the physiological properties of indole derivatives has been emphasized again by the isolation of the powerful vasoconstrictor principle, serotonin.[2] The confirmation of its structure as 5-hydroxytryptamine[3,4] prompted us to initiate a study of 5-hydroxyindole derivatives. While our work was in progress, a few communications[3-5] on this subject appeared in the literature. This paper deals with the syntheses of *N*-acetyl-5-hydroxytryptophan, 5-hydroxytryptophol and related substances of potential pharmacological importance, and reports on improved methods for the large scale preparation of the important compound, 5-hydroxytryptophan.

The synthesis of 5-hydroxytryptophan by condensation of 5-benzyloxygramine with diethyl formaminomalonate, followed by saponification, decarboxylation, and hydrogenolysis has been reported.[4] Since large quantities of 5-hydroxytryptophan and related compounds were required by us, the commercially available diethyl acetamidomalonate, rather than the formamido analog, was employed for the condensation with the benzyloxygramine[6] (I). The reaction proceeded successfully to give the indole malonicester II in 78% yield. Catalytic debenzylation of II provided the 5-hydroxy-compound III. A combined decarboxylation and deacetylation of the acetaminomalonic acid IV, which was obtained by mild saponification of the corresponding ester II,

(1) Present address: Research Division, Ethicon, Inc., Somerville, N. J.

(2) M. M. Rapport, A. A. Green, and I. H. Page, *Science*, **108**, 329 (1948); *J. Biol. Chem.*, **176**, 1243 (1948); M. M. Rapport, *J. Biol. Chem.*, **180**, 961 (1949).

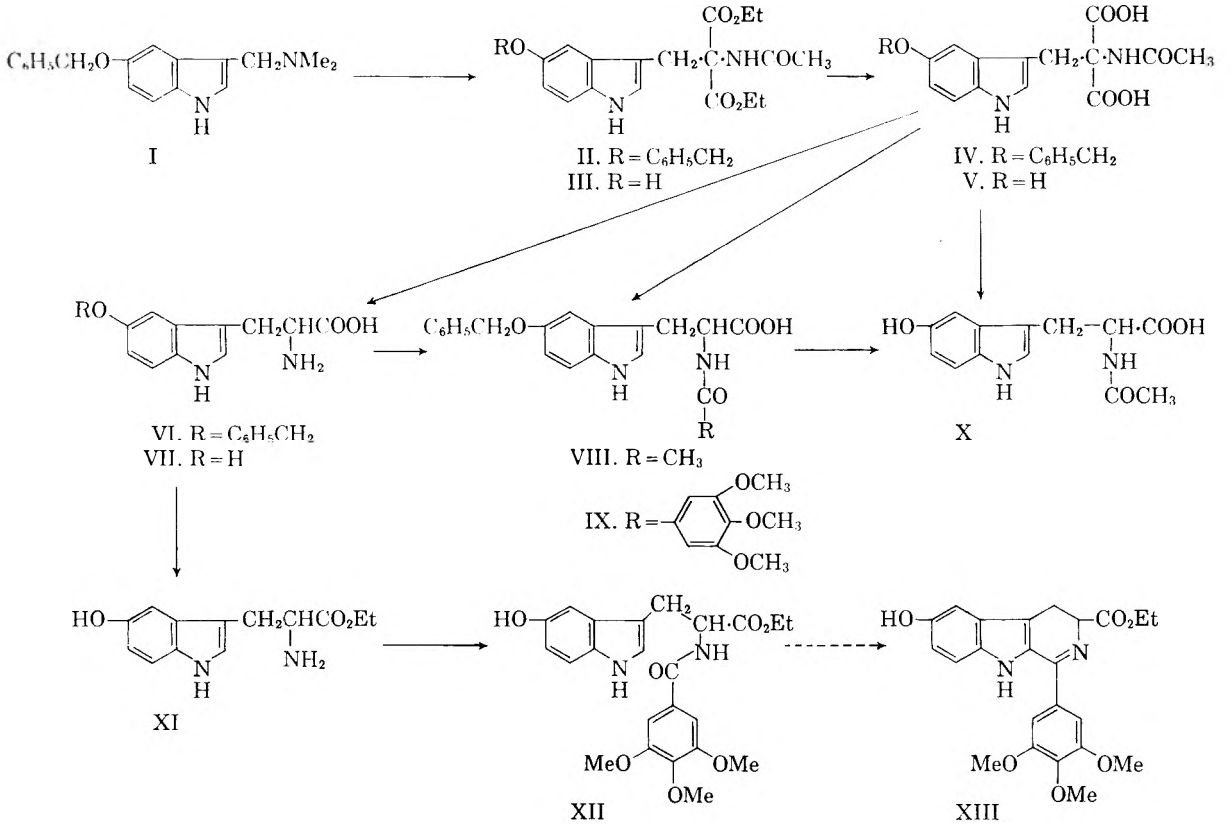
(3) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **73**, 5007 (1951).

(4) M. E. Speeter, R. V. Heinzelmann, and D. I. Weisblat, *J. Am. Chem. Soc.*, **73**, 5514 (1951).

(5) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953).

(6) During our early experiments this compound was prepared by modification of the method of H. Kühn and O. Stein [*Ber.*, **70**, 567 (1937)], and later by the procedure of Ek and Witkop[7] with improved yields. We are indebted to Dr. B. Witkop for making available to us their procedure far in advance of publication.

(7) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).



promptly gave 5-benzyloxytryptophan (VI) in excellent yield.

Acylation of VI with the appropriate acid chlorides, in the usual manner, gave the *N*-acetyl and *N*-3,4,5-trimethoxybenzoyl derivatives VIII and IX as expected. The *N*-acetyl-5-hydroxytryptophan (X) was produced by the catalytic reduction of VIII in ethanol without difficulty. Alternatively, two shorter and more convenient routes, which bypassed VI for the preparation of X, were also found. The first involves decarboxylation of IV in boiling water, without affecting the acetyl group, to yield VIII from which X was obtained as before. The second involves debenzylation of IV to give V, followed by rapid decarboxylation in hot ethyl acetate to provide X in a pure state. It is interesting to note that the carboxyl groups of the indolemalonic acid IV became much more unstable after debenzylation.

The high insolubility of 5-benzyloxytryptophan (VI) in many organic solvents caused its catalytic debenzylation to be difficult and incomplete,[8] especially when reasonably large amounts of material were used. However, after some experimentation, a convenient method was developed whereby relatively large quntities of VI, dissolved in dilute alkaline solution, were hydrogenolyzed rapidly and completely to afford VII in 91% yield. The 5-hydroxytryptophan was then converted to the ethyl ester (XI), which upon treatment with 3,4,5-trimethoxybenzoyl chloride in chloroform using potassium carbonate solution, produced the amide (XII).

Snyder and Werber[9] obtained two harmans in poor yields by the cyclization of *N*-formyl and *N*-acetyltryptophan with polyphosphoric acid and phosphorus oxychloride. However, the condensation of the ester, methyl α-formylamino-β-(3-indole)propionate, was unsuccessful. In the present instance, it seemed desirable to obtain the 3,4-dihydro-β-carboline derivative (XIII) from XII and numerous attempts were made to effect the cyclization with various agents including polyphosphoric acid. However, no pure product could be isolated.

5-Benzyloxyindole-3-acetamide[2] (XIV) and -acetic acid (XV) were simultaneously formed in equally good yields, without difficulty of separation,[10] by refluxing 5-benzyloxygramine (I) with sodium cyanide[11] in aqueous ethanol. Subsequently, they were readily debenzylated to give the corresponding 5-hydroxyindole-3-acetamide (XVI) and -acetic

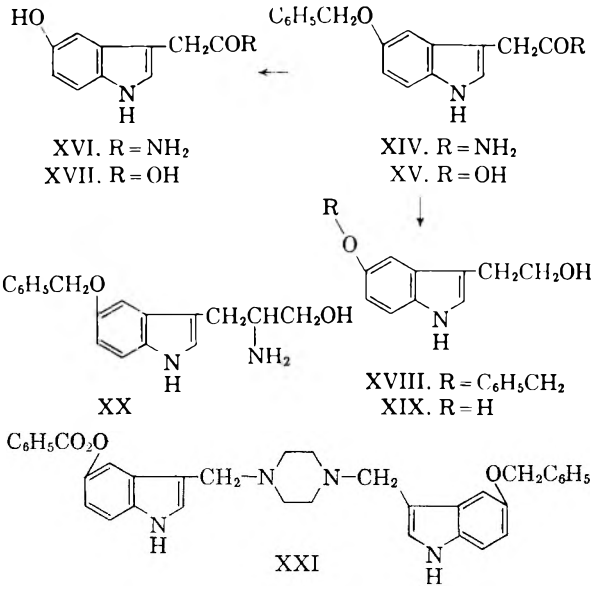
(8) After completion of our work, it was reported that the debenzylation of VI was carried out by suspension in equal parts of ethanol and water.[7] Independently, we tried both water and 95% ethanol as two of several solvents for this purpose. The results, however, were unsatisfactory.

(9) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950).

(10) Some difficulty in isolation of pure sample of XV from XIV was noted.[7] However, this was not observed by us.

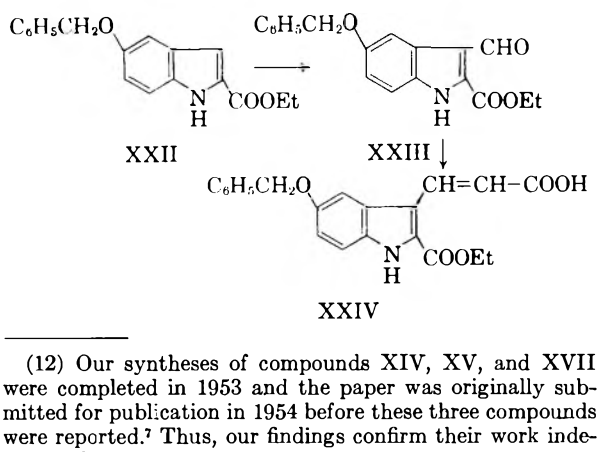
(11) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

acid[12] (XVII), an important metabolic product of serotonin.[13]



On the other hand, lithium aluminum hydride reduction of the indoleacetic acid XV gave the expected alcohol XVIII, which on hydrogenolysis afforded the very unstable compound, 5-hydroxytryptophol (XIX). β-Amino-α-(5-benzyloxy-3-indole) propanol (XX) was prepared by the analogous reduction of 5-benzyloxytryptophan. Condensation of 5-benzyloxygramine with piperazine yielded *N,N'*-bis(5-benzyloxyskatyl)piperazine (XXI).

In another series, ethyl 5-benzyloxyindole-2-carboxylate[14] (XXII) was converted in excellent yield to the 3-formyl derivative (XXIII) by modification of the method for preparation of 2-carbethoxyindole-3-carboxaldehyde.[15] It seems possible to decarbethoxylate[15] XXIII to yield 5-benzyloxyindole-3-carboxaldehyde which would be a useful intermediate for the preparation of many 5-hydroxyindole derivatives. However, this reaction was not attempted. Condensation of XXIII with malonic acid in the presence of a base[16] gave β-(2-carbethoxy-5-benzyloxy-3-indole)acrylic acid (XXIV).



EXPERIMENTAL[17]

5-Benzyloxygramine methiodide. Ten g. of methyl iodide was added to a solution of 3 g. of 5-benzyloxygramine (I) in 75 ml. of ethyl acetate and the mixture allowed to stand at room temperature. After 5 hr. the ethyl acetate was decanted, and the residue was treated with acetone and then filtered. The yield of methiodide was 4 g. (88%), m.p. 173–175° dec.

Anal. Calcd. for $C_{19}H_{23}N_2OI$: N, 6.63. Found: N, 6.48.

Ethyl α-acetamino-α-carbethoxy-β-(5-benzyloxy-3-indole)-propionate (II). Powdered sodium hydroxide (1 g.) was added to a stirred, boiling mixture of 17.5 g. of 5-benzyloxygramine and 13.6 g. of ethyl acetaminomalonate in 80 ml. of dry toluene under nitrogen. The reaction was continued for 11 hr. The mixture was filtered hot through a Büchner funnel and the filtrate was cooled at 5° overnight. The precipitated, light brown crystalline solid, after filtration and washing with petroleum ether, weighed 22 g. (78.5%), and melted at 156–158°. A colorless sample for analysis was obtained by recrystallization of the crude material from aqueous ethanol, m.p. 166–168°.

Anal. Calcd. for $C_{25}H_{28}N_2O_6$: N, 6.19. Found: N, 6.28.

Ethyl α-acetamino-α-carbethoxy-β-(5-hydroxy-3-indole)-propionate (III). A solution of 8 g. of the crude ester (II) in 300 ml. of ethanol was hydrogenated at 40 p.s.i. pressure using 3 g. of 10% palladium-on-carbon as the catalyst. After 2 hr., the mixture was filtered and the filtrate concentrated to 35 ml. The crystalline product, which separated, weighed 6 g. (93%), m.p. 234–235°.

Anal. Calcd. for $C_{18}H_{22}N_2O_6$: N, 7.73. Found: N, 7.65, 7.70.

α-Acetamino-α-carboxy-β-(benzyloxy-3-indole)propionic acid (IV). A mixture of 20 g. of the crude ester (II) in 160 ml. of 10% sodium hydroxide was refluxed gently for 6 hr. The alkaline solution was treated with Norit and filtered. Cracked ice was added to the filtrate which was then acidified with excess hydrochloric acid. The resulting pink product was filtered off and washed twice with a little ice water. After drying, it weighed 15.5 g. (90%), m.p. 157–160°. Further purification was made by recrystallization twice from ethanol at 60° to yield small colorless needles, m.p. 162–163°.

Anal. Calcd. for $C_{21}H_{20}N_2O_6$: N, 7.07. Found: N, 6.98.

5-Benzyloxytryptophan (VI). A suspension of 15 g. of IV of IV in 80 ml. of water was refluxed with stirring for 4.5 hr. Then 40 ml. of 30% sodium hydroxide solution was added to the flask and refluxing was continued for another 24 hr. After treating with Norit, the alkaline solution was acidified with acetic acid. The light pink colored, heavy precipitate was filtered and recrystallized from 30% acetic acid to give 10.5 g. (90%) of almost colorless needles, m.p. 275–276° dec. (reported[5] m.p. 280°).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: N, 9.03. Found: N, 8.92.

N-Acetyl-5-benzyloxytryptophan (VIII). (*a*) *By acetylation of* VI. To a solution of 1 g. of the crude tryptophan (VI) in 15 ml. of 20% sodium hydroxide 3 ml. of acetic anhydride in several portions was added with vigorous shaking and occasional cooling. Acidification of the alkaline solution with acetic acid yielded a solid, weighing 1.1 g. (97%), m.p. 163–166°. It was recrystallized from aqueous ethanol to give colorless, small needles, m.p. 166–167°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: N, 7.95. Found: N, 7.60.

(*b*) *By decarboxylation of* IV. The malonic acid (IV) (7 g.) was stirred and refluxed with 100 ml. of water for 3.5 hr.

(12) Our syntheses of compounds XIV, XV, and XVII were completed in 1953 and the paper was originally submitted for publication in 1954 before these three compounds were reported.[7] Thus, our findings confirm their work independently.

(13) E. Titus and S. Udenfriend, *Federation Proc.*, **13**, 411 (1954); A. Sjoerdsma, H. Weissbach, and S. Udenfriend, *Am. J. Med.*, **20**, 520 (1956).

(14) W. R. Boehme, *J. Am. Chem. Soc.*, **75**, 2502 (1953).

(15) A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946).

(16) *Cf.* J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syntheses*, **31**, 35 (1951).

(17) All melting points are uncorrected.

The pale brown solid, which separated on cooling, was crystallized from dilute ethanol to yield 5.1 g. (82%) of needles, m.p. 165–166°. There was no m.p. depression with a sample obtained by method (a).

N-(3,4,5-Trimethoxybenzoyl)-5-benzyloxytryptophan (IX). A mixture of 5.1 g. of 5-benzyloxytryptophan (VI) and 4.1 g. of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of pyridine was heated on a steam bath for 45 min. The resulting solution was then poured into ice water with stirring. The clear aqueous solution was separated from the small portion of dark, gummy material and acidified with hydrochloric acid. The colorless precipitate, after filtration and recrystallization from 80% ethanol, yielded 1.54 g. (19%) of colorless prisms, m.p. 202–204°.

Anal. Calcd. for $C_{28}H_{28}N_2O_7$: N, 5.55. Found: N, 5.51.

N-Acetyl-5-hydroxytryptophan (X). (*a*) *By hydrogenolysis of* VIII. A mixture of 5.2 g. of *N*-acetyl-5-benzyloxytryptophan (VIII) and 1 g. of 10% palladium-on-carbon catalyst in 100 ml. of absolute ethanol was hydrogenated at room temperature at 40 p.s.i. pressure for 3.5 hr. After filtering off the catalyst, the solvent was evaporated under reduced pressure below 40°. The light pink, crystalline solid residue was triturated with a little ethyl acetate and ether, filtered, and weighed 2.5 g. (64%) m.p. 202–205°. It was recrystallized from absolute ethanol–ether to yield colorless needles, m.p. 207–209°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: N, 10.68. Found: N, 10.65.

(*b*) *By decarboxylation of* V. Three grams of crude V, dissolved in 100 ml. of ethyl acetate in a beaker, was heated gently to boiling on a steam bath for 20–30 min. after which some colorless crystals gradually separated. Adding petroleum ether and chilling the mixture, promptly yielded 2.3 g. (90%) of pure material, m.p. 207–208°. The mixed melting point with a sample from procedure (*a*) showed no depression.

α-Acetamino-α-carboxy-β-(5-hydroxy-3-indole)propionic acid (V). A mixture of 4 g. of the benzyloxyindole acid (III) and 1 g. of palladium-on-carbon catalyst in 60 ml. of absolute ethanol was hydrogenated at room temperature under 40 p.s.i. pressure for 3 hr. The catalyst was filtered off and the solvent was evaporated at 30° under reduced pressure. The resulting sirup was crystallized from ethyl acetate–ether without heating to give colorless small, unstable needles, melting at 156–157° with decomposition, resolidifying and then remelting at 200–205°.[18] Some decarboxylation accompanied the purification, thus rendering the preparation of an analytical sample difficult.

5-Hydroxytryptophan (VII). Fifty g. of VI was dissolved in 300 ml. of 5% sodium hydroxide solution and 10 g. of 10% palladium-on-carbon catalyst was added. The mixture was hydrogenated at room temperature and 40–50 p.s.i. pressure for 3 hr. After filtration of the catalyst, the aqueous phase was separated from the toluene layer, nearly neutralized with dilute hydrochloric acid, and finally acidified with dilute acetic acid. The pale pink solid which separated was filtered, washed with a small amount of ice water, and recrystallized from hot water to yield 32.2 g. (91%) of colorless prisms, m.p. 297–298° dec. (reported[5] m.p. 293–298°).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.63. Found: N, 12.38.

Ethyl α-amino-β-(5-hydroxy-3-indole)propionate hydrochloride (XI). Five g. of 5-hydroxytryptophan (VII) suspended in 100 ml. of absolute ethanol was saturated with hydrogen chloride gas and the solution was allowed to stand at room temperature for 2 days. The alcoholic solution was concentrated at low temperature under reduced pressure to about 50 ml. after which dry ether was added. The colorless hydrochloride salt that separated was filtered, weighing 5.5 g. (85%), m.p. 234–235° dec.

Anal. Calcd. for $C_{13}H_{17}N_2O_3Cl$: N, 9.84. Found: N, 9.56.

Ethyl α-(3,4,5-trimethoxybenzoylamino)-β-(5-hydroxy-3-indole)propionate (XII). A stirred suspension of 5 g. of XI in 10 ml. of water was treated with 30 ml. of 20% sodium carbonate, then with 50 ml. of chloroform, and finally with 5 g. of 3,4,5-trimethoxybenzoyl chloride in 39 ml. of chloroform. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and filtered. Concentration of the chloroform solution separated 6 g. (78%) of crystalline solid, m.p. 169–171°. It was recrystallized once from ethyl acetate–petroleum ether (65–75°) to yield a colorless material, m.p. 170–172°.

Anal. Calcd. for $C_{23}H_{26}N_2O_7$: N, 6.33. Found: N, 6.13.

5-Benzyloxyindole-3-acetamide (XIV). A mixture of 10 g. of 5-benzyloxygramine (I), 14 g. of sodium cyanide, 112 ml. of 95% ethanol, and 28 ml. of water was refluxed gently for 81 hr. After cooling, 50 ml. of cold water was added. The crystalline, colorless solid which precipitated was filtered, washed with cold water and dried, weighing 4.05 g. (40.5%), m.p. 155–157°. Recrystallization once from absolute ethanol yielded 3.65 g. of pure material, m.p. 156–157°. (reported[3] m.p. 158°).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 9.99. Found: N, 9.88.

5-Benzyloxyindole-3-acetic acid (XV). The filtrate from the removal of the amide (XIV) was concentrated under reduced pressure to about half of its original volume, cooled with cracked ice, and then made acid to Congo red. The acid that separated was filtered, and weighed 4.2 g. (42%), m.p. 145–148°. A pure sample was obtained by recrystallization of the material from 50% ethanol to give colorless needles, m.p. 147–149°. (reported[7] m.p. 149–150.5°).

Anal. Calcd. for $C_{17}H_{15}NO_3$: N, 4.98. Found: N, 5.21.

5-Hydroxyindole-3-acetamide (XVI). A solution of 3 g. of 5-benzyloxy-3-indoleacetamide in 200 ml. of ethanol was reduced at 40 p.s.i. pressure in the presence of 2 g. of 10% palladium-on-carbon catalyst. After 4 hr. the catalyst was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 2 l. of dry ether, filtered, and concentrated to 150 ml. The product which separated weighed 1.5 g. (74%), m.p. 164–165°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: N, 14.73. Found: N, 14.73, 14.79.

5-Hydroxyindole-3-acetic acid (XVII). A solution of 5 g. of 5-benzyloxy-3-indoleacetic acid in 75 ml. of ethanol was reduced at 40 p.s.i. pressure with 2 g. of 10% palladium-on-carbon catalyst. After 3 hr. the catalyst was filtered and the filtrate evaporated to dryness under reduced pressure. The residue dissolved in 600 ml. of hot ether. Filtration and concentration to 500 ml. yielded 2 g. (59%) of pure product decomposing at 163–164°. (reported[7] m.p. 166°).

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.25.

5-Benzyloxytryptophol (XVIII). To a stirred suspension of 1.5 g. of lithium aluminum hydride in 200 ml. of anhydrous ether was added 4.2 g. of powdered 5-benzyloxy-3-indoleacetic acid (XV) in small portions during 1 hr. The mixture was heated under reflux for 6 hr. and the excess lithium aluminum hydride was carefully decomposed by dropwise addition of 10 ml. of ethyl acetate. Then 60 ml. of 10% sodium hydroxide solution was added with stirring. The ether layer was separated and the water layer was extracted once with ether. The combined ether solutions were washed with water, dried over magnesium sulfate, and evaporated at low temperature under reduced pressure. The remaining semisolid was recrystallized from benzene–petroleum ether; yield of colorless needles 2.85 g. (71%), m.p. 98–100°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: N, 5.24. Found: N, 5.27.

5-Hydroxytryptophol (XIX). A mixture of 3 g. of 5-benzyloxytryptophol and 1 g. of 5% palladium-on-carbon catalyst in 60 ml. of absolute ethanol was hydrogenated at room temperature at low pressure for 2 hr. The catalyst was filtered off and the ethanol was evaporated at slightly above room temperature with reduced pressure. The residual, reddish oil was crystallized from ethyl acetate–petroleum ether. It separated as slightly pink needles upon standing several weeks in the refrigerator. The yield was 1.1 g. (55%) m.p. 111–113°. This unstable compound not only decomposed in

(18) Since m.p. of X was 207–209°, it seemed apparent that the compound first melted with decarboxylation to form X.

air, but also turned dark red in the solvent upon standing in the ice box.

Anal. Calcd. for $C_{10}H_{11}O_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.95; H, 6.05; N, 7.78.

β-Amino-α-(5-benzyloxy-3-indole)propanol (XX). 5-Benzyloxytryptophan (9 g.) was added portionwise to a stirred and refluxing mixture of 5 g. of lithium aluminum hydride in 500 ml. of dry ether during a 2-hr. period. The heating and stirring was continued for another 3 hr. and the mixture was allowed to stand overnight. The excess lithium aluminum hydride was carefully decomposed with 10 ml. of ethyl acetate and 200 ml. of 20% aqueous sodium potassium tartarate solution was then slowly added to the reaction mixture with stirring. The ether layer was separated and the water layer was extracted twice with small portions of ether. The combined ether solutions were washed with dilute sodium bicarbonate solution, water, and then dried over magnesium sulfate. Evaporation of the ether left 5.3 g. (61%) of a slightly reddish oil which soon solidified, m.p. 106–108°. It was recrystallized from benzene to give colorless small needles, m.p. 108–109°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: N, 9.45. Found: N, 9.26.

N,N'-bis-(5-benzyloxyskatyl)piperazine (XXI). A solution of 7 g. of 5-benzyloxygramine and 0.9 g. of piperazine in 300 ml. of toluene was refluxed with stirring under nitrogen for 24 hr. Some of the product began to precipitate after a few hours. Filtration of the hot reaction mixture yielded 5.5 g. (80%) of the compound melting at 229–230°. Crystallization from dimethylformamide did not change this melting point.

Anal. Calcd. for $C_{36}H_{36}N_4O_2$: N, 10.07. Found: N, 10.01.

5-Benzyloxy-2-carbethoxy-3-indolecarboxaldehyde (XXIII). A mixture of 8 g. of *N*-methylformanilide and 9 g. of phosphoryl chloride was stirred for 15 min. under anhydrous conditions. Forty g. of ethylene dichloride was added to the mixture, followed by 14.2 g. of ethyl 5-benzyloxy-2-indolecarboxylate.[14] After stirring and refluxing for 1 hr. the reaction mixture was poured into a solution of 40 g. of sodium acetate in 80 ml. of ice water with stirring. The yellow paste which separated was triturated twice with water and once with ether to yield a finely divided solid, weighing 15 g. (96%), m.p. 240–242°. A pure sample was obtained by recrystallization of the crude material from ethylene dichloride to give light yellow, fine needles, m.p. 244–245°.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 71.03; H, 5.25; N, 4.43.

The *oxime* was obtained by the following procedure: A mixture of 3 g. of indole aldehyde, 3 g. of hydroxylamine hydrochloride in 15 ml. of pyridine, and 15 ml. of absolute ethanol was heated gently on a steam bath for 2 hr. The excess solvent was evaporated and the residue was treated with cold water. The crude product was recrystallized from dilute ethanol to give 2.6 g. (83%) of colorless prisms, m.p. 220–221°.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: N, 8.28. Found: N, 8.12.

The *2,4-dinitrophenylhydrazone* was prepared in the usual manner and was recrystallized from ethyl acetate–ethanol to give a bright red material in almost theoretical yield, m.p. 278–280°.

Anal. Calcd. for $C_{25}H_{21}N_5O_7$: N, 13.91. Found: N, 13.63.

β-(2-Carbethoxy-5-benzyloxy-3-indole)acrylic acid (XXIV). Ten drops of piperidine was added to a solution of 1.5 g. of indole aldehyde (XXIII) and 3 g. of malonic acid in 15 ml. of pyridine. The solution was heated on a steam bath at 50–70° for 80 hr., then poured into ice water and acidified with dilute hydrochloric acid. The precipitate was filtered off and treated with 10% sodium hydroxide solution. The resulting insoluble material was filtered off and the filtrate was again acidified. The precipitate was recrystallized from 90% ethanol to yield 0.56 g. (31%) of pale yellow, cottony needles, m.p. 230° dec.

Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.65; H, 5.15; N, 3.64.

PHILADELPHIA 44, PA.

[CONTRIBUTION FROM THE "LABORATORIO DE QUÍMICA BIOLÓGICA," FACULTAD DE CIENCIAS MÉDICAS, AND THE "LABORATORIOS DE INVESTIGACIÓN," E. R. SQUIBB & SONS ARGENTINA S.A.]

Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. VI. Derivatives of L-Arabinose, D-Xylose, and D-Ribose

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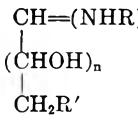
The tetraacetylated and tetrabenzoylated derivatives of L-arabinose, D-xylose and D-ribose gave, on treatment with methanolic ammonia, the *N,N'*-diacyl-pentosylidenediamines. By ammonolysis of tetrabenzoyl-L-arabononitrile and of tetrabenzoyl-D-xylononitrile, the *N,N'*-dibenzoyltetrosylidenediamines were obtained.

In our first papers[1] we described the action of methanolic ammonia on the pentaacetyl- and pentabenzoylhexoses, a reaction that leads, with opening of the pyranose or furanose ring, to the production as principal products, of the open chain *N,N'*-diacetyl-(I) or *N,N'*dibenzoylhexosylidenediamines (II). The reaction was afterwards applied to tetraacetyl and tetrabenzoyl-L-rhamnopyranose.[2] The products and yields almost duplicated the results with the corresponding D-mannose derivatives; while tetraacetyl-L-rhamnose produced only *N,N'*-diacetyl-L-rhamnosylidenediamine (III), tetrabenzoyl-L-rhamnose gave, as happened with pentabenzoyl-D-mannose, two products; the principal one was the open chain compound, *N,N'*-dibenzoyl-L-rhamnosylidenediamine (IV) and the secondary compound was a cyclic pyranose derivative, *N*-benzoyl-L-rhamnopyranosylamine.

(1) V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, 17, 1087, 1093, 1097 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, 22, 802 (1957).



(I) n = 4; R = CH_3CO; R′ = OH
(II) n = 4; R = C_6H_5CO; R′ = OH
(III) n = 4; R = CH_3CO; R′ = H
(IV) n = 4; R = C_6H_5CO; R′ = H
(V) n = 3; R = CH_3CO; R′ = OH
(VI) n = 3; R = C_6H_5CO; R′ = OH
(VII) n = 2 (L-erythro); R = C_6H_5CO; R′ = OH
(VIII) n = 2 (D-threo); R = C_6H_5CO; R′ = OH

We have extended this study to the pentoses. Experiments with D-lyxose have already been reported.[3] In this paper, the results of the ammonolysis of the tetraacetyl- and tetrabenzoyl- derivatives of L-arabinose, D-xylose and D-ribose are described.

All of the tetraacetylpentoses gave the open chain, *N,N′*-diacetylpentosylidenediamines (V). No crystalline compound could be isolated by the ammonolysis of tetraacetyl-D-xylopyranose. an experience in agreement with the results of Hockett and Chandler[4] who also could not obtain a definite product by the ammonolysis of tetraacetyl-*aldehydo*-D-xylose.

The tetrabenzoylpentoses produced the expected *N,N′*-dibenzoylpentosylidenediamines (VI). The isomeric *N,N′*-dibenzoyl-D-arabinosylidenediamine was obtained by ammonolysis with methanolic ammonia of the pentabenzoyl-D-gluconononitrile and the racemic *N,N′*-dibenzoyl-DL-arabinosylidendiamine and its tetraacetyl derivative were prepared. As in the case of the ammonolysis of the pentabenzoyl-D-galactononitrile,[3] when methanolic ammonia was employed, the benzoyl esterifying the primary hydroxyl was eliminated, while Restelli de Labriola and Duelofeu[5] using ethanolic ammonia obtained 5-*O*-benzoyl-*N,N′*-dibenzoyl-D-arabinosylidenediamine. This compound loses easily the primary benzoyl under the action of methanolic ammonia. As will be described in a further publication, this difference in activity depends not only on the higher concentration of the ammonia in methanol, but on the alcohol itself, methanol being more active as a solvent than ethanol.

With a few exceptions, the yields of the *N,N′*-diacylpentosylidenediamines were of the same order as those from the acylated compounds of the hexose series. These results, taken together with those obtained in the ammonolysis of the tetraacetyl-L-rhamnose and tetrabenzoyl-L-rhamnose[2] are interesting, because the *N,N′*-diacyldiamines of the monosaccharides (I–VI) are formed by an intramolecular mechanism[6] and for the case of the acylated pentoses and L-rhamnose, only three acyl groups can participate in it. The acyl group at carbon atom 1 does not play any important role in the reaction.[1]

In this paper, the ammonolysis of tetrabenzoyl-L-arabononitrile and of tetrabenzoyl-D-xylononitrile is also reported. Neither of these compounds could be obtained in a crystalline condition, although the analytical figures for the cyano group were indicative of a rather high purity.[7] Ammonolysis gave the expected *N,N′*-dibenzoyl-L-erythrosylidenediamine (VII) from the first nitrile and *N,N′*-dibenzoyl-D-threosylidenediamine (VIII) from the second.

EXPERIMENTAL

The methanolic ammonia employed was of 16% concentration. Melting points are uncorrected.

N,N-Diacetyl-L-arabinosylidenediamine. Tetraacetyl-α-L-arabopyranose[8] (5 g.) was dissolved in 150 ml. methanolic ammonia, and the solution after staying 24 hr. at room temperature, evaporated in vacuum. The remaining sirup was well dried, extracted three times with 20 ml. ethyl acetate, and dissolved in 25 ml. absolute ethanol. By scratching, crystals appeared and after standing overnight in the cold room, they were filtered and washed well with small amounts of boiling methanol, to get rid of an amorphous product that contaminated them. Yield: 310 mg. (7.9%) m.p. 193–194°. Recrystallized several times from methanol (Darco) the m.p. was 193–194°; $(\alpha)_D^{14°}$ +8.8°, (H_2O) Isbell and Frush[6] give m.p. 189–191°; $[\alpha]_D^{20°}$ +9.79°.

N,N′-Dibenzoyl-L-arabinosylidenediamine. The tetrabenzoyl-β-L-arabopyranose[9] (15 g.), was shaken to dissolution with 450 ml. methanolic ammonia, the solution left 24 hr. at room temperature, and evaporated to dryness in vacuum. The crystalline residue was suspended in ethanol, filtered, and washed well with the same solvent. 2.98 Grams of crystals were obtained, m.p. 192–195° and from the mother liquors, another 540 mg. were collected, giving a total yield of 35.6%. Recrystallized several times from ethanol, long needles melting 197–198°; $[\alpha]_D^{30°}$ −5.2° (c, 1.2; pyridine).

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.96; H, 5.88. Found: C, 61.24; H, 6.08.

N,N′-Dibenzoyl-D-arabinosylidenediamine. (a) *From pentabenzoyl-D-gluconononitrile.* The pentabenzoyl-D-gluconononitrile, finely ground, (15 g.) was dissolved, by shaking, in 450 ml. methanolic ammonia. After 24 hr. at room temperature the solution was evaporated in vacuum. The crystalline residue was suspended in cold ethanol, filtered, washed with the same solvent, and dried. Yield 2.97 g., m.p. 192–195°. From the mother liquors, after drying and extracting the benzamide with ethyl acetate, a further 390 mg. were isolated, m.p. 197–198° (total yield 42%). After several recrystallizations from methanol the product melted 198–199°; $[\alpha]_D^{31°}$ +5.1.

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.96; H, 5.88. Found: C, 60.67; H, 5.88.

(3) V. Deulofeu and J. O. Deferrari, *Anais acad. brasil. cienc.*, 26, 69 (1954). V. Deulofeu, J. O. Deferrari, and E. Recondo, *Anales asoc. quim. arg.*, 46, 137 (1958).

(4) R. C. Hockett and L. R. Chandler, *J. Am. Chem. Soc.*, 66, 957 (1944).

(5) E. Restelli de Labriola and V. Deulofeu, *J. Org. Chem.*, 12, 726 (1947).

(6) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, 71, 1579 (1949); V. Deulofeu and J. O. Deferrari, *Anales asoc. quim. arg.*, 38, 241 (1950); R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Am. Chem. Soc.*, 82, 1840 (1950).

(7) The determination of the nitrile group was made according to B. G. Berinzaghi, *Anales asoc. quim. arg.*, 44, 120 (1956).

(8) R. E. Deriaz, W. G. Overend, M. Stacey, E. G. Teece, and L. F. Wiggins, *J. Chem. Soc.*, 1879 (1949).

(9) H. G. Fletcher and C. S. Hudson, *J. Am. Chem. Soc.*, 69, 1145 (1947).

(*b*) *From 5-O-benzoyl-N,N'-dibenzoyl-*D*-arabinosylidenediamine.* One gram of 5-*O*-benzoyl-*N,N'*-dibenzoyl-D-arabinosylidenediamine was dissolved in 30 ml. methanolic ammonia and the solution worked as described above. *N,N'*-Dibenzoyl-D-arabinosylidenediamine (695 mg.) melting 196–197° $[\alpha]_D^{20°}$ +4.90°, were obtained. No depression was observed when mixed with the product prepared under (a).

*N,N-Dibenzoyl-*DL*-arabinosylidenediamine.* When 200 mg. of each isomer was dissolved in 10 ml. of boiling ethanol, the solution, on cooling, yielded fine needles melting 192°. The melting point was not increased by recrystallization $[\alpha]_D$ ±0.0°.

*Tetra-O-acetyl-N,N'-dibenzoyl-*L*-arabinosylidenediamine.* One gram of *N,N'*-dibenzoyl-L-arabinosylidenediamine was dissolved with gentle heating in 34 ml. of a mixture (1:1) of pyridine and acetic anhydride. After 24 hr. at room temperature, the solution was poured into 200 ml. of ice water when a precipitated formed, which crystallized very easily. Next day the crystals were filtered, washed, and dried to yield 1.18 g. of long prisms, melting at 138–140°. From the mother solution, after extracting with chloroform and processing the extract in the usual way, another 250 mg. were obtained; m.p. 141–142°. Total yield 98%. Recrystallized several times from ethanol, long prisms melting 143–145°; $[\alpha]_D^{18°}$ −73.3° (*c*, 0.74, chloroform).

Anal. Calcd. for $C_{27}H_{30}N_2O_{10}$: C, 59.80; H, 5.54. Found: C, 59.88; H, 5.49.

*Tetra-O-acetyl-N,N'-dibenzoyl-*D*-arabinosylidenediamine* was obtained in a similar way from the D-isomer. M.p. 144–145°, $[\alpha]_D^{17°}$ +73.4°.

Anal. Calcd. for $C_{27}H_{30}N_2O_{10}$: C, 59.80; H, 5.54. Found: C, 59.84; H, 5.67.

*Tetra-O-acetyl-N,N'-dibenzoyl-*DL*-arabinosylidenediamine.* A mixture of 100 mg. of each isomer was dissolved in 0.6 ml. of boiling ethanol. By cooling, 91 mg. of crystals melting 168–170° were obtained. The melting point remained constant by further recrystallization, $[\alpha]_D^{17°}$ ±0.0°.

*Tetra-O-benzoyl-N,N'-dibenzoyl-*D*-arabinosylidenediamine.* Five hundred milligrams of *N,N'*-dibenzoyl-D-arabinosylidenediamine were dissolved by gently heating in 6.25 ml. dry pyridine. The solution was cooled at room temperature and 1.25 ml. benzoyl chloride added. It was then heated 10 min. at 60° and left at room temperature overnight. Next day the suspension was poured into ice water and a sirup precipitated. After washing well with water, the sirup was dried in a desiccator and treated with ligroin, when it gave a solid. It was crystallized by dissolving in small amounts of benzene, adding ethyl ether to turbidity, and left standing at room temperature. Small needles, that after several recrystallizations melted 134–135°, when dried at 100° vacuum. Lower m.p. were obtained when the product was not well dried. $[\alpha]_D^{28°}$ +62.5° (c, 0.98, chloroform).

Anal. Calcd. for $C_{47}H_{38}N_2O_{10}$: C, 71.39; H, 4.81; N, 3.54. Found: C, 71.80; H, 4.75; N, 3.07.

L*-Arabinose diphenylhydrazone.* The alcoholic mother liquors from the preparation of *N,N'*-dibenzoyl-L-arabinosylidenediamine were evaporated to a sirup, which was extracted with ethyl acetate to eliminate the benzamide. The insoluble was dissolved in 6 ml. water and treated with 185 mg. anhydrous solid acetate and 750 mg. diphenylhydrazine hydrochloride. The solution was heated 30 min. at 75° and left standing. Crystals appeared that, after 72 hr., were filtered and washed with ethanol. L-Arabinose diphenylhydrazone (123 mg.), m.p. 195°, were collected. Identified by mixed m.p.

*N,N'-Diacetyl-*D*-ribosylidenediamine.* Tetraacetyl-β-D-ribose[10] (1.5 g.), was dissolved in 45 ml. methanolic ammonia. After standing 24 hr. at room temperature, the solution was evaporated to dryness in vacuum. The well dried residue was extracted several times with ethyl acetate, dried again, dissolved in 4 ml. absolute ethanol and evaporated slowly at room temperature. Crystals appeared after several days, that increased by scratching. They were filtered and washed well with absolute ethanol. M.p. 123–126°. Yield 150 mg. By concentration of the mother liquors 150 mg. more were obtained (m.p. 122–125°). Total yield 300 mg. (25%).

When recrystallized from boiling ethanol long needles melting 124–126° were obtained. After drying 3 hr. at 100° over phosphorus pentoxide they melted 154–155°. $[\alpha]_D^{24°}$ +14.7° (*c*, 0.68, H_2O).

Anal. Calcd. for $C_9H_{18}N_2O_6$: C, 43.20; H, 7.20; N, 11.20. Found: C, 42.90; H, 7.14; N, 10.99.

*Tetra-O-acetyl-N,N'-diacetyl-*D*-ribosylidenediamine. N,N'-*Diacetyl-D-ribosylidenediamine (50 mg.) was heated to dissolution with 1.5 ml. of a mixture of pyridine and acetic anhydride (1:1). After 24 hr. standing at room temperature, the solution was evaporated in a desiccator, when 79 mg. of crystals were obtained, melting at 175–176°. Recrystallized from ethanol prisms melting 184–185°. $[\alpha]_D^{20°}$ +18.5 (*c*, 0.54, chloroform).

Anal. Calcd. for $C_{17}H_{26}N_2O_{10}$: C, 48.69; H, 6.31; N, 6.69. Found: C, 49.58; H, 6.18; N, 6.65.

*N,N-Dibenzoyl-*D*-ribosylidenediamine.* Three grams of tetrabenzoyl-β-D-ribopyranose[11] were dissolved, by shaking, in 110 ml. of methanolic ammonia. After 18 hr. standing at room temperature, the solution was evaporated in vacuum to dryness. The residue was well extracted with ethyl acetate and the remaining solid recrystallized from water. It yielded 640 mg. of crystals (35%) melting 185–187°. For analysis it was recrystallized from water. M.p. 190°; $[\alpha]_D^{28°}$ −7.3° (*c*, 1.0, pyridine).

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 61.13; H, 6.02; N, 7.60.

*Tetra-O-acetyl-N,N'-dibenzoyl-*D*-ribosylidenediamine.* Four hundred mg. of *N,N'*-dibenzoyl-D-ribosylidenediamine were suspended in a mixture of 9 ml. (1:1) of pyridine and acetic anhydride. The suspension was gently heated to dissolution and after 16 hr. standing at room temperature, it was poured into ice water. A sirup precipitated that crystallized very easily, by washing with cold water. The crystals were filtered and recrystallized from ethanol-water. M.p. 172–173°; $[\alpha]_D^{24°}$ −10.4° (*c*, 1.1; chloroform).

Anal. Calcd. for $C_{27}H_{30}N_2O_{10}$: C, 59.77; H, 5.57; N, 5.16. Found: C, 59.64; H, 5.69; N, 5.06.

*Tetrabenzoyl-α-*D*-xylopyranose.* The following modification of the procedure of Fletcher and Hudson[12] was employed. Five grams of finely powdered D-xylose were well suspended in 30 ml. pyridine, cooled at 0°, and 24 ml. of benzoyl chloride slowly added, maintaining the temperature at 0–5°. After 2 hr. at 0°, the reaction mass was left 24 hr. at room temperature. Chloroform (150 ml.) was then added and the solution poured into chopped ice. The chloroform layer was decanted and washed twice with 3*N* sulfuric acid, with saturated sodium hydrogen carbonate solution, and with water. After drying and passing through a layer of Darco the chloroform was evaporated, leaving a sirup that when washed and scratched several times with small portions of ligroin, crystallized. The crude product was recrystallized from ethanol, when 13–14 g. (yield 71%) of large prisms melting 114–116° were obtained. After recrystallizing several times from ethanol, they melted 116–117°; $[\alpha]_D^{30°}$ +148.7 (*c*, 1.16, chloroform). Fletcher and Hudson[12] give 119–120°: $[\alpha]_D^{20°}$ +149.5°.

Anal. Calcd. for $C_{33}H_{26}O_9$: C, 69.80; H, 4.58. Found: C, 69.56; H, 4.81.

*N,N'-Dibenzoyl-*D*-xylosylidenediamine.* Finely ground tetrabenzoyl-α-D-xylopyranose (12.4 g.) was dissolved in 315 ml. of methanolic ammonia and left 48 hr. at room tem-

(10) P. A. Levene and R. St. Tipson, *J Biol Chem.*, **92**, 109 (1931).

(11) J. Jeanloz, H. G. Fletcher, and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 4052 (1948).

(12) H. G. Fletcher and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 921 (1947).

perature. The solution was then evaporated in vacuum and the residual syrup dissolved in 60 ml. ethanol. By keeping at room temperature for a few days, crystals appeared, which were filtered and washed with ethanol. 2.43 Grams of needles, m.p. 182–184°, were collected (yield 30%). Recrystallized once from water and three times from ethanol, they melted 184–185°, $[\alpha]_D^{22°}$ −2.2° (*c*, 1.4, pyridine).

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.96; H, 5.88. Found: C, 60.95; H, 6.09.

*Tetra-O-acetyl-N,N'-dibenzoyl-*D*-xylosylidenediamine.* The *N,N'*-dibenzoyl-D-xylosylidenediamine (1 g.) was acetylated with pyridine–acetic anhydride. Yield: 1.25 g. (86%) of crystals melting 178–179°. Recrystallized from ethanol, long prisms melting at 179°; $[\alpha]_D^{22°}$ −50.4° (*c*, 0.95, chloroform).

Anal. Calcd. for $C_{27}H_{30}N_2O_{10}$: C, 59.80; H, 5.54; N, 5.16. Found: C, 59.57; H, 5.55; N, 5.13.

*Tetrabenzoyl-*L*-arabonitrile.* Three grams of L-arabinose oxime were suspended in 18 ml. dried pyridine and 18 ml. of benzoyl chloride added, in such a way that the temperature of the suspension was maintained at 95–100°. The oxime dissolved and a solid precipitated. After keeping the suspension at room temperature for 16 hr., it was poured into ice water. The pasty sirup that precipitated was ground many times with fresh water and dried in a desiccator. When treated with cold methanol it became solid. It was dissolved by boiling in the same solvent, a small amount of Darco added, and after filtering, the solution was slowly cooled, when an amorphous solid precipitated. Repetition of the procedure several times, gave a noncrystalline solid that melted 90–94°. Yield 7.2 g. (70%).

For further purification, 500 mg. of the nitrile were dissolved in the smallest volume of benzene and passed through a column of 16 g. alumina, acid washed, grade I–II. After washing the column with 15 ml. benzene, the nitrile was eluted with benzene with 1% methanol, fractions of 5–7 ml. being collected. Evaporation of fractions 3–11 gave 350 mg. of a solid that was dissolved several times in boiling methanol and recovered by cooling. It was amorphous, melted 107–108°, with sintering from 94° (after drying at 76° in vacuum); $[\alpha]_D^{25°}$ −16.5° (*c*, 1.2; chloroform). The constants were not appreciably changed by further dissolution and precipitation. It could not be obtained crystalline by employing other solvents. High vacuum distillation also failed.

Anal. Calcd. for $C_{33}H_{25}NO_8$: C, 70.33; H, 4.47; N, 2.49; CN, 4.62. Found: C, 70.53; H, 4.45; N, 2.59; CN, 4.42.

*N,N'-Dibenzoyl-*L*-erythrosylidenediamine.* Two grams of the amorphous tetrabenzoyl-L-arabonitrile, melting 92–94°, were suspended in 50 ml. methanolic ammonia, dissolved by agitation, and left 18 hr. standing at room temperature. The solution was evaporated in vacuum to dryness and the dark yellow residue suspended in ethanol and filtered. Washing with ethanol was continued, until the solid was almost white. It was recrystallized from 90% ethanol, when 230 mg. (19%) of long prisms, melting 218°, were obtained. For analysis it was recrystallized several times from 90% ethanol. M.p. 220°, $[\alpha]_D^{27°}$ +13.1° (*c*, 0.34, pyridine).

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.57; N, 8.14. Found: C, 62.98; H, 5.94; N, 8.22.

*Triacetyl-N,N'-dibenzoyl-*L*-erythrosylidenediamine.* Two hundred milligrams of N,N'-dibenzoyl-L-erythrosylidenediamine were acetylated with pyridine–acetic anhydride. Needles, from absolute ethanol, m.p. 183–184°, formed. $(\alpha)_D^{27°}$ +8.9 (c, 1.0, chloroform).

Anal. Calcd. for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.49; H, 5.44; N, 5.97.

*Tetrabenzoyl-*D*-xylononitrile.* To a suspension in 54 ml. of dry pyridine, of the siruppy D-xylose oxime obtained from 9 g. of D-xylose, 45 ml. of benzoyl chloride were added, keeping the temperature between 95–100°. The red-brown suspension obtained was left at room temperature for 16 hr., poured into ice water and the sirup that precipitated, washed well with water and dried in a desiccator. By treatment with different solvents, it did not solidify. It was then dissolved in the minimum amount of cold benzene. The red solution obtained was washed well with 2*N* hydrochloric acid, with saturated solution of sodium hydrogen carbonate and with water. It was dried and chromatographed on alumina, acid washed, grade II, eluting with benzene. By evaporation of the middle eluted fractions, a solid was recovered (yield: 21 g.), which when chromatographed again, gave a product sintering at 49° and melting 61–66°; $[\alpha]_D^{24°}$ = −2.9 (*c*, 4.6; chloroform). Repetition of the chromatography did not change the constants. By chromatography on Magnesol or silica gel, no improvements were observed. Although impure, it contained an appreciable amount of nitrile.

Anal. Calcd. for $C_{35}H_{25}NO_8$: CN, 4.62%. Found: 4.12%.

*N,N'-Dibenzoyl-*D*-threosylidenediamine.* Five grams of the tetraacetyl-D-xylononitrile, purified by chromatography on alumina, were treated in the usual way with 125 ml. of methanolic ammonia. After standing 18 hr. at room temperature, the solution was evaporated in vacuum to dryness and the residue treated with 15 ml. of cold absolute ethanol. On standing at 0° it gave 560 mg. of fine needles (yield 18.3%), melting 184°. By recrystallization from 95% ethanol a m.p. 189–190° was obtained. $[\alpha]_D^{27°}$ +1.7° (*c*, 0.97; pyridine); $[\alpha]_D^{24°}$ −4.9° (*c*, 0.93; ethanol:water; 3:1).

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.57; N, 8.14. Found: C, 62.90; H, 5.72; N, 7.97.

*Triacetyl-N,N'-dibenzoyl-*D*-threosylidenediamine.* Four hundred milligrams of *N,N'*-dibenzoyl-D-threosylidenediamine were acetylated in the usual way with pyridine–acetic anhydride and worked in the usual way. Recrystallized from ethanol 95%, it gave needles m.p. 183–184°; $[\alpha]_D^{27°}$ +79.3° (*c*, 1.2, chloroform).

Anal. Calcd. for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.32; H, 5.39; N, 6.17.

Acknowledgment. We thank Mr. Joseph F. Alicino, from the Squibb Institute for Medical Research, New Brunswick, N. J., for the microanalysis, and to Dr. H. G. Fletcher, Bethesda, Md., for a sample of crystalline tetrabenzoyl-D-ribopyranose.

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Azo Dyes from Substituted 2-Aminothiazoles[1]

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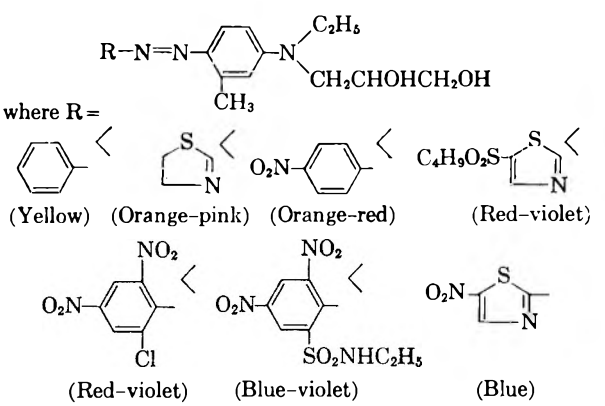
A series of 2-thiazolylazo dyes for cellulose acetate was prepared. Substituents in the 4-position have little effect on the color of 2-thiazolylazo dyes. The color of the dyes containing various groups in the 5-position deepens in the order of increasing negativity of the substituent. Thus, dyes containing the nitro group in the 5-thiazolyl position are blue to greenish blue; these dyes have superior dyeing and fastness properties. The bathochromism of the 2-thiazolylazo dyes is illustrated by comparison of the blue dyes from 2-amino-5-nitrothiazole with dyes from the benzene analog, *p*-nitroaniline; dyes from the latter are red.

The bathochromism of the 2-thiazolylazo dyes is discussed in terms of the influence of the 2-thiazolylazo structure and of substitution on the coupler and diazonium constituents.

The preparation and properties of new 2-aminothiazole intermediates are described. Certain problems encountered in nitration and oxidation reactions are discussed.

This paper concerns the effects of the position and nature of substituents in 2-aminothiazoles on the color of azo dyes prepared from them. Of primary interest is the color shift from the red of azo dyes derived from nitroanilines to the blue of analogous azo dyes[3-5] derived from 2-amino-5-nitrothiazoles. This pronounced shift exhibited by 5-nitro-2-thiazolylazo dyes is illustrated by the following series of azo dyes listed in the order of increasing deepening of color on cellulose acetate. The visible absorption spectra of certain of these dyes are shown in Fig. 1.



The 2-aminothiazoles used in this investigation are listed in Table I. Physical properties and analyses are given for new compounds. Known compounds used are listed with literature references.

2-Aminothiazole and most of its 5-substituted, 4-substituted, and 4,5-disubstituted derivatives were prepared by the reaction of thiourea with the appropriate α-halo aldehyde[6,7] (or 1,2-dichloroethyl ethyl ether[8]), α-halo ketone, or α-halo-β-keto ester. Derivatives of 2-aminothiazole containing the thio or sulfonyl group in the 5-position[9] generally were prepared by the reaction of 2-acetamido-5-bromothiazole[10] or 2-amino-5-bromothiazole[11] with the appropriate sodium mercaptide to yield initially the 5-thio compound. Oxidation of the 2-acetamido-5-alkylthiothiazole followed by hydrolysis of the acetamido group yielded the 5-sulfonyl compound.[12] The 2-amino-5-nitrothiazoles were prepared by dissolving the 2-aminothiazoles, or their acetyl derivatives, in concentrated sulfuric acid and nitrating[13] with one equivalent of fuming nitric acid at about 10°. The nitrations of 2-aminothiazole and 2-amino-4-trifluoromethylthiazole have been described.[14]

The difficulty of forming stable diazonium salts of both 2-aminothiazole and 2-amino-5-nitrothiazole has been described in connection with replacing the diazo group with halogen.[15] In the present work, 2-aminothiazole and its derivatives were diazotized

(1) Presented in part at the 131st National Meeting of the American Chemical Society, Miami, Fla., April 1957.

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(3) J. B. Dickey and E. B. Towne (to Eastman Kodak Co.), U. S. Patents 2,659,719 (1953); 2,683,708 (1954); 2,683,709 (1954); 2,730,523 (1956); 2,746,953 (1956).

(4) E. B. Towne and H. M. Hill (to Eastman Kodak Co.), U. S. Patent 2,726,247 (1955).

(5) E. B. Towne, J. B. Dickey, and M. S. Bloom (to Eastman Kodak Co.), U. S. Patent 2,839,523 (1958).

(6) M. N. Shchukina, *Zhr. Obshchei Khim.* (*J. Gen. Chem.*), **18**, 1653 (1948); *Chem. Abstr.*, **43**, 2575 (1949).

(7) O. Yu. Magidson and V. N. Sokolova, U.S.S.R. Patent 66,044 (1946); *Chem. Abstr.*, **41**, 1713 (1947).

(8) V. Traumann, *Ann.*, **249**, 31 (1888).

(9) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945); L. L. Bambas (to Parke, Davis, and Co.), U. S. Patent 2,389,126 (1945); E. Hoggarth, *J. Chem. Soc.*, 110 (1947).

(10) H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **63**, 226 (1944).

(11) R. Dahlbom and T. Ekstrand, *Svensk Kem. Tidskr.*, **57**, 229 (1945).

(12) Hydrogen peroxide oxidation of an unacetylated 2-amino-5-alkylthiothiazole, however, gave a hydrogen peroxide derivative involving the amino group. Treatment of this derivative with dilute acid yielded the 2-amino-5-alkylsulfonylthiazole.

(13) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945). See especially p. 354.

(14) J. B. Dickey, E. B. Towne, and G. F Wright, *J. Org. Chem.*, **20**, 499 (1955).

(15) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 362 (1945). See especially p. 365.

TABLE I

2-AMINOTHIAZOLES[a]

Thiazole Derivative	M.P., °C.	Yield, %[b]	Analyses							
			Calcd., %				Found, %			
			C	H	N	S	C	H	N	S
2-Amino-4-(*p*-nitrophenyl)-	266	44	48.87	3.17	19.00	14.48	48.81	3.58	18.24	13.94
2-Amino-4-(*p*-acetamidophenyl)-	240–243	64	56.65	4.72	18.03		56.62	4.87	17.91	
2-Amino-4-(2,5-dichlorophenyl)-	170–172	47	44.08	2.49	11.43		44.26	2.73	11.28	
2-Amino-5-methylthio-	130–133	53	32.88	4.11	19.18		33.64	4.27	19.06	
Acetyl derivative	192–195	95	38.29	4.25	14.89		38.94	4.46	14.62	
2-Amino-5-methylsulfonyl-	176–178	92								
Acetyl derivative	270–271	35	32.73	3.64	12.73	29.09	33.13	3.84	12.65	28.86
2-Amino-5-butylthio-	66–68	51	44.60	6.40	14.90	34.00	44.54	6.36	14.81	33.91
Acetyl derivative	143–144	95	46.96	6.09	12.17	27.82	47.00	6.12	11.98	27.82
2-Amino-5-butylsulfonyl-	94–95	72[c]	38.18	5.45	12.73	29.09	38.59	5.53	12.77	28.76
Acetyl derivative	242–243	45[c]	41.22	5.34	10.68	24.43	42.43	5.52	10.59	23.79
2-Amino-5-phenylthio-	120–121	85	51.92	3.84	13.46	30.77	52.08	4.07	13.28	29.95
Acetyl derivative	221–225	83	52.80	4.00	11.20	25.60	53.29	4.53	11.08	25.98
2-Amino-5-phenylsulfonyl-	205–215	95								
Acetyl derivative	274	82[c]	46.81	3.55	9.93	22.69	46.86	4.07	9.91	22.78
2-Amino-4-phenyl-5-methylthio-	83–90	63[c]								
Acetyl derivative	204	95	54.54	4.54	10.60	24.24	55.00	4.98	10.51	24.63
2-Amino-4-(*p*-nitrophenyl)-5-nitro-	251–252	70	40.60	2.26	21.05	12.03	40.69	2.51	21.02	12.05
2-Amino-4-(*m*-nitrophenyl)-5-nitro-	236–237	63	40.60	2.26	21.05	12.03	40.68	2.53	20.25	11.64
2-Amino-4-(2,5-dichlorophenyl)-5-nitro-	192–193	50.1	37.24	1.72	14.48		37.49	2.21	14.03	
Ethyl 2-amino-5-nitro-4-thiazolecarboxylate	178–181	19.4	33.20	3.22	19.30	14.70	33.31	3.40	19.28	15.00

[a] The following 2-aminothiazoles were also prepared: 2-amino-;[8] 2-amino-4-methyl-;[8,51] 2-amino-4-trifluoromethyl-;[14] ethyl 2-amino-4-thiazolecarboxylate;[41] 2-amino-4-phenyl-[8,33] 2-amino-4-(*m*-nitrophenyl)-;[33] 2-amino-5-methyl-,[50] 2-amino-5-thiocyanato-;[29] 2-amino-5-(*p*-nitrophenylthio)-,[9] 2-amino-5-(*p*-nitrophenylsulfonyl)-;[9] 2-amino-5-(*p*-nitrophenylazo)-;[26] 2-amino-5-bromo-;[11] 2-amino-4-phenyl-5-thiocyanato-;[29] 2-amino-4-phenyl-5-(*p*-nitrophenylthio)-;[28a] 2-amino-4-phenyl-5-(*p*-nitrophenylsulfonyl)-;[28a] ethyl 2-amino-4-trifluoromethyl-5-thiazolecarboxylate;[4] 2-amino-5-nitro-;[13] 2-amino-4-methyl-5-nitro-;[13] 2-amino-4-trifluoromethyl-5-nitro-;[14] 2-amino-4-tert-butyl-5-nitro-;[14] 2-amino-4-(butylsulfonyl)-5-nitro-.[5] [b] Purified product. [c] Crude product.

satisfactorily at 0–5° by adding the solid aminothiazole to nitrosylsulfuric acid in either acetic acid or 50% sulfuric acid solution. The resulting diazonium salt solutions were generally used within a few hours since they decomposed on long standing, even when cold. Coupling was usually accompanied by some evidence of decomposition; however, by careful addition of the diazonium salt solution at 0–5° to a solution of the coupler in an acetic-propionic acid mixture, 60–80% yields of dye were usually obtained. With a few couplers the yields of dye were as low as 40%.

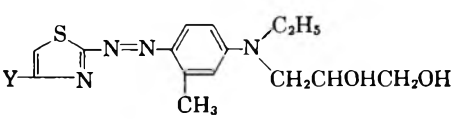
A few simple azo dyes have been prepared from 2-aminothiazole and phenols[8] and from anilines.[16,17] A yellowish red dye prepared from 2-amino-4-methylthiazole and *N*,*N*-bis(2-hydroxyethyl)-aniline has also been described.[18]

DISCUSSION

Dyes from 2-aminothiazole and 4-substituted 2-aminothiazoles. In the present work, dyes from 2-aminothiazole and 4-substituted 2-aminothiazoles were prepared using a typical aniline coupler, *N* - ethyl - *N* - (2,3 - dihydroxypropyl) - *m* - toluidine. These dyes, listed in Table II, have good gas fastness but only fair light fastness.

TABLE II

EFFECT OF 4-SUBSTITUTION ON THE COLOR OF DYES FROM 2-AMINOTHIAZOLES



Y	Color on Acetate	$\lambda_{max}^{CH_3OH}$, Mμ
H-	Orange-pink	502
CH_3-	Orange-pink	506
CF_3-	Red-pink	510
C_2H_5OOC-	Red-pink	514
2,5-$Cl_2C_6H_3$-	Red-pink	514
C_6H_5-	Red-pink	514
p-$O_2NC_6H_4$-[a]	Pink-red	517
m-$O_2NC_6H_4$-	Pink-red	517
p-$CH_3CONHC_6H_4$-	Pink-red	517

[a] Analytical Sample. *Anal.* Calcd. for $C_{21}H_{23}N_5O_4S$: C, 57.14; H, 5.21. Found: C, 56.65; H, 5.81. Spectroscopic data: λ_{max} 517 mμ, ϵ_{max} 4.57×10^4.

(16) V. Traumann, *Ber.*, 21, 938 (1888).

(17) G. T. Morgan and G. V. Morrow, *J. Chem. Soc.*, 107, 1291 (1915).

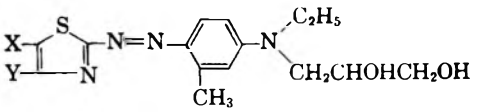
(18) J. H. Helberger and C. Taube (to General Aniline Works), U. S. Patent 2,149,051 (1939).

The dyes from 4-substituted 2-aminothiazoles are orange-pink to pink-red with absorptions of 506–517 mμ. The parent 2-aminothiazole dye absorbs at 502 mμ, hence, the influence of substitution in the 4-position is negligible. The failure of 4-substituents to effect expected color shifts in 2-thiazolylazo dyes may result from the inability of the 4-substituent to enter effectively into the resonance of the dye molecule.

Dyes from 5-substituted 2-aminothiazoles and 4,5-disubstituted 2-aminothiazoles. These dyes, listed in Table III, are red-orange to blue-violet having absorptions of 504 to 563 mμ. Although most of the dyes have only moderate light fastness, those containing a methylsulfonyl or butylsulfonyl group have good light fastness.

TABLE III

EFFECT OF 5- AND 4,5-SUBSTITUTION ON THE COLOR OF DYES FROM 2-AMINOTHIAZOLES



X	Y	Color on Acetate	$\lambda_{max}^{CH_3OH}$, Mμ
CH_3-	H-	Red-orange	504
Br-	H-	Pink-red	524
C_6H_5S-	H-	Pink-violet	530[b]
NCS-	H-	Red-violet	535
p-$O_2NC_6H_4S$-	H-	Red-violet	539
CH_3SO_2-	H-	Red-violet	544[b]
NCS-	C_6H_5-	Red-violet	545
$C_4H_9SO_2$-	H-[a]	Red-violet	550
$C_6H_5SO_2$-	H-	Violet	553[b]
C_2H_5OOC-	CF_3-	Bluish-violet	556[c]
p-$O_2NC_6H_4SO_2$-	C_6H_5-	Bluish-violet	560[b]
p-$O_2NC_6H_4SO_2$-	H-	Blue-violet	563

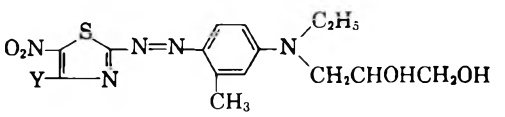
[a] Analytical Sample. *Anal.* Calcd. for $C_{19}H_{28}N_4O_4S_2$: C, 51.82; H, 6.36. Found: C, 51.17; H, 6.52. Spectroscopic data: λ_{max} 551 mμ, ϵ_{max} 4.85 × 10^4. [b] *N,N*-Bis(2-hydroxyethyl)-*m*-toluidine coupler. [c] *N*-Ethyl-*N*-(2,3-dihydroxy-2-methylpropyl)-*m*-toluidine coupler.

In contrast to the negligible effect of 4-substituents on color, 5-substituents cause a marked effect. As would be expected from resonance considerations, the color of the dyes containing the various groups in the 5-position deepens in the order of increasing negativity of the substituent; for example, the dye from 2-amino-5-thiocyanatothiazole is red-violet (535 mμ), whereas the corresponding dye from 2-amino-5-(*p*-nitrophenylsulfonyl)thiazole is blue-violet (563 mμ).

Dyes from 2-amino-5-nitrothiazole and 4-substituted 2-amino-5-nitrothiazoles. All of these dyes, listed in Table IV, are blue. They vary somewhat in tinctorial power on cellulose acetate, however. This series, like that in Table II shows that the nature of the group in the 4-position of the aminothiazole has little effect on the color of the dye. Dyes from 2-amino-5-nitrothiazole itself give good exhaustion and level dyeing and excellent affinity at dye bath temperatures as low as 40–50°. They color cellulose acetate deep, bright, blue shades. The dyed fabrics have good gas fastness, fair light fastness, and excellent dischargeability.

TABLE IV

EFFECT OF 5-NITRO SUBSTITUTION ON THE COLOR OF DYES FROM 2-AMINOTHIAZOLES



Y	Color on Acetate	Tinctorial Power on Acetate	$\lambda_{max}^{CH_3OH}$, Mμ
H-[a]	Blue	High	593
CH_3-	Blue	High	590
$(CH_3)_3C$-	Blue	Medium	590
p-$O_2NC_6H_4$-[b]	Greenish blue	Medium	600
m-$O_2NC_6H_4$-	Greenish blue	Medium	600
2,5-$Cl_2C_6H_3$-	Greenish blue	Medium	605
C_2H_5OOC-	Greenish blue	Medium	606
CF_3-	Greenish blue	Weak	613
$C_4H_9SO_2$-	Greenish blue	Weak	599[c]

[a] Analytical Sample. *Anal.* Calcd. for $C_{13}H_{19}N_5O_4S$: C, 49.32; H, 5.21. Found: C, 49.95; H, 5.74. Spectroscopic data: λ_{max} 596 mμ, ϵ_{max} 4.83 × 10^4. [b] Analytical Sample. *Anal.* Calcd. for $C_{21}H_{22}N_6O_6S$: C, 51.85; H, 4.53. Found: C, 51.74; H, 4.89. Spectroscopic data: λ_{max} 603 mμ, ϵ_{max} 3.10 × 10^4. [c] *N,N*-Bis(2-hydroxyethyl)-*m*-toluidine coupler.

Effect of coupler. The color of the 2-thiazolylazo dyes is affected not only by substituents in the thiazole ring but also by substituents in the coupler constituent. Thus, electron displacement can be enhanced by electron-donating substituents on the coupler constituent. The resulting increased polarizability should result in bathochromism. Apparently this is demonstrated; thus, for example, compared to the simple aniline coupler (*N*-ethyl-*N*-2,3-dihydroxypropyl-*m*-toluidine), *N,N*-bis(2-hydroxyethyl)-2-methoxy-5-acetamidoaniline yields a 5-nitro-2-thiazolylazo dye with a bathochromic shift of 33 mμ in the λ_{max} value.[19]

Electron-attracting substituents on the coupler cause hypsochromic shifts in the dye. Thus, *m*-chloroaniline couplers, relative to *m*-toluidine couplers, shift the color of the azo dye toward red.[20] Electron-attracting substituents in the dialkylamino group of the coupler also produce hypsochromic shifts. The following series of 5-nitro-2-thiazolylazo dyes incorporating fluorine-containing couplers[21] shows this hypsochromic shift. The shift is in the order predicted from the effect of fluorine on physical properties (*e.g.*, boiling point, basicity). The change in color is from blue to violet and suggests increasing interference with the

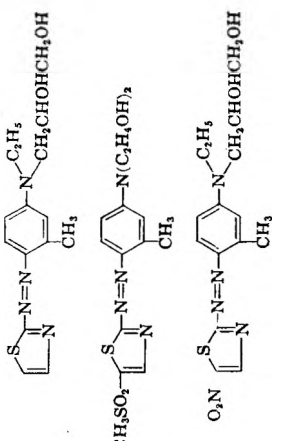
(19) J. B. Dickey, E. B. Towne, M. S. Bloom, W. H. Moore, B. H. Smith, Jr., D. G. Hedberg, *J. Soc. Dyers and Colourists*, 74, 123 (1958).

(20) Unpublished results.

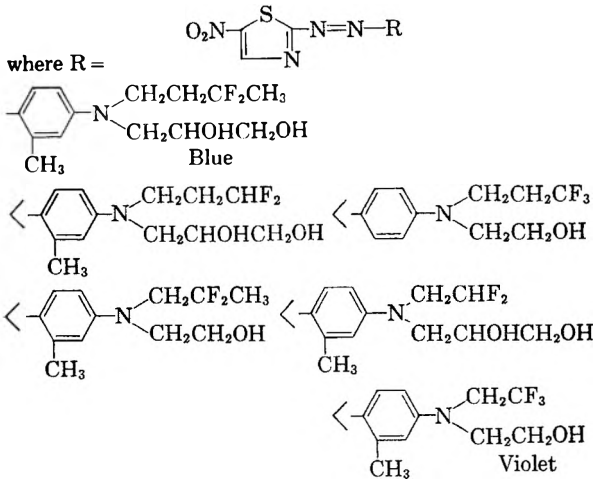
(21) J. B. Dickey, *et al.*, *Ind. Eng. Chem.*, 46, 2213 (1954).

TABLE V

BATHOCHROMISM OF 2-THIAZOLYLAZO DYES

	$\lambda_{max}^{CH_3OH}$, mμ	$\lambda_{max}^{CH_3OH}$, mμ	$\Delta\lambda_{max}^{CH_3OH}$, mμ
	502	420	+82
	544	450	+94
	593	495	+98
		597	—

electron-donating properties of the dialkylamino group, the interference being dependent on the number of fluorine atoms and the proximity to the amino nitrogen atom.



Significance of the 2-thiazolylazo structure. The greatest significance of this work is the color shift from the red of azo dyes derived from *p*-nitroaniline to the blue of analogous azo dyes derived from 2-amino-5-nitrothiazole. It should be emphasized, however, that bathochromism relative to the benzene analogs is exhibited by all the 2-thiazolylazo dyes studied. Negative groups strategically placed in the thiazole ring are not required in order to bring about a bathochromic shift; for example, dyes from 2-aminothiazole display this effect.

As shown in Table V by the comparison of analogs incorporating a simple aniline coupler, the bathochromism of the 2-thiazolylazo dyes is an inherent property of the thiazole system itself; the bathochromism does not derive from the substituent groups. However, the greater polarizability of the thiazole system (relative to the benzene system), in addition to effecting a general bathochromism in 2-thiazolylazo dyes, also allows a greater electronic displacement to be effected by electronegative substituents. This displacement results in an increased absorption shift from the benzene analog in the 5-methylsulfonyl-2-thiazolylazo dye (+94 mμ) and the 5-nitro-2-thiazolylazo dye (+98 mμ) compared to the 2-thiazolylazo dye (+82 mμ).

The bathochromism displayed by the 2-thiazolylazo dyes is not unique. For example, a bathochromic shift characterizes the chalcone derivatives of thiophenes described by Buu-Hoï.[22] Triarylmethane dyes containing a thiophene ring exhibit a shift in absorption of the y-band to longer wave lengths.[23] However, the magnitude of the bathochromic shift (80–100 mμ) exhibited by the 2-

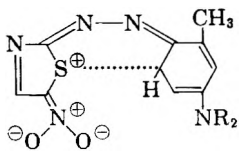
(22) N. P. Buu-Hoï, N. Xuong, and M. Sy, *Bull. soc. chim. France*, 1646 (1956).

(23) V. V. Ghaisas, B. J. Kane, and F. F. Nord, *J. Org. Chem.*, **23**, 560 (1958).

thiazolylazo dyes and the recently described 2-thienylazo dyes[19] is remarkable. To illustrate, a blue dye (λ_{max} 593 mμ) is obtained in the 5-nitro-2-thiazolylazo series with a simple aniline coupler. A blue phenylazo dye (λ_{max} 597 mμ) is obtained only in certain cases, for example, when the diazonium constituent contains three highly negative groups and when the coupler is one conferring a pronounced bathochromic effect (Table V). The dye from 2-amino-5-nitrothiazole and this coupler is, however, much greener (λ_{max} 628 mμ).

To effect the bathochromism of these thiazolylazo and thienylazo dyes, the energy difference between the ground states and the excited states must be less than for the analogous phenylazo dyes. On the basis of the presumably greater polarizability of the 2-thiazolyl system than the phenyl system, the 2-thiazolylazo dyes would be expected to have greater resonance stabilization of the excited states than analogous phenylazo dyes. However, the lower energy difference of the 2-thiazolylazo dyes (and the 2-thienylazo dyes) may be due to less resonance stabilization of the ground state: the 2-thienylazo dyes[19] are also bathochromic and the resonance energy of thiophene is less than that of benzene.[24] The possibility that both more excited-state stabilization and less ground-state stabilization participate in the bathochromism of 2-thiazolylazo and 2-thienylazo dyes cannot be disregarded.

In addition to conventional excited-state structures which involve polarized *trans* configurations, there is a novel structural possibility for the 2-thiazolylazo and 2-thienylazo dyes which provides an alternative explanation for the bathochromic shift. The decreased difference in energy levels between ground and excited states may be attributed to additional resonance stabilization of the excited state through contributions of a cyclic form.



(24) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N. Y., 1942, pp. 136, 138.

(25) The cyclic structure requires that the azo compound assume the cis configuration. Although comparison of *cis-trans* isomers of azobenzenes[45] indicates that the *cis*-2-thiazolylazo configuration should be less stable than the trans configuration, the cyclic structure, which cannot exist for the *cis*-azobenzenes, would possibly tend to overcome this instability. However, from the configuration of *cis*-azobenzene[45] it would be inferred that the *cis*-2-thiazolylazo configuration would not be coplanar nor would the C-S distance be such as to suggest effective interaction to yield a cycle. By comparison with *cis-trans* isomers of azobenzene[46-49] it would be expected that dyes with the *cis*-2-thiazolylazo configuration would absorb less intensely than those with the *trans*. The high intensity of the absorption by the 2-thiazolylazo dyes thus does not support the postulated *cis* form.

In addition to other objections,[25] the bathochromism of triarylmethane dyes containing a thiophene[23] ring seems an effective argument against such a structure, since these dyes are bathochromic, but presumably would not form an analogous cyclic structure. Attempts to evaluate the possibility of the existence of the cyclic form by the preparation of certain 2-thiazolylazo dyes have been inconclusive. The introduction of electron-donating or electron-attracting groups at suitable positions in the coupler ring should modify the tendency for the formation of the cyclic structure and thereby modify the absorption characteristics of the dyes. All modifications examined produced hypsochromic shifts. The introduction of a nitro group did not confer the required bathochromism. The hypsochromism caused by methyl and methoxyl groups is common to analogous phenylazo dyes as well. Thus, although in agreement with the expected effect, this hypsochromism cannot unequivocally be ascribed to the existence of the cyclic form.

Orientation upon nitration of 2-amino-4-phenylthiazoles. The nitration of 2-aminothiazoles having a phenyl or a substituted phenyl group in the 4-position has not been previously described. Attempts to nitrate 2-acetamido-4-phenylthiazole were reported unsuccessful.[26] The nitration of bis-(4-phenyl-2-thiazolyl)amine reportedly yields bis-(4-phenyl-5-nitro-2-thiazolyl)amine as the only nitration product.[27] The possible effect of the particular nitration conditions (concentrated nitric acid, concentrated sulfuric acid, and boiling acetone) on the orientation was not investigated in the present study.

In a previous paper,[14] the behavior of certain 2-amino-4-alkylthiazoles upon nitration was described. In the course of synthesizing dye intermediates for the present work, the behavior of certain 2-amino-4-phenylthiazoles upon nitration was studied.

The composition of the nitration products was established by chemical studies in addition to elemental analysis and comparison with reference compounds by infrared spectroscopy, ion exchange paper chromatography, and melting point determination. Thus, 2-amino-4-(*p*-nitrophenyl)thiazole, formed by nitration of 2-amino-4-phenylthiazole, was compared with the authentic sample prepared from *p*-nitrophenacyl bromide and thiourea. The nitration product from 2-acetamido-4-phenylthiazole was hydrolyzed to 2-amino-4-(*p*-nitrophenyl)-thiazole. The dinitration product from 2-amino-4-phenylthiazole and the mono-nitration product from 2-amino-4-(*p*-nitrophenyl)thiazole were compared by oxidation to *p*-nitrobenzoic acid. No dinitrobenzoic acid was detected, thus confirming the formation of the 5-nitrothiazolyl compound.

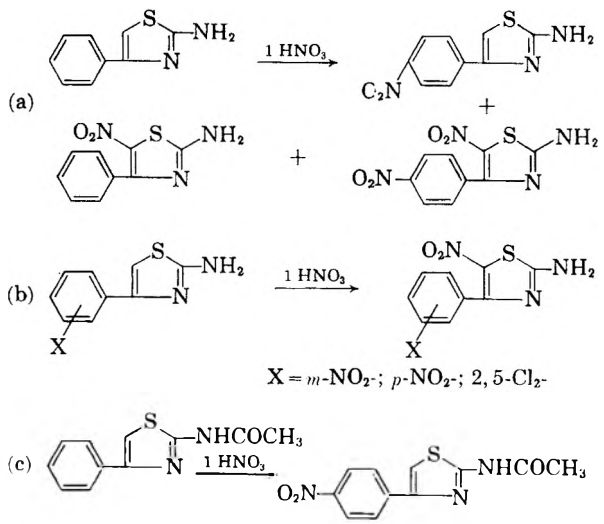
(26) M. T. Bogert and M. Chertcoff, *J. Am. Chem. Soc.*, 46, 2864 (1924).

(27) H. Beyer and G. Berg, *Ber.*, 89, 1602 (1956).

An authentic sample of 2-amino-4-phenyl-5-nitrothiazole was not available; its identity was inferred from infrared spectroscopic data.

It was also found convenient and feasible to convert the crude nitration products to azo dyes for paper chromatography. The R_f values were compared with those of reference dyes for identification. In fact, just from the color of the chromatography zones of separated azo dyes, the general nature of the 2-aminothiazole could be inferred. If the zone was blue, the dye contained a 5-nitrothiazolyl moiety and possibly also was nitrated in the phenyl group; if the zone was red, the dye was nitrated, if at all, only in the phenyl group. These inferences could also be drawn, although less exactly, from the color of the dye in solution or on cellulose acetate.

The incorporation of a phenyl group or a substituted phenyl group into 2-aminothiazole made the formation of mixtures on nitration with one equivalent of nitric acid a possibility; that is, nitration could take place on the phenyl ring, the thiazolyl ring, or both. In the case of 2-amino-4-phenylthiazole, such a mixture was formed. However, the 2-amino-4-(substituted phenyl)-thiazoles nitrated only in the 5-thiazolyl position, and 2-acetamido-4-phenylthiazole nitrated only in the *p*-phenyl position.



Bromination,[28] thiocyanation,[29] nitrosation,[30] and mercuration[31] of 2-amino-4-phenylthiazoles and 2-acetamido-4-phenylthiazoles reportedly yield 5-thiazolyl substitution exclusively. In these reactions the orientation is not affected by the nature of the attacking reagent or by the nature of the thiazole compound. Therefore, in this present work, the orientation of 2-amino-4-phenylthiazole (in part) and 2-acetamido-4-phenylthiazole on nitration to yield the *p*-phenyl-substituted product is anomalous to their other substitution reactions. The 2-amino-4(substituted phenyl)thiazoles studied did, however, yield only the 5-thiazolyl derivatives, but it is not unexpected that the 2-aminothiazolyl moiety nitrates preferentially compared to the *p*-nitrophenyl group, the *m*-nitrophenyl group, or the 2,5-dichlorophenyl group. Investigation of the nitration product from 2-amino-4-(*p*-acetamidophenyl)-thiazole was inconclusive since no pure compound could be isolated.

The orientation upon nitration of 2-acetamido-4-phenylthiazole to yield the *p*-nitrophenyl derivative suggests that the phenyl group is more reactive than the 2-acetamidothiazolyl moiety. Nitration of the phenyl group would not be expected in view of the orientation to the 5-thiazolyl position in other substitution reactions of 2-amino-4-phenylthiazole and 2-acetamido-4-phenylthiazole. However, the 2-acetamido group should be less effective than the 2-amino group in activating the 5-thiazolyl position, and thus orientation on nitration could be different.

The major components of the nitration product of 2-amino-4-phenylthiazole and one equivalent of nitric acid were 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole and 2-amino-4-(*p*-nitrophenyl)thiazole. Some 2-amino-4-phenyl-5-nitrothiazole was also formed, and some starting material was recovered. Similar nitration conditions, except for shorter reaction time, gave essentially the same products. The use of only 0.75 equivalent of nitric acid, however, gave a nitration product in which 2-amino-4-phenyl-5-nitrothiazole was not detected by infrared spectroscopy. Nitration with two equivalents of nitric acid yielded the expected 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole, together with a small amount of an unidentified compound. Conversion of the nitration product to the azo dye yielded only the dye from 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole.

EXPERIMENTAL[32]

Preparation of intermediates. Procedures for the preparation of new compounds illustrate the various types of 2-aminothiazoles used in this work. The properties of new compounds are reported in Table I; known compounds used are listed.

2-Amino-4-(p-nitrophenyl)thiazole. This compound was prepared in 44% yield by an adaptation of the method for the preparation of the *m*-nitrophenyl compound[33] by treating *p*-nitroacetophenone[34,35] and thiourea with bromine on

(28) (a) E. Hoggarth, *J. Chem. Soc.*, 114 (1947); (b) Y. Garreau, *Compt. rend.*, **222**, 963 (1946); (c) G. N. Mahapatra, *J. Am. Chem. Soc.*, **79**, 988 (1957).

(29) C. D. Hurd and H. L. Wehrmeister, *J. Am. Chem. Soc.*, **71**, 4007 (1949).

(30) H. Beyer and H. Drews, *Ber.*, **87**, 1500 (1954).

(31) G. Travagli, *Gazz. chim. ital.*, **78**, 598 (1948); M. K. Raut, *J. Indian Chem. Soc.*, **33**, 741 (1956); B. Das, *J. Sci. Ind. Research (India)*, **15B**, 613 (1956).

(32) Melting points are uncorrected.

(33) R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).

(34) H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

(35) A. H. Ford-Moore and H. N. Rydon, *J. Chem. Soc.*, 679 (1946).

a steam bath. Recrystallization from a pyridine-water mixture gave a product melting at 266°.

In another preparation in which *p*-nitrophenacyl bromide was used, an improved yield (72%) was obtained. This method was adapted from the method of Hurd and Kharasch[36] for the preparation of the corresponding *m*-nitrophenyl compound.

2-Amino-5-butylsulfonylthiazole. A mixture of 18 g. (0.2 mole) of 1-butanethiol and 8 g. (0.2 mole) of sodium hydroxide in 140 ml. of water was stirred under nitrogen on a steam bath. A solution of 52 g. (0.2 mole) of 2-amino-5-bromothiazole hydrobromide[11] in 120 ml. of water and 120 ml. of ethyl alcohol was added. To this mixture a solution of 8 g. (0.2 mole) of sodium hydroxide in 20 ml. of water was then added. After the mixture had been stirred and refluxed for 4 hr., it was concentrated under reduced pressure, then cooled in ice to yield 27 g. (72%) of a sticky, brown solid. The 2-amino-5-butylthiothiazole was purified by continuous extraction with pentane in a Soxhlet apparatus. The extract yielded 19 g. (51%) of light tan platelets, m.p. 66–68°.

A mixture of 6.8 g. (0.036 mole) of 2-amino-5-butylthiothiazole, 4.1 g. (0.036 mole) of acetic anhydride, and 25 ml. of acetic acid was allowed to stand overnight at room temperature. After being heated on a steam bath for 30 min., the solution was poured onto ice to yield 8.4 g. (100%) of 2-acetamido-5-butylthiothiazole, m.p. 141–143°. Recrystallization from hexane gave the analytical sample, m.p. 143–144°.

A mixture of 7.8 g. (0.034 mole) of 2-acetamido-5-butylthiothiazole, 17 g. (0.14 mole) of a 30% solution of hydrogen peroxide, and 75 ml. of acetic acid was allowed to stand overnight at room temperature. After being heated on a steam bath for 2 hr., the reaction mixture was cooled and filtered. The product was recrystallized from ethyl alcohol to obtain 4 g. (45%) of 2-acetamido-5-butylsulfonylthiazole, m.p. 242–243°. The filtrate was concentrated to yield 1.7 g. of starting material, m.p. 140–143°.

A mixture of 20 ml. of concentrated hydrochloric acid, 10 ml. of water, and 2 g. (0.0076 mole) of 2-acetamido-5-butylsulfonylthiazole was refluxed with stirring for 2 hr. The solution was diluted with an equal volume of cold water and brought to a *p*H of 6 with solid sodium acetate. The resulting white solid was filtered and washed with water to yield 1.2 g. (72%) of 2-amino-5-butylsulfonylthiazole, m.p. 94–95° after recrystallization from benzene.

Hydrogen peroxide derivative of 2-amino-5-butylsulfonylthiazole. In an attempt to prepare 2-amino-5-butylsulfonylthiazole directly[37] from 2-amino-5-butylthiothiazole by oxidation with hydrogen peroxide, a product different from the authentic compound derived from 2-acetamido-5-butylthiothiazole was obtained. Oxidation of 9.4 g. of 2-amino-5-butylthiothiazole with hydrogen peroxide in acetic acid gave 7 g. of a white solid, m.p. 166–167° after recrystallization from ethyl alcohol. The melting point and analysis do not agree with those of authentic 2-amino-5-butylsulfonylthiazole (see Table I). Although in poor agreement with calculated values, the analysis indicates the addition of four oxygen atoms and the empirical formula $C_7H_{14}N_2O_4S_2$.

Anal. Calcd. for $C_7H_{14}N_2O_4S_2$: C, 33.0; H, 5.5; N, 11.0; O, 25.2; S, 25.2. Found: C, 31.32; H, 4.95; N, 10.41; S, 27.76.

The same compound (m.p. 170–171°) was obtained by using the same oxidation conditions with authentic 2-amino-5-butylsulfonylthiazole, m.p. 94–95°. The melting point of a mixture of the two hydrogen peroxide derivatives was undepressed, m.p. 168–170°.

(36) C. D. Hurd and N. Kharasch, *J. Am. Chem. Soc.*, 68, 653 (1946).

(37) J. Goerdeler and P. Linden [*Ber.*, 89, 2742 (1956)] reported the direct oxidation of 5-amino-3-ethylthio-1,2,4-thiadiazole to the corresponding sulfoxide and sulfone. The conditions used (monoperoxyphthalic acid in chloroform at −30°) may account for their success.

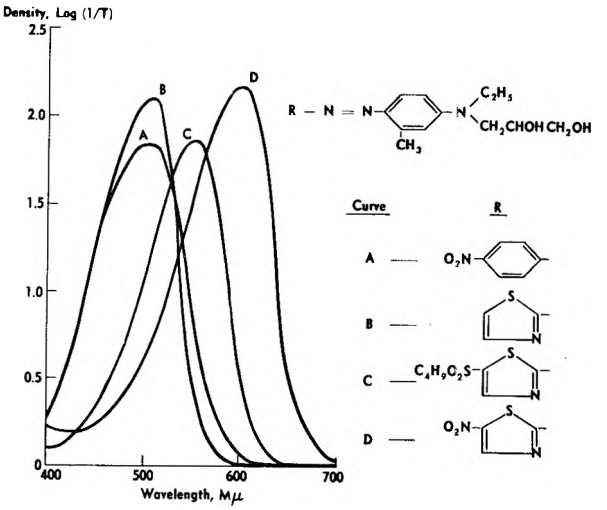


Fig. 1. Color-deepening effect of 5-substitution in 2-thiazolylazo dyes

A melting point of a mixture with authentic 2-amino-5-butylsulfonylthiazole was depressed, m.p. 94–163°. The analysis of the hydrogen peroxide derivative obtained from 2-amino-5-butylsulfonylthiazole was the same as that obtained from 2-amino-5-butylthiothiazole.

Anal. Found: C, 31.36; H, 5.01; N, 10.40; S, 27.81; O, 23.76.

The standard peroxide test (KI/HOAc) demonstrated only trace amounts of peroxide in the hydrogen peroxide derivative. However, refluxing the hydrogen peroxide derivative in deaerated acetic anhydride (under nitrogen) in the presence of potassium iodide resulted in a strong peroxide test. Similar procedures with dilute hydrochloric acid also resulted in a strong peroxide test. It is noteworthy that these two reactions were found to convert the hydrogen peroxide derivative to 2-amino-5-butylsulfonylthiazole or its acetyl derivative.

The hydrogen peroxide derivative is characterized by the following infrared absorption bands: 6.25, 8.37, 9.05, 9.30, 9.65, 9.80, 10.40, 10.55, 11.2, 11.5, and 14.4μ. The 2-amino-5-butylsulfonylthiazole hydrogen peroxide derivative shows marked pertubation of the NH_2 stretching absorption. There is a shift of these absorptions from 2.95 and 3.00μ for 2-amino-5-butylsulfonylthiazole to a broad absorption centered at 3.06μ. This shift suggests amino group involvement in the structure of the hydrogen peroxide derivative (in confirmation of its chemical behavior) possibly by hydrogen bonding of the amino group with the oxygen.

The infrared spectrum shows no relation to that of urea hydroperoxidate, amine oxides, or gramine oxide-hydrogen peroxide derivative.[38]

Acetylation of the hydrogen peroxide derivative of 2-amino-5-butylsulfonylthiazole gave a good yield of a white solid, m.p. 242–244° after recrystallization from ethyl alcohol. The melting point of a mixture with authentic 2-acetamido-5-butylsulfonylthiazole (m.p. 242–243°) was not depressed, m.p. 241–243°. These compounds were also shown to be identical by infrared spectroscopy.

A sample of the hydrogen peroxide derivative of 2-amino-5-butylsulfonylthiazole was refluxed for 2 hr. with 10% hydrochloric acid solution to yield a white solid, m.p. 91–94° after recrystallization from benzene. The melting point of a mixture with authentic 2-amino-5-butylsulfonylthiazole (m.p. 94–95°) was undepressed, m.p. 92–94°.

In another reaction which also involved cleavage of the hydrogen peroxide derivative, diazotization converted it to

(38) D. W. Henry and E. Leek, *J. Am. Chem. Soc.*, 79, 5254 (1957).

a dye which paper chromatography showed to be identical to the dye from 2-amino-5-butylsulfonylthiazole.

2-Amino-5-methylsulfonylthiazole. To a solution of 20 g. (0.5 mole) of sodium hydroxide in 200 ml. of water was added 20 g. (0.1 mole) of 2-acetamido-5-thiocyanatothiazole.[29,39] The thiazole was hydrolyzed[40] under a nitrogen atmosphere on a steam bath for 1 hr.; the color of the solution changed from orange-red to cherry red. The stirred solution was cooled to 0°, and 12.6 g. (0.1 mole) of dimethyl sulfate was added dropwise. During the addition, a brown-buff, crystalline solid separated. The reaction mixture was allowed to stand at room temperature overnight under nitrogen. The solid was then collected on a filter, washed with water until neutral, and dried. The brown-buff crystals of 2-amino-5-methylthiothiazole weighed 7.8 g. (53% yield) and melted at 125–130°. A sample recrystallized from hexane melted at 130–133°.

A solution of 7.4 g. (0.05 mole) of 2-amino-5-methylthiothiazole and 5.7 g. (0.055 mole) of acetic anhydride in 25 ml. of acetic acid was allowed to stand overnight at room temperature. The solution was concentrated and poured onto ice. The precipitate was filtered, washed with water, and dried to obtain 8.9 g. (95%) of 2-acetamido-5-methylthiothiazole, m.p. 192–195° after recrystallization from ethyl alcohol.

To a suspension of 7 g. (0.037 mole) of 2-acetamido-5-methylthiothiazole in 50 ml. of acetic acid was added 17 g. (0.15 mole) of a 30% solution of hydrogen peroxide. The temperature of the reaction mixture rose to 40° and solution was effected. The solution was allowed to stand overnight at room temperature, and then it was warmed on a steam bath for several hours. The solution was concentrated to yield 2.8 g. (35% yield) of 2-acetamido-5-methylsulfonylthiazole, m.p. 270–271° after recrystallization from ethyl alcohol. A mixture of 10 ml. of concentrated hydrochloric acid, 5 ml. of water, and 2.5 g. (0.01 mole) of 2-acetamido-5-methylsulfonylthiazole was refluxed for 2 hr. When the solution had cooled, colorless crystals formed. After the cold solution had been neutralized, the product was collected on a filter, washed with water, and dried to yield 1.8 g. (92%) of 2-amino-5-methylsulfonylthiazole, m.p. 176–178° after recrystallization from ethyl alcohol.

By the use of the hydrolysis method of Bellavita and Vantaggi,[40] 2-amino-4-phenyl-5-thiocyanatothiazole[29] was similarly converted to the sodium mercaptide derivative, which was directly methylated by the above method to yield 2-amino-4-phenyl-5-methylthiothiazole (63%). It was quantitatively acetylated to yield 2-acetamido-4-phenyl-5-methylthiothiazole, m.p. 204° after recrystallization from ethyl alcohol.

2-Amino-4-(p-nitrophenyl)-5-nitrothiazole. 2-Amino-4-(*p*-nitrophenyl)thiazole (4.4 g., 0.02 mole) was slowly dissolved in 20 ml. of concentrated sulfuric acid which was stirred and kept at 10–12°. While the sulfuric acid solution was stirred at 4°, 1 ml. (0.02 mole) of 90% nitric acid was added at such a rate that the temperature remained constant. The stirred reaction mixture was then allowed to warm to room temperature. After standing overnight, it was poured into ice water with stirring. The resulting precipitate was collected on a filter and washed with water until neutral to yield 5.2 g. (98%), m.p. 251–252° after recrystallization from acetic acid.

Ethyl 2-amino-5-nitro-4-thiazolecarboxylate. It has been reported that the nitration of either ethyl 2-amino-4-thiazolecarboxylate or its acetyl derivative yields only unreacted starting material.[18] In the present work nitration was satisfactorily effected, although in some runs the crude nitration product tended to decompose.

To 50 ml. of concentrated sulfuric acid, kept below 15° by means of an ice bath, 17.2 g. (0.1 mole) of ethyl 2-amino-4-thiazolecarboxylate[41] was added. Then 5 ml. of fuming nitric acid was added while the temperature was kept below 15°. After the acid had been added, the bath was allowed to warm to room temperature overnight. The yellow solution was poured onto ice, and the yellow solid that separated was collected by filtration. Neutralization of the filtrate with ammonium hydroxide yielded more solid. The combined solids were recrystallized from ethyl alcohol to yield 4.0 g. (19.4%) of ethyl 2-amino-5-nitro-5-thiazolecarboxylate, m.p. 178–181°.

Determination of products from nitration of 2-amino-4-phenylthiazole. I. *Nitration with one equivalent of nitric acid: long reaction time.* To 47 ml. of concentrated sulfuric acid in a 100-ml. three-necked flask, 8.8 g. (0.05 mole) of 2-amino-4-phenylthiazole was added at 10–14° with stirring. The stirred solution was treated at 3–5° over a period of 30 min. with a mixture of 3.5 g. (0.05 mole) of fuming nitric acid (sp. gr. 1.49–1.50) and 3 ml. of concentrated sulfuric acid. Stirring was continued for 15 min. at this temperature. After the stirred reaction mixture warmed to room temperature, it was allowed to stand overnight protected from moisture.

The reaction mixture was poured into 500 ml. of an ice-water mixture, yielding a reddish solid which was collected on a filter. The product was washed with cold water, then with saturated sodium acetate solution until it was neutral to Congo Red paper. After the product, Fraction A, was washed with water and dried in air, it weighed 6.4 g., m.p. 228–230° (dec.).

The combined filtrate and washings from Fraction A, after being neutralized to Congo Red paper, were chilled to yield 1.2 g. of a yellow solid, Fraction B, m.p. 192–200° (dec.).

The filtrate from Fraction B was neutralized to litmus paper with 20% sodium hydroxide solution yielding 1.7 g. of a solid, Fraction C, m.p. 143–145°.

Fraction A was shown by infrared spectroscopy to be a mixture of 2-amino-4-(*p*-nitrophenyl)thiazole and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. The mononitro compound is characterized by absorption bands at 7.55, 8.3, 9.6, 11.85, and 13.85μ. The dinitro compound is characterized by bands at 7.85, 11.55, 12.15, 13.43, and 14.1μ.

In another nitration experiment the material corresponding to Fraction A was studied by paper chromatography and by ion exchange paper chromatography (see *Chromatographic Methods*). By comparison of the nitration product with concurrently chromatographed reference compounds, again both 2-amino-4-(*p*-nitrophenyl)thiazole and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole were identified. The crude dye incorporating the *m*-toluidine coupler was prepared, and by concurrently chromatographing reference dyes, the dyes from both 2-amino-4-(*p*-nitrophenyl)thiazole and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole were identified. Evidence for the presence of 2-amino-4-phenyl-5-nitrothiazole in very low concentration was found in both the ion exchange paper chromatogram of the nitration product and in the paper chromatogram of the dye prepared from this mixture.

Fraction B was identified by infrared spectroscopy as a mixture of 2-amino-4-(*p*-nitrophenyl)thiazole and possibly 2-amino-4-phenyl-5-nitrothiazole. Infrared absorption bands at 8.8, 12.6, and 14.3μ characterize the compound tentatively identified as 2-amino-4-phenyl-5-nitrothiazole. The ion exchange paper chromatogram of Fraction B confirmed the presence of 2-amino-4-(*p*-nitrophenyl)thiazole and the compound tentatively identified as 2-amino-4-phenyl-5-nitrothiazole. A trace amount of 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole was also detected.

In Fraction C, the starting material, 2-amino-4-phenylthiazole, which is characterized by infrared absorption bands at 9.7, 10.95, 14.5, 14.95, and 15.2μ, was identified.

(39) V. Bellavita, *Ann. chim. appl.*, **38**, 449 (1948); *Chem. Abstr.*, **44**, 154 (1950).

(40) V. Bellavita and L. Vantaggi, *Ann. chim. (Rome)*, **41**, 194 (1951); *Chem. Abstr.*, **46**, 486 (1952).

(41) H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **30**, 1201 (1947).

II. *Nitration with one equivalent of nitric acid: short reaction time.* This experiment was similar to I. It differed only in reaction time. Instead of allowing the reaction mixture to stand overnight, it was poured into an ice-water mixture after stirring at 2–5° for 10 min. following the addition of nitric acid. The nitration product was fractionated as described in I.

Fraction A, m.p. 223° (dec.) weighed 7.7 g. It was identified by infrared spectroscopy as a mixture of 2-amino-4-(*p*-nitrophenyl)thiazole and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. Oxidation of a portion of Fraction A by sodium dichromate yielded a main fraction of pure *p*-nitrobenzoic acid; a small second fraction consisted of *p*-nitrobenzoic acid and an unidentified nonacidic compound. Benzoic acid was not detected in these fractions by infrared spectroscopy.

Fraction B, m.p. 187–190° (dec.), weighed 0.6 g. and was identified by infrared spectroscopy as a mixture of 2-amino-4-phenylthiazole, the compound tentatively identified as 2-amino-4-phenyl-5-nitrothiazole, 2-amino-4-(*p*-nitrophenyl)thiazole, and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. The paper chromatogram of the dye from Fraction B showed the presence of the azo dyes from all four of the amines that infrared spectroscopy had indicated.

Fraction C, m.p. 139–142°, weighed 1.4 g. It was shown by infrared spectroscopy to contain 2-amino-4-phenylthiazole.

III. *Nitration with 0.75 equivalent of nitric acid.* This experiment was also similar to I. It differed only in that the amount of nitric acid used (2.6 g., 0.0375 mole) was 75% of the theoretical amount.

Fraction A, m.p. 202–203°, weighed 5.1 g. It was identified by infrared spectroscopy as a mixture of 2-amino-4-(*p*-nitrophenyl)thiazole and 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole.

Fraction B, m.p. 138–142°, weighed 1.9 g. It was shown by infrared spectroscopy to contain principally 2-amino-4-phenylthiazole.

IV. *Nitration with two equivalents of nitric acid.* This experiment was also similar to I. It differed in that two equivalents (7.0 g., 0.10 mole) of nitric acid were used. The crude product, m.p. 221–226°, weighed 11.9 g. and represented an 89.5% yield of 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. A sample recrystallized from a benzene–ethyl alcohol mixture melted with decomposition at 250–251°, in agreement with the melting point of the authentic compound.

The azo dye from the crude nitration product was shown by paper chromatography to be identical with the authentic dye from 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. No other components were detected. However, by infrared spectroscopy the crude nitration product was shown to be a mixture consisting mainly of 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole. A small amount of an unknown compound characterized by an infrared absorption band at 12.63μ was also present. The failure of the unknown compound to form the azo dye suggests that it may not be a primary aromatic amine.

The recrystallized nitration product was found by infrared spectroscopy to be pure 2-amino-4-(*p*-nitrophenyl)-5-nitrothiazole.

Preparation of dyes, dyeing and testing. The 2-aminothiazoles were diazotized using nitrosylsulfuric acid and the resulting diazonium compounds were coupled in a propionic-acetic acid mixture, anhydrous sodium acetate being added to neutralize to Congo Red paper.[19]

Dyeings of 10-g. samples of jersey fabric knit from dull cellulose acetate filament yarn were made using 33.3-mg. dye samples.[19]

All fastness tests were in accordance with the procedures of the American Association of Textile Chemists and Colorists.[42]

(42) American Association of Textile Chemists and Colorists, *Technical Manual and Year Book*, Vol. 32, Howes Publishing Co., New York, N. Y., 1956, pp. 72–97.

Chromatographic methods. For paper chromatography of azo dyes, Whatman 3MM paper was used for samples of 10 to 20 μg., and Whatman seed-test paper[43] was used for samples of 10 to 100 mg. The samples were applied in acetone solution, the small samples being applied as spots, and the large samples being applied as streaks. Ascending development was more convenient than descending development and gave sharper separation of zones. Circular paper chromatography was found to be a useful and rapid method for determining the composition of crude dyes and for determining the best developer composition.

For these azo dyes an acetone-heptane mixture (3:7 v/v) was found to be generally very satisfactory for development. This developer caused satisfactorily rapid migration with requisite separation of zones.

To identify an azo dye, it was run concurrently on a strip of Whatman 3MM paper with reference dyes. From the color of spots and from their rate of migration from the base line (compared to that of reference dyes), it was possible to assign structures. Mixtures of dyes, such as those from the nitration product of 2-amino-4-phenylthiazole, did not cause difficulties in identification.

For ion exchange paper chromatography of 2-aminothiazoles, H. Reeve Angel Ion Exchange Paper, Grade SA-1 was used.[44] This strong acid ion exchange paper was furnished in Na^+ form. The H^+ form was regenerated by acidification with dilute hydrochloric acid (1:1) then treated with distilled water to remove mineral acid. After the paper had been dried, the samples in acetone solution were applied in spots. The top phase of a mixture of 250 ml. of butyl alcohol, 250 ml. of water, and 2 ml. of concentrated hydrochloric acid was used to obtain the chromatogram by ascending development.

Amines were identified by comparing their rates of migration with those of reference amines concurrently chromatographed on a strip of ion exchange paper.

Determination of visible absorption spectra. The absorption spectra given in Fig. 1 were obtained using a General Electric recording spectrophotometer. The dyes were studied as solutions in butyl alcohol at a concentration of 1 part in 50,000 by weight.

The λ_{max} values given in the tables were determined with a Cary recording spectrophotometer (Model 14) using a 1-cm. cell. The dyes were dissolved in anhydrous methanol, in a concentration giving a satisfactorily high absorbance. The dyes used for this determination were not given rigorous purification. However, careful purification by chromatography did not significantly affect the λ_{max} values.

For ϵ_{max} value determination and elemental analysis, dyes were purified by repeated paper chromatography. The ϵ_{max} values were obtained with a Cary recording spectrophotometer (Model 14) using a 1-cm. cell. The dyes were dissolved in anhydrous methanol in 7.5×10^{-6} mole/l. concentration.

Determination of infrared absorption spectra. The infrared absorption spectrograms were recorded on a Baird Infrared Recording Spectrophotometer (Model AB2) using the potassium bromide pressed-pellet technique.

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(49) The intensity of the weak absorption band of *cis*-azobenzene is greater than that of the trans isomer in the visible spectrum (λ_{max} around 430 mμ) because of an electronic transition of the type N → A. This transition involves electrons localized in the azo group. The electronic transition which is associated with the polarized, excited state of azobenzene (and other azo dyes) is of the type N → V. The absorption band in the azobenzene isomers related to this N → V transition (which is generally responsible for the color of azo dyes) is of much greater intensity for *trans*-azobenzene. In simple azobenzene derivatives, however, this band is in the ultraviolet region; in more polar derivatives, the N → V transition is in the visible region and thus determines the color of the dye.

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Acknowledgment. The authors are indebted to Dr. R. H. Wiley, University of Louisville, for valuable suggestions and help concerning the discussion of the relation of structure to the color of these azo dyes.

KINGSPORT, TENN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Ethyl *N*-Methyl-2-pyridone-4-carboxylate and Derivatives

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The alkaline potassium ferricyanide oxidation of *N*-alkylpyridinium salts has been used as a method for the preparation of 4-carboxy-*N*-methyl-2-pyridone which was converted into its ethyl ester and several other derivatives.

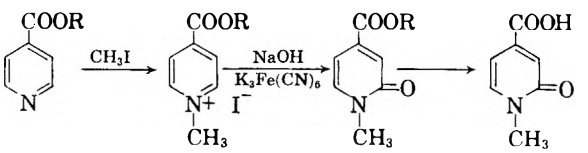
Although the 3-, 5-, and 6-, carboxy-*N*-methyl-2-pyridones have been reported in the literature,[2–5] we have found no report of *N*-methyl-4-carboxy-2-pyridone (I). The preparation of ethyl *N*-methyl-2-pyridone-4-carboxylate was undertaken in order to test the analgesic activity of this compound and several of its derivatives.

The alkaline potassium ferricyanide oxidation of *N*-methylpyridinium iodide to *N*-methyl-2-pyridone is a well established reaction.[6] Sugasawa and Suzuta[7] oxidized 1-(3,4-methylenedioxyphenethyl)-4-carbethoxypyridinium bromide with alkaline potassium ferricyanide to *N*-(3,4-methylenedioxyphenethyl)-4-carboxy-2-pyridone. M. L. Peterson[8] reported the alkaline ferricyanide oxidation of 2,5-dicarbomethoxy-*N*-methylpyridinium methosulfate and its betaine to *N*-methyl-5-carboxy-2-pyridone.

The alkaline ferricyanide oxidation of *N*-methyl-3-carboxamidopyridinium iodide has been widely studied. Most recently Pullman and Colowick[9] have demonstrated that both the 2- and 6-pyridones of *N*-methyl-3-pyridine carboxamide are formed upon oxidation.

Thyagarajan[10] has recently reviewed the alkaline potassium ferricyanide oxidation reaction.

The attempted alkaline potassium ferricyanide oxidation of both *N*-methyl-4-carboxypyridinium iodide and its betaine under the usual conditions[5,6] failed to yield any 2-pyridone, starting material being recovered. However the oxidation of the methiodides of isonicotinic acid esters were studied with greater success. The product isolated was the 4-carboxy-*N*-methyl-2-pyridone; the ester was never detected.



R = CH_3, CH_2CH_3, $CH(CH_3)_2$

It is generally accepted[10–12] that the oxidation takes place *via* the pseudo base. A more detailed postulation of the mechanism of the ferricyanide oxidation of *N*-alkylpyridinium hydroxides to form *N*-alkyl-2-pyridones is proposed by Bradlow and Vanderwerf.[13]

The yield of *N*-methyl-4-carboxy-2-pyridone depended on the rate of addition of the reagents to the reaction mixture. The sodium hydroxide solution was added to a concentrated aqueous solution

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of the pyridinium iodide at twice the rate of addition of the potassium ferricyanide solution. By decreasing the amount of pyridinium iodide used and keeping the rate of addition of reagents constant, the yield of 2-pyridone was increased from 46% to 96%.

When the addition time was kept constant, larger yields were obtained from the higher esters: 80% yield from the oxidation of *N*-methyl-4-carboisopropoxypyridinium iodide, 62% yield from *N* - methyl - 4 - carboethoxypyridinium iodide, and 46% from the oxidation of *N*-methyl-4-carbomethoxypryidinium iodide. The possibility of obtaining a quantitative yield from the oxidation of each of the pyridinium iodides would be greatly enhanced by adding the reagents over a period of several days.

Ethyl *N*-methyl-2-pyridone-4-carboxylate and *N*-methyl-2-pyridone-4-carboxamide were prepared from the acid *via* *N*-methyl-2-pyridone-4-carboxylic acid chloride and *N*-methyl-2-pyridone-4-carboxylic acid hydrazide was synthesized from the ester in the usual manner.

EXPERIMENTAL[14]

Oxidation of N-methyl-4-carbomethoxypyridinium iodide. *N*-Methyl-4-carbomethoxypyridinium iodide,[15] 2.00 g. (0.0073*M*), dissolved in water (10 ml.), was placed in an Erlenmeyer flask. Solutions of sodium hydroxide, 4.0 ml. (1.68 g., 0.242*M* in 3 ml. of water), and potassium ferricyanide, 12 ml. (4.8 g., 0.019*M* in 8 ml. of hot water), were prepared. At one-hour intervals, 1.0-ml. portions of sodium hydroxide and 1.5-ml. portions of potassium ferricyanide were added to the pyridinium salt solution with agitation after each addition. The heat of the reaction kept the mixture slightly above room temperature. The potassium ferricyanide solution was added warm to prevent precipitation. After the addition of the final 1.5-ml. portion of potassium ferricyanide, the reaction mixture was kept warm (40–55°) on a steam bath for 1 hr., then cooled and acidified with 6*N* hydrochloric acid. Granular crystals precipitated and were removed by filtration. Recrystallization from hot methanol yielded *N*-methyl-4-carboxy-2-pyridone, 1.05 g. (96%), m.p. 254–254.5°.

Anal. Calcd.: C, 54.91; H, 4.61; N, 9.15. Found: C, 54.80; H, 4.81; N, 9.07.

When this reaction was carried out on 25 and 50 g. samples of *N*-methyl-4-carbomethoxypyridinium iodide, yields of only 50% could be attained.

The oxidation of both *N*-methyl-4-carboxypyridinium iodide and the betaine of *N*-methyl-4-carboxypyridine[16] with alkaline potassium ferricyanide failed to give *N*-methyl-4-carboxy-2-pyridone.

Isopropyl isonicotinate. Isonicotinic acid, 20.0 g. (0.162*M*), was refluxed with thionyl chloride (80 ml.) for 0.5 hr. The excess thionyl chloride was removed *in vacuo* and isopropyl alcohol, 100 g. (1.66*M*), added; the reaction mixture was refluxed for 3 hr. Crystallization began upon cooling. After standing at room temperature overnight, the isopropyl isonicotinate hydrochloride was collected on a filter, washed with 50% isopropyl alcohol–ether followed by ether and dried; 26.5 g. (0.13*M*, 82%), m.p. 186–187° dec.

Isopropyl isonicotinate hydrochloride was converted to the free base by neutralization in aqueous solution with calcium carbonate, extraction with ether and distillation; b.p. 94–104° (7 mm.), 13.0 g. (60%). A sample for analysis was redistilled, b.p. 94° (3 mm.).

Anal. Calcd.: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.08; H, 6.64; N, 8.40.

The attempted preparation of *t*-butyl isonicotinate using this same procedure was unsuccessful.

N-methyl-4-carboisopropoxypyridinium iodide. A 95% yield of *N*-methyl-4-carboisopropoxypyridinium iodide, m.p. 139–141° (recrystallized from absolute ethanol–ether), was obtained according to the method of Supniewski and Serafinowna.[15]

Anal. Calcd.: C, 39.10; H, 4.59; N, 4.55; I, 41.32. Found: C, 38.91; H, 4.72; N, 4.42; I, 41.35.

Oxidation of N-methyl-4-carboisopropoxypyridinium iodide. The alkaline potassium ferricyanide oxidation of this pyridinium salt was carried out as before to give an 80% yield of *N*-methyl-4-carboxy-2-pyridone.

Oxidation of N-methyl-4-carboethoxypyridinium iodide. N-Methyl-4-carboethoxypyridinium iodide, m.p. 110–113° (made in 89% yield as indicated for the isopropyl ester) was oxidized by the general procedure described for the methyl ester to give a 62% yield of *N*-methyl-4-carboxy-2-pyridone.

N-Methyl-2-pyridone-4-carboxylic acid chloride. *N*-Methyl-4-carboxy-2-pyridone, 1.0 g. (0.065*M*), and purified thionyl chloride,[17] 16.3 g. (10 ml., 0.137*M*), were warmed at 55–60° for 1.5 hr. and the excess thionyl chloride was then removed by vacuum distillation. The crude acyl chloride crystallized upon cooling and was used as such in the following reaction.

Ethyl N-Methyl-2-pyridone-4-carboxylate. This acid chloride and absolute ethanol, 15.8 g. (20 ml., 0.344*M*), were refluxed for 2 hr. The excess ethanol was removed by vacuum distillation and the residue, insoluble in ether, was taken up in 50 ml. of chloroform, washed twice with 20-ml. portions of 0.5*N* sodium carbonate, and the organic layer dried over anhydrous magnesium sulfate. The chloroform was removed *in vacuo*, care being taken not to overheat the oily residue. Upon cooling, the oil crystallized and was recrystallized from 30 ml. of anhydrous ether. Ethyl *N*-methyl-2-pyridone-4-carboxylate, 1.0 g. (83%), m.p. 89°, was obtained as luminous, white crystals which were insoluble in *n*-hexane and soluble in water, dioxane, and ethanol.

Anal. Calcd.: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.64; H, 5.90; N, 7.64.

N-Methyl-2-pyridone-4-carboxylic acid hydrazide. A solution of ethyl *N*-methyl-2-pyridone-4-carboxylate, 1.0 g. (0.005*M*), in ethanol (2 ml.) and 95 hydrazine hydrate, 0.5 g. (0.01*M*), was warmed on a steam bath for 15 min. The hydrazide which crystallized upon cooling, was recrystallized twice from hot water; 0.74 g. (67%), m.p. 258–260°.

Anal. Calcd.: C, 50.29; H, 5.42; N, 25.14. Found: C, 50.33; H, 5.37; N, 25.32.

N-Methyl-2-pyridone-4-carboxamide. *N*-Methyl-4-carboxy-2-pyridone, 15.0 g. (0.98*M*), was converted to the acid chloride with thionyl chloride and was added slowly as the warm molten liquid to a vigorously stirred solution of concentrated ammonium hydroxide, 250 ml., over a period of 2.5 hr. The reaction mixture was then stirred on a steam bath for 1 hr. and evaporated to dryness under vacuum. The residue was extracted three times with 50-ml. portions

(14) All melting points are uncorrected. Microanalyses by Microchemical Specialties Co., Berkeley, Calif. The infrared spectra of each compound was taken and found to be compatible with the structures reported.

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of boiling methanol and the combined methanol extracts were cooled and filtered to recover the crude amide, which was recrystallized twice from methanol; 4.2 g. (28%) m.p. 234–36°.

Anal. Calcd.: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.45; H, 5.07; N, 18.05.

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STANFORD, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

2-Trifluoromethylpyrimidines[1]

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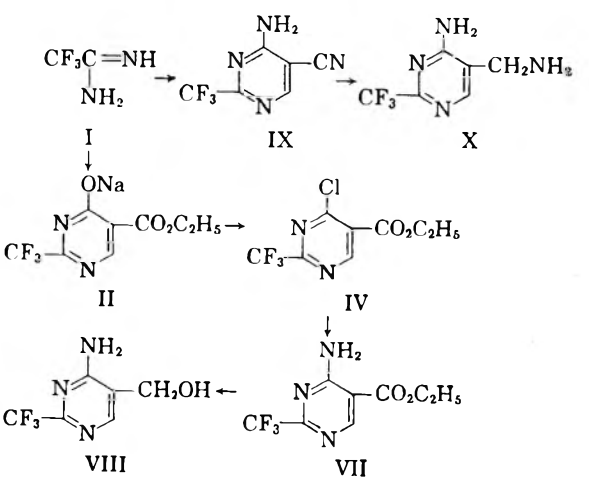
A series of 2-trifluoromethylpyrimidines has been synthesized from trifluoroacetamidine. Included was 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine which showed biological activity.

The discovery of 5-hydroxymethylcytosine in the deoxyribonucleic acid of the T-even bacteriophages of *Escherichia coli*[3a,b] is largely responsible for recent interest in related pyrimidines. The subsequent synthesis of this[4a,b] and other 5-hydroxymethylpyrimidines has led to compounds with interesting biological activity. Ulbricht and Price,[5] for example, have synthesized 4-amino-5-hydroxymethyl-2-methylthiopyrimidine (Methioprim) which has received some attention.[6]

It has been noted[7] that amethopterin-resistant mutants of *Bacillus subtilis* are collaterally sensitive to certain 2-substituted-4-amino-5-(substituted methyl)pyrimidines. The reversal of this inhibition by 4-amino-5-hydroxymethyl-2-methylpyrimidine suggested that these compounds are thiamine pyrimidine antagonists in this organism. Furthermore, since amethopterin is used clinically in cancer chemotherapy it was of interest to investigate further those pyrimidines related to the thiamin pyrimidine.

It is well known that there is a large difference in the electronic effect of the trifluoromethyl group and the methyl group but not a large difference in size. Since this type of substitution can lead to different biological activity, some 2-trifluoromethyl analogs of the thiamin pyrimidine were synthesized. Among the compounds prepared were 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (VIII) and 4-amino-5-aminomethyl-2-trifluoromethylpyrimidine (X). Because the reaction of acetamidine with (1) diethyl ethoxymethylenemalonate,[8] (2) ethoxymethylenemalononitrile,[9] and (3) ethyl ethoxymethylenecyanoacetate[8,10] had led to pyrimidines, these three routes were investigated with trifluoroacetamidine (I)[11,12] as starting material.

Diethyl ethoxymethylenemalonate was condensed with I in the presence of sodium ethoxide to form 5-carbethoxy-2-trifluoromethyl-4-hydroxypyrimidine (III). This was converted to 5-carbethoxy-4-chloro-2-trifluoromethylpyrimidine (IV). Low yields of IV were obtained from III but its sodium salt (II), obtained directly from the condensation, gave IV in 56% yield when treated with phosphorus oxychloride. This procedure is similar



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(2) To whom inquiries regarding this article should be sent. Present address, Department of Chemistry, Fairfield University, Fairfield, Conn.

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(10) Z. Foldi and A. Salamon, *Ber.*, **74**, 1126 (1941).

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(12) W. L. Reilly and Henry C. Brown, *J. Am. Chem. Soc.*, **78**, 6032 (1956).

to one found satisfactory for the preparation of 5-carbethoxy-4-chloro-2-methylthiopyrimidine.[13]

The reactivity of the 4-chloro atom in IV seemed comparable to that of the chloro in 2-alkylthio-5-carbethoxy-4-chloropyrimidines[13] in the reactions studied. The treatment of IV with ammonia and with *o*-chloroaniline gave the corresponding 4-amino (VII) and 4-(*o*-chloroanilino)pyrimidine (V) in good yield. Sodium phenoxide reacted with IV to give the expected 4-phenoxypyrimidine (VI). The reduction of VII with lithium aluminum hydride to give VIII was easily accomplished.

Ethoxymethylenemalonitrile and I gave 4-amino-5-cyano-2-trifluoromethylpyrimidine (IX), which was readily reduced with hydrogen and Raney nickel using a procedure analogous to that of Huber[14] for 2,4-diamino-5-aminomethylpyrimidine. Both X and its hydrochloride were prepared. The treatment of IX with 10% sodium hydroxide followed by acidification resulted in the preparation of the corresponding acid (XI). This compound was identical with the acid obtained by the saponification of VII. An amide(XII) was isolated when IX was heated with 0.1*N* sodium hydroxide in a manner similar to that used for 4-amino-5-cyano-2-methylthiopyrimidine.[15]

Although ethyl ethoxymethylenecyanoacetate has been condensed with amidines, ureas, and thioureas to form both 4-amino-5-carbethoxypyrimidines and 5-cyano-4-pyrimidones, depending upon which groups enter into the reaction, it apparently did not condense with I. In several experiments employing a variety of conditions the only substance identified was 1,3-dicarbethoxy-1,3-dicyano-1-propene (XIII).[16]

Although the synthetic intermediates were inactive, VIII was a potent inhibitor of *Bacillus subtilis*.[17] This inhibition, however, was distinctly different from that produced by certain other analogs of the thiamin pyrimidine; for example, inhibition by the other analogs was completely reversed by the metabolite, 4-amino-5-hydroxymethyl-2-methylpyrimidine,[7] whereas it caused only partial reversal of the inhibition by VIII. Further biological testing of the compounds prepared is in progress. The results will be reported elsewhere.

EXPERIMENTAL

Trifluoroacetamidine (I). This compound was prepared by the method of Husted[11] as modified by Reilly and Brown[12] in comparable yields. The compound gave off an ammonia odor and became viscous on standing.[11] The best yields of II and IX were obtained by using freshly prepared material.

5-Carbethoxy-2-trifluoromethyl-4-hydroxypyrimidine (III). Four tenths of a mole of sodium ethoxide was prepared by adding sodium to 400 ml. of absolute ethanol. Then, 44.8 g. (0.40 mole) of freshly prepared I dissolved in 40 ml. of absolute ethanol was added in one portion followed by 86.4 g. (0.40 mole) of diethyl ethoxymethylenemalonate during 15 min. with stirring. After dissipation of the heat of reaction, the mixture was refluxed for 3 hr. and allowed to stand overnight. The alcohol was evaporated at reduced pressure and 120 ml. of water was added. The voluminous solid which formed was filtered and washed with water and then with ether. The solid was recrystallized from acetone to give 75 g. (73%) of the crude sodium salt of III (II), m.p. 315–317°, which after recrystallization melted at 325–326°.

Five grams of crude II was dissolved in 100 ml. of water with heating, filtered, and made strongly acid by the addition of 7 ml. of 10% hydrochloric acid. A white solid formed. The mixture was extracted twice with 50 ml. of chloroform and the chloroform was allowed to evaporate. The residue was recrystallized from ligroine yielding 3.1 g. (68% from II) of III, m.p. 81–82°, which was again recrystallized from ligroine to obtain an analytical sample.

Anal. Calcd. for $C_6H_7F_3N_2O_3$: C, 40.69; H, 2.99; N, 11.86. Found:[18] C, 40.81; H, 3.42; N, 11.86.

Larger quantities of III were not prepared because a preliminary experiment using 4.4 g. of III indicated that only a 24% overall yield of VII from II could be obtained using a method analogous to that of Todd and Bergel[8] without isolation of IV. This was compared to 53% of VII from II as given in the following experiments.

5-Carbethoxy-4-chloro-2-trifluoromethylpyrimidine (IV). Twenty-seven milliliters of phosphorus oxychloride was added dropwise to 9.0 g. (0.035 mole) of II, which had been dried in a vacuum desiccator. Initially the rate of addition was slow to avoid overheating. The mixture was refluxed for 3 hr. and then the excess phosphorus oxychloride distilled at reduced pressure. Ice was added to the resulting product. The mass was extracted with ether and the ether extract was washed with water followed by potassium carbonate solution until the washings were no longer acid. Evaporation of the ether gave an oil which solidified after treatment with aqueous potassium carbonate. The crystalline mass was filtered, washed with water, and dried to give 5.2 g. (56%) of crude product, m.p. 38–39°, which was completely soluble in chloroform and was used directly for the preparation of VII. The analytical sample was obtained by recrystallizing twice from ethanol-water to give white needles, m.p. 41–42°.

Anal. Calcd. for $C_8H_6ClF_3N_2O_2$: C, 37.75; H, 2.38. Found: C, 37.74; H, 2.44.

5-Carbethoxy-4-(o-chloroanilino)-2-trifluoromethylpyrimidine (V). A solution of 1.02 g. (0.0040 mole) of IV and 1.02 g. (0.0080 mole) of *o*-chloroaniline in 10 ml. of ethanol was allowed to stand overnight. The solid formed was filtered and recrystallized from ethanol-water to give 1.03 g. (74%) of crude 5-carbethoxy-4-(*o*-chloroanilino)-2-trifluoromethylpyrimidine. The analytical sample, m.p. 138–139°, was obtained by recrystallizing twice from ethanol-water.

Anal. Calcd. for $C_{14}H_{11}ClF_3N_3O_2$: C, 48.73; H, 3.20. Found: C, 48.80; H, 3.13.

5-Carbethoxy-2-trifluoromethyl-4-phenoxypyrimidine (VI). A solution of 0.0050 mole of IV in 10 ml. of ethanol was added to a solution of 0.0050 mole of sodium phenoxide (prepared from phenol and sodium ethoxide) in 15 ml. of ethanol. The mixture was stirred for 0.5 hr. at room temperature and 0.5 hr. under reflux. The sodium chloride was filtered and 0.82 g. (52%) crude 5-carbethoxy-2-trifluoromethyl-4-phenoxypyrimidine was obtained by crystallization after the addition of water. The analytical sample, m.p. 65–66°, was obtained by recrystallizing twice from ethanol-water.

Anal. Calcd. for $C_{14}H_{11}F_3N_2O_3$: C, 53.95; H, 3.54. Found: C, 53.78; H, 3.53.

(13) E. Peters, J. F. Holland, H. Tieckelmann, B. Bryant, H. J. Minnemeyer, and C. Hohenstein, in preparation.
(14) W. Huber, *J. Am. Chem. Soc.*, 65, 2222 (1943).
(15) J. G. Nairn and H. Tieckelmann, in preparation.
(16) G. Errera, *Ber.*, 31, 1241 (1898).
(17) R. Guthrie, private communication.
(18) Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

4-Amino-5-carbethoxy-2-trifluoromethylpyrimidine (VII). Anhydrous ammonia was bubbled into a solution of 10.2 g. (0.040 mole) of crude IV in 60 ml. of absolute ethanol at 5°. After a short time crystal formation occurred. The mixture was kept cold for 1 hr. and then an equal volume of water was added. The product was cooled in an ice bath and the crystals were filtered, washed with water, and dried giving a yield of 8.9 g. (94%) of crude VII, m.p. 148–150°. The analytical sample, m.p. 150–151°, was obtained by recrystallizing twice from ethanol-water. A qualitative experiment indicated that VII can also be prepared from IV using concentrated ammonium hydroxide and 95% ethanol.

Anal. Calcd. for $C_8H_8F_3N_3O_2$: C, 40.85; H, 3.43. Found: C, 40.76; H, 3.62.

4-Amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (VIII). A solution of 7.05 g. (0.030 mole) of VII in 150 ml. anhydrous ether was added dropwise to 1.98 g. (0.051 mole) of lithium aluminum hydride in 300 ml. of ether during 1 hr. The mixture was refluxed for 80 min., cooled in an ice bath and hydrolyzed with water. After filtration, the filter cake was washed with ether. The ether solutions were evaporated (Soxhlet extraction of the filter cake gave negligible results). The residue was recrystallized from ethanol-benzene to give 3.4 g. (59%) of VIII, m.p. 179–180°. The analytical sample, m.p. 180.5–181.5°, was obtained by a second recrystallization.

Anal. Calcd. for $C_6H_6F_3N_3O$: C, 37.32; H, 3.14; F, 29.52. Found: C, 37.22; H, 3.10; F, 29.25.

Ethoxymethylenemalononitrile. This starting material, purchased from Kay-Fries Chemicals, Inc., was distilled at reduced pressure and recrystallized from absolute ethanol.

4-Amino-5-cyano-2-trifluoromethylpyrimidine (IX). A solution of 44.8 g. (0.40 mole) of freshly prepared I in 100 ml. of absolute ethanol was cooled in an ice bath and then 48.8 g. (0.40 mole) of ethoxymethylenemalononitrile in 300 ml. of absolute ethanol was added dropwise during 45 min. with stirring. Shortly after initiation of the addition, a white solid began to appear. Stirring was continued for 1 hr. after the addition was complete. The product was filtered and washed with cold ethanol. The filtrate was concentrated to 75 ml. at reduced pressure. The resulting solid was also filtered and washed. The total yield, m.p. 244–246°, was 54.2 g. (72%). The analytical sample, m.p. 245–246° (with sublimation), was obtained by recrystallizing twice from methanol.

Anal. Calcd. for $C_6H_3F_3N_4$: C, 38.31; H, 1.61. Found: C, 38.23; H, 1.73.

4-Amino-5-aminomethyl-2-trifluoromethylpyrimidine (X). Eight grams of Raney nickel[19] was added to a suspension of 9.7 g. (0.052 mole) of IX in 130 ml. of methanol containing 13 g. of dry ammonia. Hydrogenation[20] at about 60 pounds pressure resulted in the required amount of hydrogen being absorbed in about 1 hr. Shaking was continued for an additional hour. The Raney nickel was filtered and the filtrate was evaporated to dryness at reduced pressure. The resulting solid was treated with hot benzene and filtered to remove insoluble matter. The filtrate yielded 7.3 g. (74%) of crude X, m.p. 146–148°, which was orange colored. Several decolorizations with activated charcoal in benzene followed by recrystallization gave a white solid, m.p. 147–148.5°.

Anal. Calcd. for $C_6H_7F_3N_4$: C, 37.52; H, 3.67. Found: C, 37.60; H, 3.79.

The procedure for X was repeated except that after evaporation of the methanol, the mixture was acidified with concentrated hydrochloric acid and evaporated to dryness. Recrystallization from absolute ethanol yielded 8.1 g. (69%) of the hydrochloride of X. The analytical sample, m.p. 279–280°, was obtained by recrystallization from absolute ethanol.

Anal. Calcd. for $C_6H_8ClF_3N_4$: N, 24.51. Found: N, 24.24.

Treatment of the crude hydrochloride with *N* sodium hydroxide gave, after purification, a colorless sample with the same melting point as X. A mixed melting point with X showed no depression.

4-Amino-2-trifluoromethyl-5-pyrimidinecarboxylic acid (XI). One gram of IX was hydrolyzed with 25 ml. of 10% sodium hydroxide. Acidification with hydrochloric acid, followed by filtration of the precipitate and ether extraction of the filtrate, yielded 0.85 g. (77%) of the corresponding acid (crude). The analytical sample, m.p. 312–314°, (dec.), was obtained by recrystallizing twice from ethanol-water. A compound obtained from VII by saponification and acidification gave the same melting point (dec.). A mixed melting point gave no depression and the two samples had similar ultraviolet absorption curves.

Anal. Calcd. for $C_6H_4F_3N_3O_2$: C, 34.77; H, 1.99. Found: C, 34.95; H, 2.11.

4-Amino-2-trifluoromethyl-5-pyrimidinecarboxamide (XII). One gram of IX was heated with 10 ml. of 0.1*N* sodium hydroxide for 15 min., cooled, and filtered to give 0.80 g. (73%) of the corresponding amide (crude). The analytical sample, m.p. 292–293° (with sublimation), was obtained by recrystallizing twice from ethanol-water. Acidification of the alkaline filtrate from the preparation of XII gave 0.1 g. of a compound which was probably XI.

Anal. Calcd. for $C_6H_5F_3N_4O$: C, 34.96; H, 2.45; N, 27.17. Found: C, 34.69; H, 2.40; N, 27.34.

1,3-dicarbethoxy-1,3-dicyano-1-propene (XIII).[21] One-tenth mole each of I, ethyl ethoxymethylenecyanoacetate, and sodium ethoxide, dissolved in absolute ethanol, were refluxed for 2 hr. The alcohol was removed at reduced pressure and the residue was dissolved in hot water. On cooling, 5.2 g. of yellow needles formed. Recrystallization from water gave the sodium salt (dihydrate) of XIII, m.p. 270–272° (Lit. 265°)[22] which on acidification gave XIII (one-half hydrate), m.p. 188–189° (Lit. 187–188°).[16]

Anal. Calcd. for $C_{11}H_{12}N_2O_4 \cdot {}^1/_2H_2O$: C, 54.05; H, 5.36. Found: C, 53.98; H, 5.47.

Acknowledgment. The authors are indebted to Dr. Robert Guthrie and Dr. James F. Holland for their suggestions and interest.

BUFFALO 14, N. Y.

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(20) The technical assistance of Mr. Glen Tucker is gratefully acknowledged.

(21) The authors acknowledge the help of Mr. Steve G. Cottis in the identification of this compound.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pyrroles XIV. Mannich Bases of 2,5-Substituted Pyrroles[1]

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Several pyrroles substituted in the 2- and 5-positions of the pyrrole nucleus were subjected to the Mannich reaction. The resulting bases were shown to be 3-dialkylaminomethyl- and 3,4-bisdialkylaminomethyl derivatives of pyrrole. Their utility as alkylating agents was investigated.

Previous work has shown that the *alpha* hydrogen atoms of pyrrole[3] and substituted pyrroles[4] are sufficiently reactive to participate in the Mannich reaction. The resulting Mannich bases resemble gramine in their ability to alkylate a variety of substances containing active hydrogen[5-8] and have become valuable intermediates in the synthesis of new pyrrole derivatives.

It therefore was of interest to study the susceptibility of the *beta* hydrogen atoms of the pyrrole nucleus to the Mannich reaction. When this investigation was begun, two such Mannich bases were recorded in the literature. Fischer and Nenitzescu[9] had obtained what was claimed to be 2,5-dimethyl-3-carbethoxy-4-diethylaminomethylpyrrole, and Bachman and Heisey[3a] had described a 3-piperidinomethyl-2,5-dimethylpyrrole which resulted from the reaction between 2,5-dimethylpyrrole, piperidine, and formaldehyde. No proof of structure was given in either instance, although it is conceivable that substitution might have taken place on the pyrrole nitrogen or on one of the methyl groups, nor was the utility of these substances as alkylating agents investigated. More recently, Treibs and Fritz[10] have reported the preparation of several 3-substituted Mannich bases and one, 2-methyl-5-carbethoxy-3-piperidinomethyl-4-β-carboxyethylpyrrole, has been used as an intermediate in the synthesis of uroporphyrin III.[11]

2,5-Dimethylpyrrole condensed readily with dimethylamine hydrochloride and formaldehyde to give a mono- and a disubstitution product, depending on the relative quantities of pyrrole derivative, base, and aldehyde. Properties of these and other Mannich bases are listed in Tables I and II. The structures of these substances were established unequivocally as 2,5-dimethyl-3-dimethylaminomethylpyrrole (I) and 2,5-dimethyl-3,4-bisdimethylaminomethylpyrrole (II) by means of the following: (a) presence of an —NH band in the infrared spectra of the Mannich bases which indicates that substitution had not taken place on the pyrrole nitrogen atom; (b) catalytic hydrogenolysis[4d] of I and II which led to 2,3,5-trimethylpyrrole and, respectively, 2,3,4,5-tetramethylpyrrole. The latter reaction, coupled with the excellent yields achieved in the Mannich reaction, constitutes a convenient preparative method for polyalkylpyrroles.

After the completion of this part of our work there appeared a paper[12] in which a product resulting from the reaction between 2,5-dimethylpyrrole, dimethylamine hydrochloride, and formaldehyde was assigned the structure 2,5-dimethyl-1-dimethylaminomethylpyrrole without experimental proof. The properties of this material roughly correspond to those of I and there can be little question that the Indian workers actually obtained 2,5-dimethyl-3-dimethylaminomethylpyrrole. In contrast to the indole series where the order of reactivity in the Mannich reaction is $\beta > N > \alpha$,[13] the order of substitution in the pyrrole series is therefore $\alpha > \beta$ the nitrogen apparently not being substituted at all.[14]

1,2,5-Trimethylpyrrole and 1-phenyl-2,5-dimethylpyrrole similarly formed mono- and di-Mannich bases although the yields were somewhat lower (see Table I). The facile formation of a disubstitution product from 1-phenyl-2,5-dimethylpyrrole

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(10) A. Treibs and G. Fritz, *Ann.*, **611**, 163 (1958).

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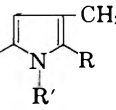
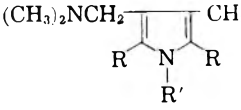
(14) This was established by using a large excess of dimethylamine hydrochloride and formaldehyde which did not result in further substitution on the pyrrole nitrogen atom.

TABLE I

COMPOUNDS OF TYPE (I)  AND (II) 

R	R′	Yield, %	M.P. or B.P., °C.	Mm.	Type	Method	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	92	99–100		I	A	$C_9H_{16}N_2$	71.00	10.59	18.4	71.25	10.31	18.1[a]
CH_3	Phenyl	49.5	130–131	1	I	B	$C_{15}H_{20}N_2$[b]	78.90	8.83	12.3	78.40	8.72	11.7[c]
CH_3	CH_3	69	73–74	1	I	B	$C_{10}H_{18}N_2$[d]	72.24	10.91	16.9	72.05	10.89	17.3[e]
Phenyl	H	73[f]	124–125		I	B	$C_{19}H_{20}N_2$	82.57	7.29	10.14	81.97	7.29	10.18
CH_3	H	90	144–145		II	A	$C_{12}H_{23}N_3$	68.99	11.01	20.1	68.93	10.89	19.9[g]
CH_3	Phenyl	61	150	1	II	B	$C_{18}H_{27}N_3$	75.74	9.54	14.7	76.33	9.57	13.9[h]
CH_3	CH_3	72.5	96–97	0.3	II	B	$C_{13}H_{25}N_3$	69.90	11.28	18.8	70.00	11.23	18.2

[a] *Methiodide*, m.p. 130° (dec.). Calcd. for $C_{10}H_{19}IN_2$: C, 40.82; H, 6.51; N, 9.52. Found: C, 40.55; H, 6.69; N, 9.47. [b] n_D^{25} 1.5500. [c] *Methiodide*, m.p. 211–212° (dec.). Calcd. for $C_{16}H_{23}IN_2$: C, 51.90; H, 6.26. Found: C, 52.39; H, 6.45. [d] n_D^{25} 1.4951. [e] *Methiodide*, m.p. 140° (dec.). Calcd. for $C_{11}H_{21}IN_2$: C, 42.86; H, 6.87; N, 9.09. Found: C, 42.46; H, 6.74; N, 9.17. [f] Yield raised to 97.5% with two equivalents of dimethylamine hydrochloride and formaldehyde. [g] *Methiodide*, m.p. 139–140°. Calcd. for $C_{14}H_{29}I_2N_3$: C, 34.19; H, 5.89; N, 8.59. Found: C, 34.53; H, 5.90; N, 8.61. [h] *Methiodide*, m.p. 100° (dec.). Calcd. for $C_{20}H_{33}I_2N_3$: C, 42.19; H, 5.84; N, 7.28. Found: C, 41.73. H, 6.58; N, 7.04.

TABLE II

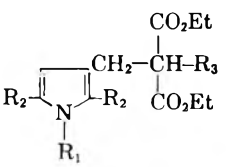
PICRATES OF MANNICH BASES

R	R′	Type	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	I	117–118	$C_{15}H_{19}N_5O_7$	47.24	5.02	18.4	46.94	5.38	18.7
CH_3	Phenyl	I	137–138	$C_{21}H_{23}N_5O_7$	55.14	5.07	14.7	54.64	4.79	14.7
CH_3	CH_3	I	137–138 (dec.)	$C_{16}H_{21}N_5O_7$	48.60	5.35	17.7	48.65	5.32	17.9
Phenyl	H	I	179–180	$C_{25}H_{23}N_5O_7$	59.64	4.20	13.9	59.77	4.75	13.5
CH_3	H	II	139–140	$C_{24}H_{29}N_9O_{14}$	43.18	4.38	18.9	42.70	4.21	18.8
CH_3	Phenyl	II	200–201 (dec.)	$C_{30}H_{33}N_9O_{14}$	48.95	4.85	16.9	49.12	4.40	16.5
CH_3	CH_3	II	181–182 (dec.)	$C_{25}H_{31}N_9O_{14}$	44.05	4.58	18.5	43.91	4.55	18.6

is in contrast to earlier observations with 1-phenylpyrrole[4a] where even under forcing conditions only one dialkylaminomethyl group could be introduced and the yield of monosubstituted product was considerably lower. One of two factors may account for this observation: (1) the two methyl groups may offset the deactivating effect of the phenyl group; (2) the phenyl group is forced out of the plane of the pyrrole nucleus by the two neighboring methyl groups and thus cannot affect the transition state. On the other hand, 2,5-diphenylpyrrole only formed a mono-Mannich base although the yield was improved considerably by the use of excess reagent.

The suitability of the 3-substituted pyrrole Mannich bases for alkylation reactions remained to be explored. It was also of interest to contrast the nitrogen-substituted bases which would be able to react only by the substitution mechanism with the nitrogen-unsubstituted compounds which might react by either the elimination-addition or substitution[15] mechanism.

In accordance with expectations, 3-dimethylaminomethyl-1-methyl- and 1-phenyl-2,5-dimethylpyrroles could not be brought into reaction with diethyl acetamidomalonate and diethyl malonate by refluxing with toluene in the presence of catalytic amounts of sodium hydroxide (elimination-addition conditions) while alkylations using I proceeded relatively smoothly. However, as has been observed previously in the pyrrole series[4a,5a,16] with compounds such as I which are capable of reacting by the elimination-addition mechanism, yields were much improved when I was quaternized before being used as an alkylating agent (substitution conditions), III and IV being formed in 95%, resp. 85% yield. Similarly, when the *N*-



III. R_1 = H, R_2 = CH_3, R_3 = NH—C(=O)—CH_3
IV. R_1 = H, R_2 = CH_3, R_3 = NHCHO
V. R_1 = H, R_2 = phenyl, R_3 = NHCHO

(15) For a discussion of these terms, as well as of the general problem of alkylation by means of indole and pyrrole Mannich bases, see the following reviews: (a) J. H. Brewster and E. L. Eliel, *Organic Reactions*, VII, 99 (1953); (b) H. Hellmann, *Angew. Chem.*, 65, 473 (1953).

(16) W. Kutscher and O. Klamerth, *Ber.*, 86, 352 (1953)

substituted Mannich bases were quaternized, the alkylation of malonic ester could be accomplished satisfactorily. These results furnish further evidence for the correctness of current views concerning alkylation by means of indole and pyrrole Mannich bases.

In the alkylation of 1-methylgramine methiodide with hot aqueous sodium cyanide, two products were isolated.[17] The first was the expected product, 1-methyl-3-indoleacetonitrile, and the second, in much smaller yield, was 1,3-dimethyl-2-cyanoindole, presumably formed by an allylic rearrangement during the alkylation process. Under comparable conditions, the methiodides of 1,2,5-trimethyl- and 1-phenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole furnished volatile nitrile fractions in 26% and 45% yield, respectively. The presence of an unconjugated (2250 cm.$^{-1}$) nitrile band in the infrared spectra of these products suggested that no rearrangement had taken place. This was confirmed in the case of the 1,2,5-trimethyl derivative by hydrolysis to 1,2,5-trimethyl-3-pyrroleacetic acid which was synthesized independently from ethyl diazoacetate and 1,2,5-trimethylpyrrole.[18]

Hydrolysis of III was expected to furnish 2,5-dimethyl-3-pyrrolealanine which was of interest as a potential metabolite antagonist.[5a] The product which showed some activity against *E. coli* gave a positive ninhydrin test and appeared to be homogeneous on paper chromatography, but analysis indicated a considerable degree of contamination, as was observed previously in analogous cases.[1,4a,5a,19] Hydrolysis of IV yielded 2,5-diphenyl-3-pyrrolealanine which was inactive against *S. cervisiae*.

EXPERIMENTAL[20]

Mannich reactions of substituted pyrroles. The following general procedures were used for the preparation of the Mannich bases listed in Table I.

Method A: A solution of 85 g. (1.05 mole) of dimethylamine hydrochloride in 79 g. (1.05 mole) of 40% formalin was added to 100 g. of 2,5-dimethylpyrrole in a three-necked flask fitted with stirrer, reflux condenser, nitrogen inlet tube, and dropping funnel at such a rate that the temperature did not exceed 60°. The mixture was diluted with water, extracted with ether, and the aqueous layer poured into 200 ml. of 25% sodium hydroxide solution. An oil separated which crystallized on standing and was recrystallized from ligroin (60–110°), yield 148 g. (92%), m.p. 99–100°.

For disubstitution, the quantities of dimethylamine hydrochloride and formalin were doubled.

Method B: A mixture of 20 ml. of a 33% aqueous solution of dimethylamine and 20 ml. of acetic acid was allowed to come to room temperature and mixed with 8.5 ml. of 40% formalin. The resulting solution was added dropwise to 17.1 g. (0.08 mole) of 1-phenyl-2,5-dimethylpyrrole in a nitrogen atmosphere, with stirring, and worked up as described previously. The oil which separated on pouring into alkali was extracted with ether, washed, and distilled *in vacuo*, b.p. 140–150° (3 mm.), yield 11.1 g. (49.5%).

For disubstitution, two moles of aqueous dimethylamine solution and two moles of formalin in sufficient acetic acid to ensure a homogeneous reaction mixture was added to 0.8 mole of pyrrole derivative.

Picrates (Table II) of the Mannich bases were precipitated by mixing alcoholic solutions of the base and picric acid and were recrystallized from ethanol.

Methiodides were prepared by adding the Mannich base, dissolved in a minimum of absolute ethanol, to 10% excess methyl iodide with vigorous stirring at ice bath temperature. The products were recrystallized from absolute ethanol.

Hydrogenolysis of Mannich bases. A small high-pressure bomb containing 20 g. of II in 100 ml. of ethanol and 4 g. of Raney nickel (W-2) was charged with hydrogen to a pressure of 80–100 atm. and heated at 100° for 48 hr. The solvent was removed *in vacuo* and the residue steam-distilled. The distillate contained 7.7 g. (72%) of 2,3,4,5-tetramethylpyrrole, m.p. 107–108°, lit.[4d] 107–108°.

In a similar manner, hydrogenolysis of 20 g. of I at 80–90° for 8 hr. furnished 1.5 g. of 2,3,5-trimethylpyrrole, b.p. 79–80° (15 mm.), lit.[21] 79–80° (15 mm.), and 7.5 g. of unreduced starting material. The yield of trimethylpyrrole could undoubtedly be improved by lengthening the reaction period.

Diethyl 2,5-dimethyl-3-pyrrolemethyl-α-acetamidomalonate (III). In a 300-ml. flask fitted with dropping funnel, condenser, and nitrogen inlet tube was placed 100 ml. of absolute ethanol and 1.72 g. of clean sodium. After the sodium had dissolved, 16.2 g. of diethyl acetamidomalonate and 11.5 g. of I were added. While cooling in an ice bath, 15.8 g. of dimethyl sulfate was added dropwise at such a rate that the temperature did not exceed 35°. Stirring was continued overnight, the solvent was removed at reduced pressure, the residue diluted with water, and chilled. The solid, wt. 18.4 g. (74%), m.p. 173–175°, was recrystallized from ethanol-water to a constant m.p. of 176–177°.

Anal. Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.24: H, 7.46; N, 8.64. Found: C, 59.69; H, 7.45; N, 8.38.

Reaction of 26 g. of I with 32.4 g. of diethyl acetamidomalonate in 300 ml. of toluene containing 1 g. of powdered sodium hydroxide, until the evolution of basic gases ceased, furnished 24 g. (45%) of the product, m.p. 175–177°.

Diethyl 2,5-dimethyl-3-pyrrolemethyl-α-formamidomalonate. Condensation of 20.3 g. of diethyl formamidomalonate and 11.5 g. of I in ethanol by quaternization *in situ* as described in the previous preparation yielded 19.2 g. (86%) of product, m.p. 137–138.5°.

Anal. Calcd. for $C_{12}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.24; H, 7.01; N, 9.20.

Hydrolysis of this material (6 g.) with 50 ml. of 25% sodium hydroxide solution for 2.5 hr., cooling, acidification to *p*H 6, filtering, acidification of the filtrate to *p*H 5, scratching to induce crystallization and chilling, yielded 3.3 g. of material, m.p. 280° (dec.), which gave a positive ninhydrin test. Several reprecipitations of this material and washing with ice water, ethanol, and ether gave a sample which gave only one spot on paper chromatography and inhibited *E. coli* at a level of 1 ml./ml. The analysis indicated the presence of inorganic contaminants which could not be removed by further crystallization or reprecipitation.

(17) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948).

(18) In view of the relatively low yields and the formation of undistillable noncrystallizable residues, presumably amides, which evolved ammonia on further treatment with base, the presence of a small amount of rearrangement product cannot be excluded with certainty, however.

(19) H. Behringer and H. Taul, *Ber.*, **90**, 1398 (1957).

(20) Melting points and boiling points are uncorrected. Analyses were carried out by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were run by Miss M. T. Esquivel on a Perkin-Elmer Model 21 double-beam recording spectrometer.

(21) C. D. Nenitzescu and E. Solomonica, *Ber.*, **64**, 1924 (1931).

Diethyl 2,5-dimethyl-3-pyrrolemethyl malonate. Alkylation of 50 g. of diethyl malonate with 31.5 g. of I by the quaternization procedure yielded 35.5 g. (78.5%) of product, b.p. 173–175° (2 mm.). The analytical sample boiled at 152° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.25; H, 7.86; N, 5.21.

Diethyl 2,5-diphenyl-3-pyrrolemethyl-α-formamidomalonate. Reaction of 20.8 g. of 2,5-diphenyl-3-dimethylaminomethylpyrrole and 20.3 g. of diethyl formamidomalonate by the *in situ* quaternization method resulted in 31.05 g. (94.5%) of a colorless solid, m.p. 163–164°. The analytical sample, after recrystallization from ethanol-water, melted at 164–165°.

Anal. Calcd. for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.90; H, 6.12; N, 6.05.

2,5-Diphenyl-3-pyrrolealanine. A mixture of 5 g. of the preceding, 10 g. of potassium hydroxide, and 50 ml. of 80% ethanol was refluxed overnight in a stainless steel beaker fitted with cover and reflux condenser. The cooled solution was acidified to pH 5; the resulting solid, wt. 1.5 g. (42%), m.p. 217–218° (dec.), gave a positive ninhydrin test. It was purified repeatedly by dissolving in dilute base, reprecipitating with dilute acid, and washing with water, ether, and ethanol.

Anal. Calcd. for $C_{19}H_{17}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.31; N, 5.40; N, 8.71.

Diethyl 1-phenyl-2,5-dimethyl-3-pyrrolemethyl malonate. To 64 g. of diethyl malonate in which 1.84 g. of sodium had been dissolved was added 26 g. of the methiodide of 1-phenyl-2,5-dimethylaminomethylpyrrole. The solution was heated at 120°, with stirring, for 6 hr. in a nitrogen atmosphere until the evolution of basic gases had ceased. Water was added and the mixture was extracted with ether. Distillation gave 23.6 g. of malonic ester and 11.4 g. (48%) of product, b.p. 194–196° (0.6 mm.). The analytical sample boiled at 164–165° (0.1 mm.), n_D^{25} 1.5230.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.90; H, 11.28; N, 18.82. Found: C, 70.00; H, 11.23; N, 18.20.

Diethyl 1,2,5-trimethyl-3-pyrrolemethylmalonate. By the above procedure there was obtained, after 24 hr., 6.8 g. (36%) of a clear liquid, b.p. 145–146° (0.9 mm.), n_D^{25} 1.4670.

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.80; H, 7.95; N, 4.87.

1,2,5-Trimethyl-3-pyrroleacetonitrile. In a 500-ml. three-necked flask fitted with nitrogen inlet and condenser was heated, with stirring, 55 g. of the methiodide of 1,2,5-trimethyl-3-dimethylaminomethylpyrrole, 30 g. of sodium cyanide, and 200 ml. of water until the evolution of basic gas (identified as trimethylamine) had ceased. The solution was extracted with ether and the dried extract distilled *in vacuo*, yield 5.5 g. (26%), b.p. 135–137° (1.5 mm.). The analytical sample boiled at 90° (0.2 mm.), n_D^{25} 1.1527, nitrile band at 2250 cm.$^{-1}$ The pot residue consisted of a tarry solid which liberated ammonia on treatment with base and probably contained some amide, due to partial hydrolysis of the nitrile.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.9. Found: C, 72.78; H, 8.32; N, 18.7.

1,2,5-Trimethyl-3-pyrroleacetic acid. (*A.*) A mixture of 5 g. of the preceding nitrile, 5 g. of potassium hydroxide, and 50 ml. of 80% ethanol was refluxed for 8 hr., diluted with water, and poured over crushed ice containing 10 ml. of concentrated hydrochloric acid. The oil which separated was taken up in ether. Removal of ether furnished 3.2 g. (82%) of a solid, m.p. 117–118°. The analytical sample, recrystallized from petroleum ether (b.p. 60–110°) melted at 120–121°.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; N, 7.84; N, 8.38. Found: C, 64.72; H, 8.09; N, 8.16.

(*B.*) To a 300-ml. flask fitted with nitrogen inlet tube, condenser, stirrer, and dropping funnel and containing 90 g. of 1,2,5-trimethylpyrrole and 4 g. of powdered copper was added dropwise, with stirring and slight warming 48 g. of ethyl diazoacetate. After completion of the exothermic reaction, stirring was continued for 3 hr., the copper was removed, and the filtrate distilled at reduced pressure. This resulted in recovery of 72.5 g. of 1,2,5-trimethylpyrrole, b.p. 70–72° (22 mm.), and isolation of 18.8 g. (59%) of the desired ethyl 1,2,5-trimethyl-3-pyrroleacetate, b.p. 124–125° (5 mm.). The analytical sample boiled at 90–91° (0.1 mm.), n_D^{27} 1.4919.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.57; H, 8.70; N, 7.27.

Hydrolysis of the ester with 80% aqueous alcoholic alkali furnished 2.76 g. (63%) of a solid m.p. 117–120° which on recrystallization melted at 120–121° and did not depress the m.p. of the substance obtained by hydrolysis of the nitrile.

1-Phenyl-2,5-dimethyl-3-pyrroleacetonitrile. Alkylation of 30 g. of sodium cyanide with 40 g. of the methiodide of 1-phenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole in the manner described for the 1-methyl analog yielded 9 g. (45%) of a fraction, b.p. 144–145° (0.6 mm.), n_D^{25} 1.5246, nitrile band at 2250 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.41; H, 7.07; N, 13.2.

1-Phenyl-2,5-dimethyl-3-pyrroleacetic acid. On saponification of 3 g. of the preceding nitrile there was obtained 2.5 g. (48%) of an acid, m.p. 151–152° after recrystallization from petroleum ether (b.p. 60–110°).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.53; H, 6.50; N, 6.46.

Acknowledgment. Thanks are due Dr. Karl Dittmer and his group for carrying out the microbiological tests.

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF NEW YORK, NEW YORK STATE COLLEGE FOR TEACHERS]

Convenient Syntheses of 1,2,3,4-Tetrahydroquinoxalines

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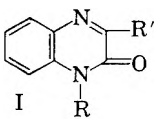
New and convenient syntheses of 1,2,3,4-tetrahydroquinoxaline (THQ) derivatives have been developed. Lithium aluminum hydride reduction of the readily available 2-keto-THQ (II) afforded THQ. Alkylation of II with simple alkyl halides yielded 1-alkyl-3-keto-THQ derivatives (III) which underwent reduction with lithium aluminum hydride to give the corresponding 1-alkyl-THQ (IV) in excellent yields (Method *A*). Sodium borohydride reduction of the methyl *p*-toluenesulfonate and ethyl iodide quaternary salts of quinoxaline afforded the corresponding IV derivatives (Method *B*). Lithium aluminum hydride reduction of 6-chloroquinoxaline yielded 6-chloro-THQ.

The pharmacological activity of piperazine derivatives is well documented and it seemed worthwhile to prepare the structurally similar 1,2,3,4-tetrahydroquinoxaline (THQ) derivatives for evaluation.

The difficulties encountered in the preparation of simple 1-alkyl-THQ derivatives have been established by Cavagnol and Wiselogle[1] who attempted monoalkylation and monoacylation of THQ with a variety of reagents using different solvents and temperatures ranging from −70° to 300°. In all cases the only products isolated were starting material or the disubstituted THQ. It was later found[2] that monoacylation could be accomplished in yields up to 70% by operating at *p*H 6–7.

Cavagnol and Wiselogle[1] found that monophenylsulfonation could be accomplished in good yields and were able to synthesize a variety of 1-alkyl-THQ derivatives (IV) by the sequence: Quinoxaline→THQ→1-phenylsulfonyl-THQ→1-alkyl-4-phenylsulfonyl-THQ→IV. The over-all yields (based on quinoxaline) were 42–58%.

The synthesis of a few 1-substituted THQ compounds has recently been accomplished[3] by the lithium aluminum hydride reduction of 1-alkyl-2-keto-1,2-dihydroquinoxalines (I) which are prepared by the reaction of *N*-substituted *o*-phenylenediamines with α-ketoacids. A few complex 1-substituted THQ derivatives have been prepared by catalytic reduction of quinoxaline quaternary salts.[3]



Two new and convenient syntheses have been developed for simple IV type compounds.

Method *A* utilizes as starting material the readily available 2-keto-THQ (II). Compound II is prepared[4] by simply heating *o*-phenylenediamine and chloroacetic acid in dilute aqueous ammonia. Alkylation of II with ethyl-, *n*-propyl- and *n*-butyl iodides and benzyl chloride in ethanolic solution gave moderate to good yields (Table I) of the 1-alkyl-3-keto-THQ (III). All of the III compounds possessed wide melting ranges and were purified with great difficulty.[5] However, lithium aluminum hydride reduction of the crude III type compounds gave excellent yields of IV. The IV compounds were all characterized by their neutral equivalents and conversion to the known benzoyl and phenylsulfonyl derivatives.[1]

Lithium aluminum hydride reduction of II furnished THQ in 65% yield.

Method *B* utilizes the sodium borohydride reduction[6] of quinoxaline quaternary salts (V) to give the IV derivatives. This method is not of as great general synthetic importance as method *A* since quaternization of quinoxaline with higher alkyl halides proceeds in poor yields.[7] However, this method is probably the best for preparation of the 1-methyl and 1-ethyl THQ derivatives (IVa and IVb). Thus, methyl quinoxalinium *p*-toluenesulfonate[8] (Va) was obtained in quantitative yield and subsequent reduction gave a 64% yield

(1) J. C. Cavagnol and F. Y. Wiselogle, *J. Am. Chem. Soc.*, **69**, 795 (1947).

(2) J. S. Morley, *J. Chem. Soc.*, 4002 (1952).

(3) J. Druey and A. Huni, *Helv. Chim. Acta*, **35**, 2301 (1952).

(4) W. H. Perkin, Jr., and G. C. Riley, *J. Chem. Soc.*, **123**, 2399 (1923).

(5) P. van Romburgh and W. B. Deys, *Proc. Acad. Sci. Amsterdam*, **34**, 1004 (1931). This reference cites the only recorded alkylation of II. Ethyl iodide and II were reacted without solvent in a sealed tube at 100° to give 1-ethyl-3-keto-THQ in unspecified yield, m.p. 98–99°. In experiments carried out by Mr. Robert Hyde in these laboratories, none of the 98–99° product could be isolated by the above method. The product isolated by our procedure (IIIb) had m.p. 112–114° and gave the correct analysis (Table I).

(6) For references on the borohydride reduction of other quaternary salts see: N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, pp. 789–93.

(7) (a) Y. T. Pratt in *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, New York, 1957, Vol. 6, p. 472. (b) W. K. Easly and C. T. Bahner, *J. Am. Chem. Soc.*, **72**, 3803 (1950).

(8) C. T. Bahner, L. R. Barclay, G. Biggerstaff, D. L. Bilancio, G. W. Blanc, M. Close, M. M. Isenberg, and E. Pace, *J. Am. Chem. Soc.*, **75**, 4838 (1953).

TABLE I

1-ALKYL-1,2,3,4-TETRAHYDRO-3-KETOQUINOXALINES (III)

Formula	Crude Yield	m.p.°C.	Analyses Calcd. C	H	N	Found C	H	N
IIIb, $C_{10}H_{12}N_2O$	60	112–114	68.15	6.87	15.90	68.45	6.99	15.86
IIIc, $C_{11}H_{14}N_2O$	51	97–99	69.44	7.42	14.73	69.63	7.60	14.55
IIId, $C_{12}H_{16}N_2O$	61	101–103	70.55	7.90	13.74	70.44	7.90	13.60
IIIe, $C_{15}H_{14}N_2O$	90	130[a]	75.60	5.92	11.76	75.27	6.20	11.59

[a] Prior softening.

TABLE II

1-ALKYL-1,2,3,4-TETRAHYDROQUINOXALINES

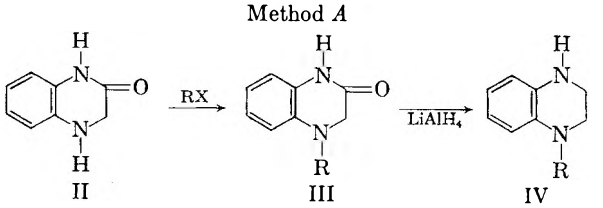
Formula	Method	Yield	B.P. °C.	Mm.	Neutral Equivalents Calcd.[a]	Found
IVa $C_9H_{12}N_2$	*B*	64	163–169	21	148	148
IVb $C_{10}H_{14}N_2$	*A*	80	170–173	21	162	162
IVb	*B*	72	168–173	21		
IVc $C_{11}H_{16}N_2$	*A*	91	176–179	20	176	176
IVd $C_{12}H_{18}N_2$	*A*	76	187–191	21	190	191
IVe $C_{15}H_{16}N_2$	*A*	82	242–250	19	224	232

[a] The neutral equivalents were determined by titration with perchloric acid in acetic acid.

of IVa. The ethyl iodide[9] salt (Vb) was obtained in 76% yield and afforded 72% of IVb on reduction.

The 76% yield of Vb could be achieved only if the quaternization was carried out in refluxing acetonitrile. Attempted quaternization of quinoxaline with *n*-propyl iodide, *n*-butyl iodide, and benzyl chloride in refluxing acetonitrile gave only small amounts of crystalline material accompanied by extensive decomposition.

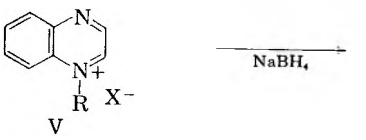
Method *A*



II III IV

b. R = Et
c. R = *n*-C_3H_7
d. R = *n*-C_4H_9
e. R = benzyl

Method *B*



V

IVa, R = CH_3
IVb, R = C_2H_5

a. R = Me; X = $C_7H_7SO_3^-$
b. R = Et; X = I^-

Although the over-all yields of the type IV compounds prepared by the new procedures do not represent any great improvement in over-all yield (based on *o*-phenylenediamine), the metal hydride syntheses are certainly less time-consuming than the earlier method of Cavagnol and Wiselogle[1] and appear to be the method of choice for moderate scale preparation of simple monoalkyl-THQ compounds.

The methyl compound (IVa) was also converted to the urea derivative, the phenylurea derivative, and 1,1,4-trimethyl-1,2,3,4-tetrahydroquinoxalinium iodide.

We have also prepared 6-chloro-THQ in 65% yield by the lithium aluminum hydride reduction[10] of 6-chloroquinoxaline. Cavagnol and Wiselogle[1] obtained only trace amounts of 6-chloro-THQ by catalytic reduction.

It is planned to prepare several new derivatives of the IV compounds which will be substituted with groups that may confer biological activity. Several of the compounds described in this paper have been submitted for pharmacological evaluation to Dr. Carl Pfeiffer, Division of Basic Health Sciences, Emory University, Atlanta, Ga.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Analyses are by Mr. K. D. Fleischer and his staff of the Microanalytical Laboratory of Sterling-Winthrop Research Institute, Rensselaer, N. Y.

1,2,3,4-Tetrahydro-2-ketoquinoxaline (II). This compound was prepared by the method of Perkin and Riley.[4] When run on a 2.2 mole scale the yield of unpurified product was 65%. The product was obtained as tan crystals, m.p. 130–135° after drying at 100°. The crude material was used in all experiments.

1,2,3,4-Tetrahydroquinoxaline. A suspension of 8.0 g. of lithium aluminum hydride in 500 cc. of dry ether was prepared in a 1 l. flask equipped with an air stirrer and efficient condenser with a calcium chloride tube attached. To this suspension was added, with stirring, 14.3 g. (0.097 m.) of II

(9) O. Hinsberg, *Ann.*, **292**, 245 (1896).

(10) F. Bohlmann, *Ber.*, **85**, 390 (1952), reported the reduction of quinoxaline to THQ with lithium aluminum hydride.

in small portions. After the original reaction had subsided the contents were stirred and refluxed for 4 hr. The reaction mixture was treated cautiously with the minimum amount of water to effect decomposition and the inorganic material was filtered and washed with ether. Evaporation of the ether solution and recrystallization from benzene–petroleum ether gave 8.4 g. (64.6%) of white crystals, m.p. 94–97°. The reported[1] m.p. is 98.5–99°.

The *dibenzoyl derivative* melted at 205–207°. The reported[1] m.p. is 206–207°.

General method for alkylation of II. A suspension of 0.2 mole of anhydrous sodium carbonate, 0.1 mole of II, 0.11 mole of the alkyl iodide (or benzyl chloride) and 75–100 cc. of 95% ethanol was stirred and refluxed overnight. The reaction mixture was poured into 1 l. of water and the resultant oils crystallized rapidly. The brown solids were washed with water and dried in a vacuum desiccator (calcium chloride) overnight. The dried solids usually had very wide melting ranges but were used directly for lithium aluminum hydride reduction. Purification of small samples for analysis was accompanied by large losses of material, and several recrystallizations were usually needed to obtain the melting points recorded in Table I for the 1-alkyl-1,2,3,4-tetrahydro-3-ketoquinoxalines (III). Attempted alkylation with methyl iodide gave a very poor yield of solid. Compound IIIb was recrystallized from benzene-hexane, the others from ethanol. Compound IIIc was obtained as white crystals, the others formed yellow crystals.

1-Alkyl-1,2,3,4-tetrahydroquinoxalines by method A. The crude III was added in small portions to a suspension of a large excess of lithium aluminum hydride (about a 1:3 hydride to III weight ratio) suspended in dry ether and contained in a flask equipped with an efficient condenser (calcium chloride tube). After the initial reaction had subsided the reaction mixture was refluxed 1 hr., then treated dropwise with the minimum amount of water required for decomposition. The inorganic material was filtered, washed with benzene, and the combined solutions evaporated at reduced pressure. The resultant oils were immediately distilled at reduced pressure through a Claisen head. The products were yellow oils which darkened rapidly.

Methyl quinoxalinium p-toluenesulfonate (Va). A mixture of distilled quinoxaline (10 g.) and 20 cc. of methyl *p*-toluenesulfonate was allowed to remain at room temperature for four days. The resultant solid was broken up under dry ether, filtered, and dried. A quantitative yield of light purple solid, m.p. 143–147° was obtained and used for subsequent reduction. Recrystallization from ethanol-ether gave white crystals, m.p. 150–152°. The reported[8] melting point is 150°. The salt was quite hygroscopic.

1,2,3,4-Tetrahydro-1-methylquinoxaline (IVa) *by method B.* Crude Va (98 g.) was dissolved in 150 cc. of water and extracted once with ether to remove non-ionic impurities. The water solution was added dropwise with stirring over 0.5 hr. to a solution of 35 g. of sodium borohydride in 1 l. of water and cooled by a cold water bath. After 10 min. of additional stirring, the product was separated by three extractions with benzene. The combined extracts were stirred with 10 g. of charcoal, filtered, and evaporated immediately at reduced pressure. Distillation through a Claisen head gave 31 g. (64.1%) of a yellow oil, b.p. 163–169° (21 mm.).

Initially, considerable decomposition of product was observed when the reduction of the methiodide was carried out in methanol-water and the extracts dried over magnesium sulfate prior to distillation.

Ethyl quinoxalinium iodide (Vb). Reaction of quinoxaline and ethyl iodide without solvent at room temperature and at 50° gave very poor yields. The following procedure gave the best results. A solution of quinoxaline (10 g.), ethyl iodide (20 cc.), and dry acetonitrile (50 cc.) were refluxed overnight. The red crystals were filtered and a second crop obtained by dilution with ether. The yield was 16.0 g. (76%), m.p. 141–143° (dec.). The reported[9] m.p. is 146° (dec.).

1-Ethyl-1,2,3,4-tetrahydroquinoxaline (IVb) *by method B.* The reduction of Vb was carried out as with Va except the solid ethiodide was added in small portions to the sodium borohydride solution. The product was separated with ether and distilled immediately.

Characterization of the 1-alkyl-1,2,3,4-tetrahydroquinoxalines. In addition to the neutral equivalents reported in Table II, all of the compounds were characterized by conversion to the benzoyl and phenylsulfonyl derivatives. Good agreement with recorded[1] melting points was obtained in all cases and the yields of pure derivatives were usually greater than 90%. The picrate of IVa also had the correct melting point.[1]

1,1,4-Trimethyl-1,2,3,4-tetrahydroquinoxalinium iodide. This compound was prepared by refluxing a mixture of 5 g. IVa, 12 cc. methyl iodide, 3.72 g. of sodium carbonate, and 30 cc. of absolute ethanol for 3.5 hr. The insoluble material was extracted with boiling methanol and the combined solutions were diluted with ether. The resultant white solid was recrystallized from absolute ethanol to give 2.8 g. of white crystals, m.p. 215–216°.

Anal. Calcd. for $C_{11}H_{11}IN_2$: C, 43.43; H, 5.63; I, 41.72. Found: C, 43.63; H, 5.86; I, 42.12.

1,2,3,4-Tetrahydro-1-methyl-4-phenylcarbamylquinoxaline. This compound was prepared by treating a solution of 2.9 g. IVa in 20 cc. of petroleum ether with 3.0 cc. of phenyl isocyanate. Recrystallization of the resultant solid gave 2.2 g. of white needles, m.p. 129–130°.

Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.88; H, 6.41; N, 15.72. Found: C, 71.72; H, 6.48; N, 15.46.

1-Carbamyl-4-methyl-1,2,3,4-tetrahydroquinoxaline. This compound was prepared by treating a solution of 3 g. of IVa in 15 cc. of acetic acid and 30 cc. of water with a solution of 6 g. of potassium cyanate in 20 cc. of water. After warming on the steam bath for 5 min. and cooling the product separated. Recrystallization from aqueous ethanol gave 1.9 g. of white crystals, m.p. 124–125°.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.98. Found: C, 63.12; H, 6.85; N, 21.83.

6-Chloro-1,2,3,4-tetrahydroquinoxaline. To a suspension of 5 g. of lithium aluminum hydride in 750 ml. of dry ether was added slowly with stirring 20 g. of 6-chloroquinoxaline[1] in 500 ml. of dry ether. After the initial reaction had subsided, the mixture was stirred and refluxed for 6 hr. Water (15 cc.) was added dropwise to the stirred solution and the insoluble material filtered and washed with benzene. The combined solutions were evaporated to give a white solid which was recrystallized from benzene–petroleum ether to give 13.4 g. (65.5%) of white crystals, m.p. 112–114°. The reported[1] m.p. is 113–114°.

The *dibenzoyl derivative* melted at 168–169°. The reported[1] m.p. is 168.5–169°.

Acknowledgment. The senior author wishes to express his thanks to Dean O. E. Lanford, President E. R. Collins, and Dr. D. V. Tieszen whose combined efforts made possible a special summer stipend and financial support of the work. Thanks are also due the Sterling-Winthrop Research Institute for microanalyses and use of library facilities.

ALBANY, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Trimerization of Benzonitrile with Sodium

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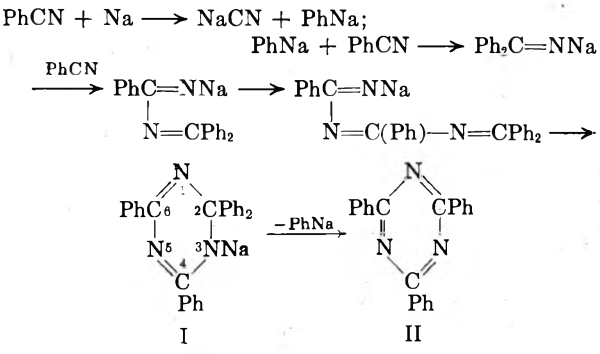
The formation of kyaphenin (2,4,6-triphenyl-s-triazine) by the action of sodium on benzonitrile has been reinvestigated. The yield of kyaphenin from 2,2,4,6-tetraphenyl-2,3-dihydrotriazine sodium salt by elimination of phenylsodium is significantly increased by treatment with carbon dioxide, sulfur dioxide, or benzonitrile. Methylation of 2,2,4,6-tetraphenyl-2,3-dihydrotriazine sodium salt yields two isomeric *N*-methyl derivatives. An attempt has been made to interrelate and interpret these reactions.

Benzonitrile may be trimerized to kyaphenin, 2,4,6-triphenyl-s-triazine (II) by the action of acids[2] or sodium.[3] While the acid trimerization can be explained simply, the reaction with sodium evidently proceeds in a more complex manner. Lottermoser[3] identified a tetraphenyldihydrotriazine (I, Na = H) as the main product, as well as sodium cyanide and small amounts of II, in the reaction of benzonitrile with sodium in boiling benzene. The initial stage of this reaction was clarified by Anker and Cook[4]; and Swamer, Reynolds, and Hauser[5] formulated the sodium trimerization as follows:

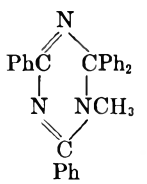


I II

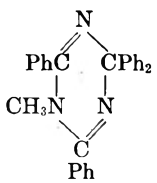
We have studied these reactions further, especially the reactions of I. The treatment of benzonitrile with sodium in boiling benzene for 4 hr. yielded 80–85% of I and 1–3% of II, in agreement with Lottermoser[3] except that the time required for complete reaction was greatly reduced by use of sodium dispersion. However, further heating in boiling benzene or at higher temperatures in other solvents did not result in improved yield of II, indicating that spontaneous elimination of phenylsodium does not occur under the conditions employed.

The yield of II was increased considerably by treatment of I with carbon dioxide or with sulfur dioxide (Table I). The simple assumption that this might be due to equilibrium shift by reaction with phenylsodium to form sodium benzoate or sodium benzenesulfinate is contradicted by the fact that treatment of I with carbon dioxide at elevated temperature under 100 atm. of carbon dioxide pressure prevented completely the formation of II beyond the 1–3% normally obtained in the absence of carbon dioxide.

Treatment of I with methyl iodide yielded two isomeric *N*-methyl derivatives for which the structures 2,2,4,6-tetraphenyl-3-methyl-2,3-dihydro-1,3,-5-triazine (III) and 2,2,4,6-tetraphenyl-5-methyl-2,5-dihydro-1,3,5-triazine (IV) are suggested. The



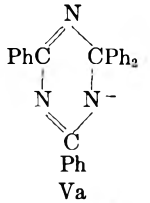
III, m.p. 191°



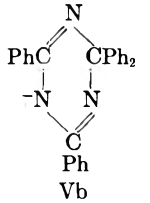
IV, m.p. 210°

evidence offered in support of the suggested structures, in addition to elementary analysis, molecular weight, and mixed melting point determinations is as follows: both show substantially zero value in determination of active hydrogen while I (Na = H) yielded one mole of methane in a control determination; ultraviolet absorption curves (Fig. 1) show significant differences and, for III, maxima indicating conjugation of double bonds, presumably to be ascribed to the *N*-ring. The participation of both nitrogen atoms in alkylation of analogous cyclic amidines has been reported, for example, in the case of 4(5) methylimidazole, which yields 1,4- and 1,5-dimethylimidazoles on treatment with methyl iodide.[6]

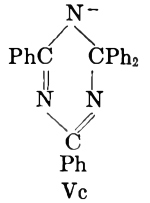
It seems therefore that the anion of I may be represented as a resonating system (V a,b,c) with



Va



Vb



Vc

(1) Present address: American Cyanamid Co., Stamford, Conn.

(2) A. Cook and D. Jones, *J. Chem. Soc.*, 278 (1941).

(3) A. W. von Hofmann, *Ber.*, 1, 198 (1868); A. Lottermoser, *J. prakt. Chem.*, 54, 132 (1896).

(4) R. Anker and A. Cook, *J. Chem. Soc.*, 323 (1941).

(5) F. Swamer, G. Reynolds, and C. Hauser, *J. Org. Chem.*, 16, 43 (1951).

(6) H. Gilman, *Organic Chemistry*, John Wiley and Sons, Inc., New York, 1953, vol. IV, p. 792.

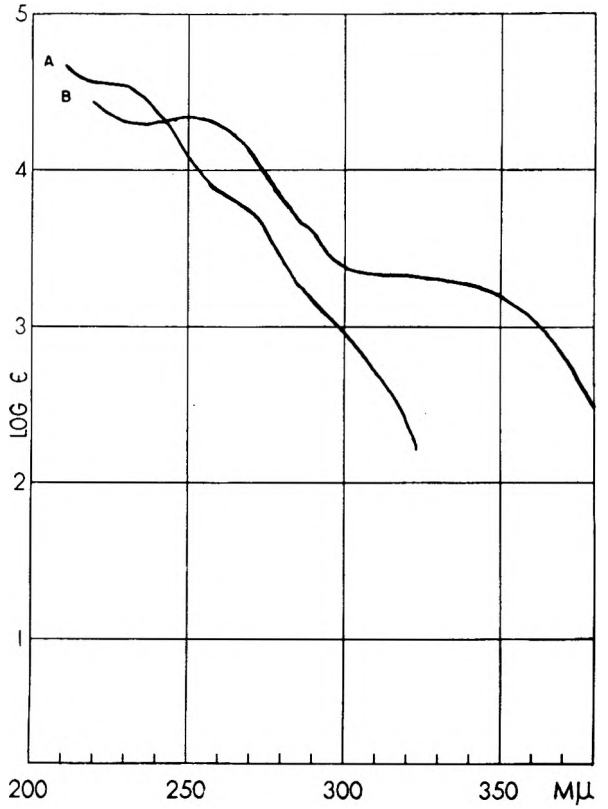


Fig. 1. Ultraviolet spectrum of: A, 2,2,4,6-tetraphenyl 5-methyl 2,5-dihydro-s-triazine; B, 2,2,4,6-tetraphenyl 3-methyl 2,3-dihydro-s-triazine.

resulting stabilization which impedes the aromatization of I to II by spontaneous loss of phenylsodium. We suggest that reaction of this anion with carbon dioxide and with sulfur dioxide forms in each case two carbamate or sulfinate ions RCO_2^- and RSO_2^- (R = V a and V b) in proportions which depend upon the contribution of each end-form to the resonance hybrid, as well as symmetry and steric factors. The resulting loss of resonance stability and increased electron density in the vicinity of carbon atom 2 is followed by transition to II by loss of benzoate or benzenesulfinate ion. This is probably undergone most readily by the unsymmetrical ion (R = V a), which would be expected to form in the lesser amount. The yield of II has not exceeded 23% in the experiments reported here by us or previously by others.

In further study of the report of von Hofmann[3] in which II was shown to form by the action of sodium on boiling benzonitrile, the action of benzonitrile on I in boiling benzene and xylene was investigated (Table I). As with carbon dioxide and sulfur dioxide the yield of II was again significantly increased, suggesting that analogous adducts of I with benzonitrile may be postulated as RC(Ph)=NNa (R = V a and V b). Kyaphenin (II) would form from the unsymmetrical adduct (R= V a) with separation of sodium diphenylketimine to start a fresh trimerization cycle in the manner suggested previously.[5] It may be noted that the postulated formation of additional II from freshly formed sodium diphenylketimine in the second and succeeding cycles does not increase the over-all yield of II significantly. This is to be anticipated in view of the approximately 3:1 ratio of symmetrical to unsymmetrical adduct formed in each cycle, which results rapidly in substantially complete consumption of freshly formed sodium diphenylketimine to yield the symmetrical adduct (R = V b) which does not aromatize.

In confirmation of the hypothesis that introduction of high electron-density (anionic) groups as carboxylate, sulfinate, and benzaldimino is necessary to effect aromatization, I was treated with further reagents to yield *N*-substitution products (Table II). No significant amounts of II were obtained in any case. Separation of isomers was not attempted; the compounds reported are probably the symmetrical forms corresponding to V b.

TABLE I

EFFECT OF CO_2,[a] SO_2,[a] AND C_6H_5CN[b] ON FORMATION OF II FROM I

Reagent	Time, Hr.	Temp., °C.	% Conversion
None	114	138	1
CO_2	3	80	4
	22	80	10
	4	138	12
	23	138	23
	48	138	23
SO_2	24	138	10
C_6H_5CN	5	82	7
	4	185	10
	24	138	21
	117	138	22

Percentage conversions are based on [a] benzonitrile and [b] sodium tetraphenyldihydro-s-triazine.

TABLE II

N-DERIVATIVES FROM SODIUM TETRAPHENYLDIHYDRO-S-TRIAZINE (I)[a]

Reagent	Time, Hr.	Temp., °C.	% yield	Formula	M.P., °C.
$(CH_3)_2SO_4$[b]	20	80		$C_{28}H_{23}N_3$	210
$ClCO_2C_2H_5$[c]	3	25	30	$C_{30}H_{25}O_2N_3$	155–156
C_6H_5COCl[d]	3	25	20	$C_{34}H_{25}ON_3$	232–233

[a] Heptane was used as solvent. [b] Product was identified by comparison with that obtained using methyl iodide. [c] Mole Weight calcd., 459; found by saponification No., 454. [d] % N calcd., 8.55; found, 8.51 (Dumas).

EXPERIMENTAL

Sodium tetraphenyldihydro-s-triazine (I). A mixture of sodium (3.0 g., 0.13 mole) and 150 ml. of dry thiophene-free benzene was placed in a 500-ml. three-necked flask fitted with a mercury-sealed stirrer, thermometer, dropping funnel, and reflux condenser with drying tube. The sodium was used as a 50% dispersion in kerosine, average particle size 15μ. The mixture was heated to 80° and benzonitrile (24 g., 0.23 mole) in 50 g. of benzene was added with stirring over 1 hr. Heating and stirring were continued for 3 hr. during which a dark red precipitate of I formed in suitable con-

dition for use in further reactions. Assay of the reaction mixture was made as follows: after cooling to room temperature in an atmosphere of nitrogen the solids were separated by filtration, allowed to air slake and then washed with water to remove sodium cyanide. The remaining insoluble solid was recrystallized from alcohol and yielded 19 g. (85%) of 2,2,4,6-tetraphenyldihydrotriazine, m.p. 190–191° in agreement with Lottermoser.[3] The benzene filtrate was distilled to remove the benzene and the residue was recrystallized from alcohol to yield 0.54 g. (3%) of II, m.p. 229–230° in agreement with that reported previously.[3,5]

Reaction of I *with carbon dioxide.* A portion of I was prepared (as above) from 0.23 mole of benzonitrile and 0.13 mole of sodium, using xylene as solvent. The mixture was heated to reflux and dry CO_2 was introduced through a fritted glass bubbler with stirring for 23 hr. The reaction-mixture, which contained suspended solids, was treated as in the preceding paragraph. The xylene solution yielded 2.72 g. of II, and the xylene-insoluble solids gave 1.34 g. after water washing and recrystallization from alcohol. The total yield of II was 4.06 g. (22.6%) based on the benzonitrile used. The procedures for other experiments with carbon dioxide and with sulfur dioxide differed from the above only in the solvent used and the reaction time and temperature.

Reaction of I *with benzonitrile.* A portion of I was prepared as above from 30 g. (0.26 mole +11% excess) of benzonitrile and 3 g. (0.13 mole) of sodium, using xylene as solvent. The excess of benzonitrile was added to ensure complete disappearance of the sodium in the first stage of the reaction. A further quantity of benzonitrile (0.195 mole) was then added and the mixture was refluxed with stirring for 24 hr. For this operation it appeared advantageous to partially fill the reaction vessel with glass beads, whose grinding action promotes the reaction between solid and liquid reactants. Subsequent treatment of the reaction mixture as described above yielded 4.09 g. of II (20.5%).

Methylation of I. A portion of I was prepared from benzonitrile (0.23 mole) and sodium (0.13 mole) in refluxing heptane with the aid of glass beads. After cooling the reaction mixture to 30° under nitrogen, methyl iodide (16.5 g., 0.116 mole) in 10 ml. of heptane was added over 1 hr. with stirring at 30–40°, and the stirring continued for 0.5 hr. The mixture was filtered to remove solid reaction products and the heptane filtrate was discarded. The separated solid was thoroughly washed with five 200-ml. portions of benzene and the combined benzene washes were applied to a column of 385 g. of alumina (Alcoa F-20), 1″ × 4′. The chromatogram was developed with benzene and yielded: II, m.p. 229–230°, 0.533 g. (3%); III, m.p. 191°, 0.920 g. (3.95%); IV, m.p. 210°, 3.173 g. (13.6%).

Anal. Calcd. for $C_{28}H_{23}N_3$: C, 83.8; H, 5.7; N, 10.5; mol. wt., 401. Found (III): C, 83.5; H, 5.9; N, 10.6; mol. wt., 403. (IV): C, 84.3; H, 5.3; N, 9.9; mol. wt., 401.

Active hydrogen: Calcd. for I (Na = H): 1 mole CH_4/mole subst.; found, 0.9 mole CH_4. III and IV both yielded 0.0 mole CH_4.

Mixed melting points: III–IV, 167–180°; III–I (Na = H), 155–170°; III–II, 175–205°.

Further derivatives of I. Treatment of I with other reagents under the conditions described above yielded *N*-substitution products (Table II). When heated alone or in solvents at elevated temperatures (without prior purification) these failed to yield further isolable amounts of II. The melting points and analyses shown were determined after recrystallization of the principal (probably symmetrical) isomer.

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[CONTRIBUTION FROM THE GRADUATE SCHOOL OF ARTS AND SCIENCES, UNIVERSITY OF BUFFALO]

Reaction of Cyanogen with Organic Compounds. XII. Glycols and Glycol Monoethers[1]

H. M. WOODBURN, ALAN B. WHITEHOUSE,[2] AND BERNARD G. PAUTLER[3]

Received June 16, 1958

Ethylene glycol, 1,2-propanediol, 1,3-propanediol, and 2,3-butanediol, as well as the methyl, ethyl, and butyl monoethers of ethylene glycol, react with cyanogen in the presence of hydrogen chloride to yield moderately stable symmetrical oxaldiimidate dihydrochlorides. Neither 1,2-, 1,3-, nor 1,4-butanediol reacts with cyanogen under these conditions. In the presence of aqueous potassium cyanide, cyanogen and the glycol monoethers produce stable cyanoformimidates. Potassium carbonate and ammonium hydroxide are equally effective catalysts. With catalytic amounts of sodium, glycol monoethers and cyanogen produce stable oxaldiimidates. 2-Methoxyethylcyanoformimidate reacts with methyl Cellosolve to form the oxaldiimidate. Other combinations of glycol ethers and cyanoformimidates have thus far been unreactive.

This investigation is part of a series dealing with the reaction of cyanogen with bifunctional compounds. In previous papers we have described the behavior of aliphatic and aromatic diamines,[4,5] amino mercaptans,[6] and amino alcohols.[7] Although published information concerning the reaction of cyanogen with monohydroxy alcohols is scanty,[8,9] the studies referred to above indicated that glycols might logically form any of the following type products: cyanoformimidates, $HO(CH_2)_xOC(=NH)CN$, oxaldiimidates, $HO(CH_2)_xOC(=NH)-C(=NH)O(CH_2)_xOH$, bi-

(1) Parts of this paper are from a thesis submitted by A. B. Whitehouse in partial fulfillment of the requirements for the Ph.D. degree, June 1957.

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(3) Postdoctoral Fellow, Mallinckrodt Chemical Works.

(4) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

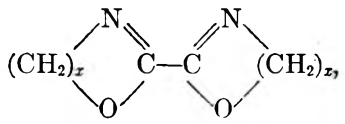
(5) H. M. Woodburn and J. R. Fisher, *J. Org. Chem.*, **22**, 895 (1957).

(6) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(7) H. M. Woodburn and E. L. Graminski, *J. Org. Chem.*, **23**, 819 (1958).

(8) J. U. Nef, *Ann.*, **287**, 274 (1895).

(9) A. Pinner and Fr. Klein, *Ber.*, **11**, 1475 (1878).

cyclic compounds, 

condensation polymers.

Actually only cyanoformimidates and oxaldiimidates were isolated. The absence of cyclization observed with amino alcohols was noted also with glycols.

Of the three methods reported to yield cyanogenation products from ethanol,[8,9] only that employing hydrogen chloride was applicable to glycols since either sodium or potassium cyanide caused the formation of tar from which no product could be isolated. Presumably the free oxaldiimidate is much less stable than its hydrochloride. Best yields were obtained when dry cyanogen and dry hydrogen chloride were passed into the glycol solution simultaneously. Although the presence of a solvent was not required to bring about a reaction, since pure glycols produced white precipitates when treated with cyanogen and hydrogen chloride, the high viscosity of glycols made filtration impossible and the product could not be obtained in a pure state. Dimethyl Cellosolve was found to possess high solvent action for glycols, cyanogen, and hydrogen chloride. Also, it was easily obtained in an anhydrous condition by fractionation over sodium and was preferable to diethyl ether which has poor glycol solvency.

Success in the glycol reaction often appears to depend on the purity of the glycol. For example, the practical grade of 1,3-propanediol obtained from Distillation Industries, Inc., even when distilled before use, gave a product which decomposed too rapidly for analysis. Treatment of the glycol with activated carbon followed by distillation gave a reagent which produced a stable oxaldiimidate dihydrochloride.

The following glycols, treated with cyanogen and hydrogen chloride, produced oxaldiimidate dihydrochlorides in yields of 22–74%: ethylene glycol, 1,3-propanediol, 1,2-propanediol, and 2,3-butanediol.

$$HO(CH_2)_xOH + (CN)_2 + 2HCl \longrightarrow HO(CH_2)_xOC(=NH_2Cl)-(=NH_2Cl)CO(CH_2)_xOH$$

1,2-Butanediol, 1,3-butanediol, and 1,4-butanediol failed to react even though it was shown that conditions were suitable since added ethylene glycol gave an immediate product.

Ethylene glycol, 1,3-propanediol, and 2,3-butanediol are symmetrical compounds; hence there can be no doubt concerning the structure of the diimidate product. 1,2-Propanediol, however, contains both a primary and a secondary hydroxy group and should, theoretically, form an oxaldiimidate in three ways. To throw light on this question a mixture of ethylene glycol (which contains only primary hydroxy groups) and 2,3-butanediol (which contains only secondary hydroxy groups) was cyanogenated using a quantity of cyanogen such that each of the glycols was present in excess. Hence the cyanogen should react only with that glycol offering the faster reaction. The product from the mixture was the oxaldiimidate dihydrochloride of ethylene glycol. It was concluded that the primary hydroxy group of 1,2-propanediol should have reacted more rapidly than the secondary and that the principal product of its cyanogenation should be *sym*-bis(2-hydroxypropyl)oxaldiimidate.

This result makes it difficult to understand the behavior of the butanediols since the one which reacted contains only a secondary hydroxy group whereas all the others contain at least one primary hydroxy group.

The monomethyl-, monoethyl-, and monobutyl ethers of ethylene glycol reacted with cyanogen and hydrogen chloride in dimethyl Cellosolve solution but the products which were obtained were too unstable for analysis. Therefore other methods of cyanogenation were investigated.

In the presence of sodium, the pure monoethers gave fair yields of oxaldiimidates. Because of their rather high boiling points, these liquids decomposed appreciably upon distillation even under reduced pressure. Their hydrochloride, made by passing anhydrous hydrogen chloride into a dimethyl Cellosolve solution of the free base, corresponded in instability and decomposition temperatures to those prepared directly from monoether, cyanogen, and hydrogen chloride.

Under conditions similar to those used on ethanol by Nef,[8] we treated the monoethers with cyanogen in the presence of aqueous potassium cyanide. In this case the products were cyanoformimidates,

$$ROC_2H_4OH + (CN)_2 \xrightarrow{KCN} ROC_2H_4OC(=NH)CN$$

They were unstable liquids, turning yellow and finally brown at room temperature but easily purified by vacuum distillation.

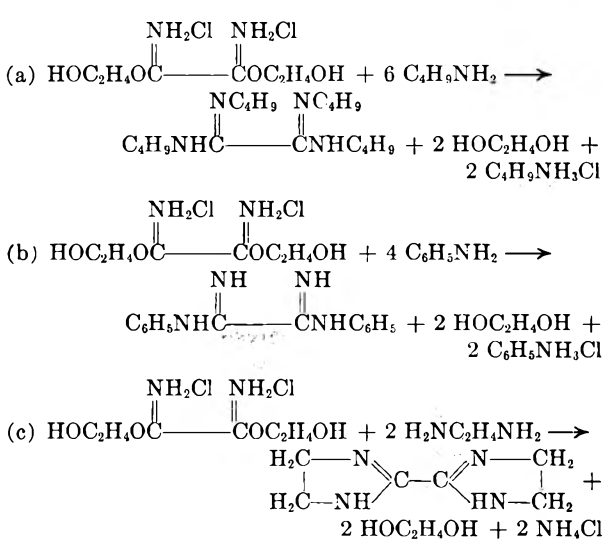
Potassium carbonate was an equally effective catalyst for the reaction, and even better yields were obtained when diethyl ether was used as solvent and ammonium hydroxide as catalyst.

Because sodium as catalyst caused both nitrile groups of cyanogen to react, we attempted to catalyze the reaction of cyanoformimidates with Cellosolves to yield oxaldiimidates. This was actually accomplished with the reaction pair 2-methoxyethyl cyanoformimidate and methyl Cellosolve,

$$CH_3OC_2H_4OC(=NH)CN + CH_3OC_2H_4OH \longrightarrow CH_3OC_2H_4OC(=NH)-(=NH)COC_2H_4OCH_3$$

However, no other combinations were successful whether the ether portions were identical or not. Thus the attractive possibility of producing an unsymmetrical oxaldiimidate was not realized. After more than 10 years of effort we have not yet succeeded in making an unsymmetrical oxamidine or oxaldiimidate.

Incidental to this work was the study of certain reactions such as (a), (b), and (c) which proved the structure of the oxaldiimidates and demonstrated the chemical similarity of oxaldiimidates and oxamidines.[10]



The three products (a) tetrabutyloxamidine, (b) diphenyloxamidine, and (c) bis(Δ^2-2-imidazolinyl) have been prepared independently by the action of cyanogen on butyl amine,[11] aniline,[12] and ethylenediamine.[4]

EXPERIMENTAL

Reagents. Cyanogen was prepared and purified essentially by the method of Janz.[13] We found it expedient, however, to add 100 ml. of water to the initial pot charge of copper sulfate. The resulting slurry could be stirred more readily than dry copper sulfate at the beginning of the reaction, and it reduced local heating and polymerization of the cyanogen.

After purification, the cyanogen was frozen in a Dry Ice–acetone trap at −80°. This allowed its weight to be easily determined. Removal of the freezing bath caused the cyanogen to distill quietly into the reaction vessel.

Glycols and glycol ethers were commercially available with the exception of 1,2-butanediol. This was synthesized according to a method used by Gattermann for ethylene glycol.[14] One mole (160 g.) of bromine was dissolved in 50 ml. of carbon tetrachloride, cooled by means of an ice bath, and C.P. butene-1 admitted. When the bromine was used up, as shown by the discharge of the red color, the mixture was washed with aqueous sodium carbonate, then water, and dried over calcium chloride. Fractionation through a 20-in. column packed with glass helices yielded 207 g. (92%) of 1,2-dibromobutane; b.p. 78.0–78.5°/45 mm.

A mixture of 0.47 mole (103 g.) of 1,2-dibromobutane, 30 g. of glacial acetic acid, and 0.9 mole (90 g.) of fused potassium acetate was refluxed for 2 hr. The crude mixture was distilled and to the distillate was added 103 g. of the dibromide and 1.35 moles (132 g.) of potassium acetate. This was in turn refluxed for 8 hr. and the crude mixture again distilled. The distillate was fractionated, yielding 30 g. (30%) of 1,2-butanediol diacetate; b.p. 74°/3 mm.

Dry methanol was prepared by distillation from magnesium methoxide. Dry hydrogen chloride was passed in until a 2.5% by weight solution was obtained. A mixture of 50 g. of the methanol solution and 50 g. of the butanediol diacetate was then refluxed for 1 hr., and fractionated. Methyl acetate was drawn from the head of the column very slowly at 58°. The temperature gradually rose to 64°, yielding a mixture of methyl acetate and methanol. The remaining liquid was distilled under reduced pressure over calcium sulfate, yielding 24 g. (92%) of pure 1,2-butanediol. Sodium was avoided in drying butanediols since it caused dehydration and polymerization during distillation.

Reaction of cyanogen with glycols. sym-Bis(2-hydroxyethyl)oxaldiimidate dihydrochloride from ethylene glycol. Sixty-two g. (1.0 mole) of ethylene glycol was mixed with 50–75 ml. of dry diethyl ether in an absorption bottle protected from the atmosphere by a calcium chloride drying tube and cooled in an ice salt bath. Dry hydrogen chloride was passed through the mixture for a few minutes, after which cyanogen and hydrogen chloride were passed in *simultaneously*. The reaction mixture was treated in this manner with an estimated half mole of cyanogen, causing the mixture to become turbid. After standing overnight in the ice box, a white solid precipitated, which was filtered off, washed well with ethanol, and placed in a desiccator containing both sulfuric acid and sodium hydroxide to dry. The yield based on glycol was 34%.

Anal. Calcd. for $C_6H_{14}N_2O_4Cl_2$: C, 28.9; H, 5.6; N, 11.2; Cl, 28.5. Found: C, 28.8; H, 5.7; N, 11.0; Cl, 28.6.

Although yields of more than 70% could be obtained by the substitution of dimethyl Cellosolve for diethyl ether, the purity of the product was not as high as that obtained above and much time was required for recrystallization.

sym-Bis(2-hydroxypropyl)oxaldiimidate dihydrochloride from 1,2-propanediol. A mixture of 24 g. (0.32 mole) of dry 1,2-propanediol and 90 g. of dry dimethyl Cellosolve was cooled to 0° in an ice bath. Hydrogen chloride and cyanogen (15.3 g.; 0.29 mole), both anhydrous, were admitted to the solution simultaneously. The mixture was protected from moisture by a calcium chloride tube and, after a short time, became turbid. It was allowed to stand for 0.5 hr. after the reagents had been added, was then filtered by suction, and was washed with dry dimethyl Cellosolve. The product was dried under vacuum in the presence of sulfuric acid and sodium hydroxide. The yield was 32 g. (74% based on glycol) of white solid melting at 168–170° (dec.).

Anal. Calcd. for $C_8H_{18}O_4N_2Cl_2$: C, 34.7; H, 6.6; N, 10.1; Cl, 25.6. Found: C, 34.4; H, 6.8; N, 10.0; Cl, 25.9.

sym-Bis(3-hydroxypropyl)oxaldiimidate dihydrochloride from 1,3-propanediol. A pure and relatively stable product could be obtained in this case only if the glycol as purchased had been purified by shaking with activated carbon, filtering, and vacuum-distilling over calcium sulfate. A solution of 15.4 g. (0.2 mole) of this specially purified 1,3-propanediol, dissolved in 90 g. of dry dimethyl Cellosolve, was cooled to 0°. Dry hydrogen chloride and dry cyanogen (10.0 g.; 0.19 mole) were passed in simultaneously. The product, worked up as described above, was a white solid weighing 10.3 g. (37% yield based on glycol); m.p. 87–88°.

Anal. Calcd. for $C_8H_{18}O_4N_2Cl_2$: C, 34.7; H, 6.6; N, 10.1; Cl, 25.6. Found: C, 34.3; H, 6.4; N, 10.0; Cl, 25.9.

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(12) A. W. Hofmann, *Ber.*, **20**, 2252 (1887).

(13) G. J. Janz, *Inorg. Syntheses*, **5**, 43 (1957).

(14) L. Gattermann, *Laboratory Methods of Organic Chemistry*. The Macmillan Company, New York, N. Y., 1932, p. 102.

sym-Bis(1-methyl-2-hydroxypropyl)oxaldiimidate dihydrochloride from 2,3-butanediol. A solution containing 14.4 g. (0.16 mole) of anhydrous 2,3-butanediol and 90 g. of dry dimethyl Cellosolve was cooled to 0° and treated simultaneously with dry hydrogen chloride and cyanogen (13.9 g.; 0.27 mole). After 2 hr., precipitation appeared to be complete, and the white, crystalline solid was filtered by suction and worked up as described above. The yield was 5.4 g. (22% based on glycol); m.p. 148–152° (dec.).

Anal. Calcd. for $C_{10}H_{22}O_4N_2Cl_2$: C, 39.4; H, 7.3; N, 9.2; Cl, 23.2. Found: C, 39.1; H, 7.6; N, 9.1; Cl, 23.5.

Cyanogenation of a mixture of ethylene glycol and 2,3-butanediol. A mixture of 0.1 mole (6.2 g.) of dry ethylene glycol and 0.1 mole (9.0 g.) of dry 2,3-butanediol was dissolved in 30 g. of anhydrous dimethyl Cellosolve and cooled to 0°. Dry hydrogen chloride and dry cyanogen (2.1 g.; 0.04 mole) were admitted simultaneously. The mixture, protected from moisture by a calcium chloride tube, formed a white precipitate, which was filtered by suction, washed with dry solvent and dried under vacuum in the presence of sulfuric acid and sodium hydroxide. The solid melted at 183–185° and contained 28.8% chlorine, which obviously indicated that the product was the *dihydrochloride of sym-bis-(2-hydroxyethyl)-oxaldiimidate.* See above.

Reaction of cyanogen with the monoethers of ethylene glycol. 2-Methoxyethyl cyanoformimidate from methyl Cellosolve. (a) *Potassium cyanide present.* A solution containing 23.1 g. (0.3 mole) of methyl Cellosolve, 7 g. of potassium cyanide, and 100 ml. of distilled water was cooled to 0°. Cyanogen (12.0 g.; 0.23 mole) was passed in and the solution was immediately extracted with ether. After 24 hr., the solution was extracted a second time, and the ethereal solutions were combined and dried over calcium chloride. The oil remaining after evaporation of the ether was distilled under vacuum giving 7.5 g. (25% yield based on cyanogen) of colorless liquid; b.p. 54–55°/1.5 mm; n_D^{25} 1.4362; d_4^{25} 1.0719.

Anal. Calcd. for $C_5H_8O_2N_2$: C, 46.9; H, 6.29; N, 21.9; mol. wt. 128. Found: C, 46.6; H, 6.6; N, 22.1; mol. wt. 138.

(b) *Ammonia and ether present.* A solution of 45 g. (0.59 mole) of methyl Cellosolve dissolved in 150 ml. of ethanol-free ether was cooled to 0°. One-half ml. of concentrated ammonium hydroxide was added and 30 g. (0.58 mole) of cyanogen was passed in. The mixture was filtered to remove a solid presumed to be oxamide, and the ether was evaporated from the filtrate. Distillation of the residue produced methyl Cellosolve and a product having a boiling range of 53–55°/1.5 mm. The yield was 25.0 g. or 34% based on cyanogen.

2-Ethoxyethyl cyanoformimidate from ethyl Cellosolve. A solution containing 50 g. (0.55 mole) of ethyl Cellosolve, 7 g. of potassium cyanide, and 100 ml. of distilled water was cooled to 0° and treated with 13 g. (0.25 mole) of cyanogen. The brown solution was extracted with ether, dried with calcium chloride, and distilled. The product was a colorless liquid boiling at 48°/1.5 mm. Yield 8.0 g., 23% based on cyanogen.

Anal. Calcd. for $C_6H_{10}O_2N_2$: C, 50.7; H, 7.1; N, 19.7; mol. wt., 142. Found: C, 50.5; H, 6.9; N, 19.5; mol. wt. 134.

2-Butoxyethyl cyanoformidate from butyl Cellosolve. A cold solution of 60 g. (0.51 mole) of butyl Cellosolve and 7 g. of potassium cyanide in 150 ml. of distilled water was treated with 16.1 g. (0.31 mole) of cyanogen. The mixture became turbid, then brown. It was extracted with ether; the extracts being dried over calcium chloride and distilled. A colorless liquid weighing 15.2 g. (28.7% yield based on cyanogen) resulted; b.p. 75–77°/1.5 mm.

Anal. Calcd. for $C_8H_{14}O_2N_2$: C, 56.5; H, 8.3; N, 16.5; mol. wt. 170. Found: C, 56.2; H, 8.2; N, 16.8; mol. wt. 158.

sym-Bis(2-methoxyethyl)oxaldiimidate from methyl Cellosolve. A solution of 6 g. (0.26 mole) of freshly cut sodium in 54.8 g. (0.72 mole) of anhydrous methyl Cellosolve was cooled to 0° and treated with 13.8 g. (0.27 mole) of dry cyanogen. One hundred ml. of water was then added and the mixture extracted with ether. After drying over calcium chloride, the extract was distilled, yielding 9.3 g. (6.5% based on Cellosolve) of liquid boiling at 115°/1.5 mm; m.p. 41–43°.

Anal. Calcd. for $C_8H_{16}O_4N_2$: C, 47.0; H, 7.9; N, 13.7; mol. wt. 204. Found: C, 47.0; H, 8.0; N, 13.5; mol. wt. 190.

The *dihydrochloride* was prepared by saturating an ether solution of the oxaldiimidate with anhydrous hydrogen chloride. The resulting white solid melted at 95° but was too unstable to analyze.

The dihydrochloride was prepared directly by the following method: A solution containing 30.4 g. (0.4 mole) of anhydrous methyl Cellosolve and 50 g. of anhydrous dimethyl Cellosolve was cooled to 0° and treated with 15.4 g. (0.3 mole) of cyanogen. Dry hydrogen chloride was then passed into the mixture and the resulting white, crystalline precipitate was filtered. It was washed three times with solvent and dried in vacuum over sulfuric acid and sodium hydroxide. The yield was 5.2 g. (9.4% based on Cellosolve) of product melting at 95°. It was too unstable for analysis.

sym-Bis(2-ethoxyethyl)oxaldiimidate from ethyl Cellosolve. From a solution of 5 g. (0.22 mole) of freshly cut sodium in 45 g. (0.5 mole) of anhydrous ethyl Cellosolve, treated at 0° with 15 g. (0.29 mole) of cyanogen, was obtained 9.8 g. (8.5% yield, based on Cellosolve) of product boiling at 117°/1.5 mm. and melting at 30–32°. The product was recovered as described under methyl Cellosolve.

Anal. Calcd. for $C_{10}H_{20}O_4N_2$: C, 51.7; H, 8.7; N, 12.1; Mol. wt. 232. Found: C, 51.6; H, 8.7; N, 12.1; Mol. wt., 211.

The *dihydrochloride* prepared by saturating an ether solution of the oxaldiimidate with hydrogen chloride, or directly from ethyl Cellosolve, cyanogen, and hydrogen chloride as described above, melted at 95° but was too unstable to analyze.

sym-Bis(2-butoxyethyl)oxaldiimidate from butyl Cellosolve. From 4 g. (0.17 mole) of freshly cut sodium in 60 g. (0.51 mole) of butyl Cellosolve treated with 16.3 g. (0.31 mole) of cyanogen was obtained 19.3 g. (26.8% yield based on Cellosolve) of liquid boiling at 137–140°/1.5 mm.

Anal. Calcd. for $C_{14}H_{28}O_4N_2$: C, 58.3; H, 9.8; N, 9.7; mol. wt. 288. Found: C, 58.4; H, 9.9; N, 10.0; mol. wt. 252.

The *dihydrochloride* prepared by saturating an ether solution of the oxaldiimidate with hydrogen chloride, or directly from butyl Cellosolve, cyanogen, and hydrogen chloride, melted at 85° but was too unstable to analyze.

Associated reactions: sym-Bis(2-methoxyethyl)oxaldiimidate from 2-methoxyethyl cyanoformimidate and methyl Cellosolve. A small piece of sodium was dissolved in 3 g. (0.04 mole) of anhydrous methyl Cellosolve in a clean, dry flask fitted with a calcium chloride tube. When the solution had cooled, 5.2 g. (0.04 mole) of freshly distilled 2-methoxyethyl cyanoformimidate was added slowly, with continued cooling. The mixture was allowed to stand for 0.5 hr. at room temperature. The red solution was extracted with petroleum ether, and the extract was treated with decolorizing carbon and evaporated, leaving 1.6 g. (19.6% yield) of *sym-bis(2-methoxyethyl)oxaldiimidate* melting at 41–43°.

The same procedure was employed with all combinations of the cyanoformimidates prepared above and methyl, ethyl, and butyl Cellosolve. Only tars and starting materials were recovered. In no case was an oxaldiimidate isolated.

Tetra-n-butyloxamidine from sym-bis(2-hydroxyethyl)-oxaldiimidate and butylamine. One gram of *sym*-bis(2-hydroxyethyl)oxaldiimidate dihydrochloride was dissolved in 15 ml. of *n*-butyl amine. There was considerable evolution of heat accompanying the mixing. The solution was refluxed for 1 hr., after which 50 ml. of distilled water was added, forming a white precipitate. This was filtered and recrystallized from petroleum ether (activated carbon present), producing a white, silky product melting at 84–86°. Admixture of tetra-*n*-butyloxamidine[15] resulted in a melting point of 84–85°.

(15) H. M. Woodburn, B. Morehead, and M. C. Chen, *J. Org. Chem.*, 15, 541 (1950).

Tetra-n-butyloxamidine from sym-bis(2-methoxyethyl)oxaldiimidate and butylamine. A mixture of 3.0 g. (0.11 mole) of *sym*-bis(2-methoxyethyl)oxaldiimidate dihydrochloride and 12.0 g. (1.64 moles) of *n*-butylamine was refluxed for 3 hr. The solution was poured into 300 ml. of water and the precipitate filtered by suction. Recrystallization from petroleum ether gave white crystals melting at 85–86°. Admixture with tetra-*n*-butyloxamidine[15] resulted in a melting point of 85–86°.

sym-Di-n-butyloxamidine dihydrochloride from sym-bis(2-hydroxypropyl)oxaldiimidate dihydrochloride and butylamine. A solution of 1.0 g. (0.004 mole) of *sym*-bis(2-hydroxypropyl)oxaldiimidate dihydrochloride dissolved in 0.6 g. (0.008 mole) of *n*-butylamine was mixed with 25 ml. of dimethyl Cellosolve and refluxed for 5 min. Petroleum ether was added to the cooled mixture until it turned turbid. An oil separated, which was frozen solid by the use of Dry Ice. The solvent was then decanted and the residue dissolved in ethanol. Dry hydrogen chloride was passed into the solution and the white precipitate filtered by suction. It melted at 270°. When mixed with pure di-*n*-butyloxamidine dihydrochloride,[11] it melted at 268–269°.

sym-Diphenyloxamidine from sym-bis(2-hydroxyethyl)oxaldiimidate and aniline. By dissolving the diimidate dihydrochloride in aniline and allowing the solution to stand at room temperature for several hours, a 32% yield of *sym*-diphenyloxamidine[16] was obtained. Recrystallized from benzene, the product melted at 208–212°; mixed with diphenyloxamidine at 210–214°.

Bis(Δ²-2-imidazolinyl) from sym-bis(2-hydroxyethyl)oxaldiimidate and ethylenediamine. Two grams of the diimidate was dissolved in 15 ml. of 95% ethylenediamine solution and heated in a hot water bath for 5 min. On cooling, a white solid precipitated. The mixture was diluted with water and the solid filtered off and recrystallized from alcohol. Melting point (sealed tube) 289–292°; mixed with bis-(Δ²-2-imidazolinyl),[4] 286–290°.

BUFFALO 14, N. Y.

(16) A. W. Hofmann, *Ann.*, 66, 130 (1848).

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

Acenaphthene Chemistry. IV.[1] The Aluminum Chloride Catalyzed Diacylation of Acenaphthene

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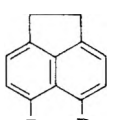
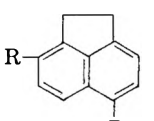
3,6-Dibenzoylacenaphthene is formed by the direct acylation of acenaphthene in the Friedel-Crafts reaction. It was converted into the dioxime which was rearranged to the dibenzamide and then hydrolyzed to 3,6-diaminoacenaphthene. The diacetylacenaphthene formed by direct acetylation was shown to be 3,6-isomer and not the 5,6-diacetyl compound as reported.

The literature gives numerous examples of electrophilic substitution in the acenaphthene nucleus. Reactions such as nitration, sulfonation, halogenation, and acylation with aluminum chloride give predominately 5-substituted acenaphthenes.[3] It has been established that monoacetylation will produce a small amount of the 3-isomer.[4,5] If these mono substituted derivatives are subjected to further electrophilic attack the entering group shows a strong preference for the 6 position.[6–9] Disubstituted derivatives have been prepared by the Friedel-Crafts reaction. Thus Dziewonski and Spirer[10] prepared a diacetyl derivative m.p. 149° which they described as the 5,6-isomer I since the dioxime is reported to rearrange to the diacetamide II which was hydrolyzed to the known 5,6-diaminoacenaphthene III. Similar reactions were used to characterize a dipropionyl derivative.[11] The formation of 4,7-di-*t*-butylacenaphthene by means of the Friedel-Crafts reaction has been definitely established.[3]





I.	R = $COCH_3$	VII.	R = NH_2
II.	R = $NHCOCH_3$	VIII.	R = $NHCOC_6H_5$
III.	R = NH_2	IX.	R = COC_6H_5
IV.	R = COC_6H_5	X.	R = $COCH_3$
V.	R = $NHCOC_6H_5$	XI.	R = $NHCOCH_3$
VI.	R = COOH	XII.	R = COOH

In our work the 5,6-dibenzoylacenaphthene (IV) was desired. The patent literature[12] describes a dibenzoylacenaphthene, m.p. 143°, and a diacetyl

(1) For paper III see H. J. Richter and B. C. Weberg, *J. Am. Chem. Soc.*, 80, 6446 (1958). The support of this work by an Ohio Oil Co. Fellowship and a grant from the National Institute of Health (Cy-2997-Cy) is respectfully acknowledged.

(2) A portion of the dissertation submitted to the Graduate School of the University of Colorado in partial fulfillment of the requirements for the Ph.D. degree.

(3) H. E. Nurnsten and A. T. Peters, *J. Chem. Soc.*, 729 1950.

(4) D. Nightingale, H. E. Ungnade, and H. E. French, *J. Am. Chem. Soc.*, 67, 1262 (1945).

(5) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, 61, 1272 (1939).

(6) F. Sachs and G. Mosebach, *Ber.*, 43, 2473 (1910); 44, 2852(1911).

(7) C. Graebe, *Ann.*, 327, 77 (1903).

(8) H. J. Richter, *J. Org. Chem.*, 21, 619 (1956).

(9) K. Dziewonski and M. Rychlik, *Bull. intern. acad. polon. sci.*, A, 179 (1925).

(10) K. Dziewonski and J. Spirer, *Bull. intern. acad. polon. sci.*, A, 232 (1931).

(11) K. Dziewonski and J. Moszew, *Bull. intern. acad. polon. sci.*, A, 242 (1931).

(12) O. Wulff, R. Sedhmayr, and W. Eckert, U. S. Patent 1,747,535 (1930) British Patents 291,347 (1929) and 279,506 (1928).

derivative, m.p. 146°, but no structures are assigned. A dibenzoylacenaphthene, m.p. 149–150°, was obtained in 33% yield by the acylation of acenaphthene with two equivalents of benzoyl chloride with aluminum chloride as the catalyst. This product was converted into the dioxime and rearranged. A comparison of this product with the dibenzamide V prepared from the known 5,6-diaminoacenaphthene (III) showed them to be different. The possibility that the reaction may have stopped after the rearrangement of only one of the oxime groups because of precipitation of the product was excluded since no further rearrangement occurred when it was dissolved in much solvent and again subjected to rearranging conditions.

Since Dziewonski and Spirer prepared and supposedly proved the structure of 5,6-diacetylacenaphthene, under the conditions of the haloform reaction this compound should form 5,6-acenaphthenedicarboxylic acid (VI). A diacetyl compound, m.p. 148–149°, was obtained in 19% yield by acylation in carbon disulfide and converted into a diacid in excellent yield. This acid did not melt below 340°. Freund and Fleischer[13] reported a m.p. of 293–294°, for the anhydride formed at this temperature. This result cast serious doubt on the structure reported as 5,6-diacetylacenaphthene. It is conceivable that a substituent in the 5-position would hinder attack at the 6-position and thus favor the formation of a 3,6-isomer in diacylation. There are no reported instances of 3,6-diacylation of acenaphthene.

Hydrolysis of the product obtained from the Beckmann rearrangement of dibenzoylacenaphthene dioxime with refluxing 70% sulfuric acid yielded slightly less than one equivalent of benzoic acid. An amine was isolated from this reaction which reacted with benzoyl chloride to reform the original product. An analysis of the amine indicated an amino-benzamidoacenaphthene.

With 100% phosphoric acid as the reagent for hydrolysis,[14] 1.22 equivalents of benzoic acid was isolated. The formation of more than one equivalent of benzoic acid indicated that the rearrangement formed a dibenzamide. A diamine, m.p. 100–101° was isolated from the reaction mixture.

Following the procedure of Morgan and Harrison,[15] there was obtained a 17% yield of 3-nitroacenaphthene which on further nitration formed the 3,6-dinitro compound. This was reduced to 3,6-diaminoacenaphthene (VII) m.p. 100–101°. The 3,6-dibenzamide VIII obtained from this diamine did not depress the melting point of the product obtained by rearranging the dioxime of the dibenzoylacenaphthene obtained by direct acylation. The infrared spectra were superimposable. The dibenzoyl derivative m.p. 149–150° is thus 3,6-dibenzoylacenaphthene (IX).

In view of the above results, the work described by Dziewonski and Spirer[10] for proving the structure of diacetylacenaphthene was repeated. The diacetyl compound, m.p. 149–150° (lit.[10] 149°), was converted into the dioxime using the procedure described. This compound melted at 206–208° instead of 196° as reported. The analysis indicated a diacetylacenaphthene dioxime. This was subjected to the Beckmann rearrangement using Dziewonski and Spirer's procedure. Two products were isolated, one of which was readily soluble in glacial acetic acid and the other only very slightly soluble. The latter compound, m.p. 208–210°, had the composition of a monoacetate intermediate whereas the former compound, m.p. 300–301°, analyzed for a diacetamidoacenaphthene. This could not be hydrolyzed with dilute hydrochloric acid. Dziewonski and Spirer had reported a single product, m.p. 227–228°, which is reported to be hydrolyzed with 6% hydrochloric acid to give 5,6-diaminoacenaphthene.

When the monoacetate intermediate was again subjected to the conditions of the Beckmann rearrangement using twice the volume of solvent, the diacetamide, m.p. 300–301°, was formed. This diacetamidoacenaphthene XI was synthesized from 3,6-diaminoacenaphthene (VII). A mixture of this compound and the diacetamidoacenaphthene from the rearrangement of the dioxime of diacetylacenaphthene obtained by direct acylation melted without depression and their infrared spectra were superimposable. Thus the diacetylacenaphthene melting at 149° is the 3,6-isomer X and not the 5,6-isomer as reported by Dziewonski and Spirer. The diacid, prepared by the haloform reaction on this diacetylacenaphthene must then be the 3,6-isomer XII. It is not inconceivable that two diacetylacenaphthenes exist that melt at 149°, but due to the great difference in symmetry of the two isomers, it seems unlikely. Although Dziewonski and Spirer's preparation of the compound involved a much higher reaction temperature, they stated that their product was identical to the diacetylacenaphthene found by Fleischer and Wolff[16] who used a procedure similar to that used in this work.

During the course of the work, before the structure of the dibenzoyl derivative was established, it was assumed to be the 5,6-derivative and attempts were made to synthesize the products resulting from the rearrangement of the theoretically possible isomeric dioximes. The dioxime could exist as *syn,syn*-diphenyl-, *syn,anti*-diphenyl-, and *anti,anti*-diphenyl-dioximes. Under the conditions for a Beckmann rearrangement, these oximes could yield a dibenzamide, a benzamide-

(13) M. Freund and K. Fleischer, *Ann.*, **399**, 222 (1913).

(14) G. Berger and S. C. J. Oliver, *Rec. trav. chim.*, **46**, 600 (1927).

(15) G. T. Morgan and H. A. Harrison, *J. Soc. Chem. Ind.*, **49**, 413 T (1930).

(16) K. Fleischer and P. Wolff, *Ber.*, **53**, 925 (1920).

anilide, and a dianilide respectively. The products prepared in this study included the dianilide of 3,6-acenaphthene dicarboxylic acid which was first-presumed to be the 5,6-isomer, the 5,6-dibenzamide, and a benzamide-anilide. In the preparation of the benzamide-anilide, 5-acenaphthanilide was nitrated to form a nitroacenaphthanilide. The reaction of 5-acenaphthoyl chloride with *o*-nitroaniline and with *p*-nitroaniline formed two of the possible nitro anilides, neither of which was identical with the product obtained from the nitration of 5-acenaphthanilide. These results indicate that nitration of the anilide occurred on the unsubstituted ring of acenaphthene. The nitration product was reduced and converted into a benzamide. This benzamidoacenaphthanilide has properties strikingly similar to the product obtained by rearranging dibenzoylacenaphthene dioxime. Both compounds crystallized from 1-butanol as colorless plates and both compounds melt at 276–277°. However, a mixture of the two substances melted with a depression of more than 30°.

EXPERIMENTAL

3,6-Dibenzoylacenaphthene (IX). Acenaphthene (30.8 g., 0.200 mole) and 63.0 g. (0.451 mole) of freshly distilled benzoyl chloride were dissolved in 250 ml. of dry nitrobenzene. The stirred solution was cooled to 3° and 60.0 g. (0.448 mole) of powdered anhydrous aluminum chloride was added during the course of 1.5 hr. at such a rate that the temperature did not rise above 5°. The flask was packed in ice and allowed to warm up overnight. The dark solution was then maintained at 30° for 1 hr., at 40° for 1 hr., and finally at 50° for 1 hr. After cooling the solution to room temperature, it was hydrolyzed with ice and hydrochloric acid. The nitrobenzene was removed by steam distillation leaving a black tarry mass which hardened on cooling. The water was drained from the residue which was then extracted with 300 ml. of hot ethanol. This extract was filtered with the aid of a hot funnel. The dark brown filtrate deposited tan crystals on cooling. This extraction procedure was continued until the ethanol filtrates ceased depositing crystals. The combined crude crystals weighed 24.0 g. (33%) and melted at 145–148°. The yields in this preparation varied from 15% to 33%. Two recrystallizations from ethanol with charcoal gave colorless prisms, m.p. 148.5–149.5°.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.17; H, 5.01. Found: C, 85.95; H, 5.28.

2,5-Dibenzoylnaphthalic anhydride. To a solution of 1.07 g. (0.0030 mole) of 3,6-dibenzoylacenaphthene dissolved in 15 ml. of glacial acetic acid was added 1.5 g. (0.067 mole) of chromic anhydride dissolved in a minimum of water. The solution was heated at reflux for 1 hr. during which time a crystalline solid separated. After cooling the mixture, the solid was separated by filtration. There was thus obtained 0.72 g. (58%) of product, m.p. 245–249°, which was dissolved in 5% sodium hydroxide solution and filtered to remove the small amount of occluded chromium hydroxide which precipitated. The solution was acidified and the precipitated acid crystallized twice from glacial acetic acid. The anhydride separated as colorless crystals, m.p. 250–251°.

Anal. Calcd. for $C_{26}H_{14}O_5$: C, 76.84; H, 3.47. Found: C, 76.98; H, 3.32.

2,5-Dibenzoylnaphthalimide. One g. (0.0025 mole) of 2,5-dibenzoylnaphthalic anhydride, prepared as described above, was dissolved in 100 ml. of 5% sodium hydroxide solution. On cooling the sodium salt crystallized. Water was added to form a clear solution at room temperature which was then acidified with 10% hydrochloric acid to liberate the acid which separated as a white precipitate. The 2,5-dibenzoylnaphthalic acid lost water at about 105° to form the anhydride which then melted at 249–250°. A solution of 0.40 g. (0.00094 mole) of the diacid in 50 ml. of concentrated ammonium hydroxide was boiled for 1 hr. During this time a white solid precipitated. After cooling the mixture, the product was removed by filtration and washed with water. Crystallization from toluene gave white needles, m.p. 246–249°.

Anal. Calcd. for $C_{26}H_{15}NO_4$: N, 3.46. Found: N, 3.57.

3,6-Dibenzoylacenaphthene dioxime. To 200 ml. of ethanol was added 3.30 g. (0.00910 mole) of 3,6-dibenzoylacenaphthene, 4.5 g. (0.065 mole) of hydroxylamine hydrochloride, and 5.2 g. (0.13 mole) of sodium hydroxide dissolved in a minimum of water. After 3 hr. of heating at reflux, about 25 ml. of water was added to dissolve some precipitated salt. After cooling, the solution was filtered and acidified to *p*H 2. The cream colored precipitate was filtered with suction, washed with cold water, and dried. The crude product (3.44 g., 96.5%) melted at 268–272°. One crystallization from ethanol, followed by two recrystallizations from 1-butanol with decolorizing charcoal gave colorless crystals, m.p. 271–273°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: N, 7.14. Found: N, 7.19.

3,6-Dibenzamidoacenaphthene (VIII). To a solution of 75 ml. of glacial acetic acid and 38 ml. of acetic anhydride was added 7.20 g. (0.0184 mole) of 3,6-dibenzoylacenaphthene dioxime. Hydrogen chloride was passed through the solution. Within a few minutes, heat was given off and the solid dissolved forming an orange solution. After passing hydrogen chloride gas through the solution for 4 hr., the flask was stoppered and left overnight. A yellow oil separated. The solution and oil were poured into one liter of cold water causing precipitation of a cream colored solid. This was filtered, washed with water, and dried. There was obtained 7.1 g. (99%) of crude product, m.p. 273–277°. Crystallization from 1-butanol with decolorizing charcoal gave colorless plates, m.p. 276–277°. A warm solution of this compound in equal parts of glacial acetic acid and acetic anhydride was again saturated with hydrogen chloride and allowed to stand overnight. The solid which separated when the solution was diluted with water indicated no further reaction.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: N, 7.14. Found: N, 7.18.

Hydrolysis of 3,6-dibenzamidoacenaphthene with 70% sulfuric acid. A mixture was prepared from 0.50 g. (0.0013 mole) of 3,6-dibenzamidoacenaphthene and 25 ml. of 70% sulfuric acid. The mixture was heated at reflux which caused the solid to dissolve slowly and sublimed benzoic acid to crystallize in the condenser. After 30 min. the starting material had dissolved completely. The mixture was cooled and then diluted with 250 ml. of cold water. The benzoic acid was separated by filtration and after drying was found to amount to 0.13 g. (42%). The hydrolysis filtrate was made alkaline with 10% sodium hydroxide solution which caused a green color to form in the solution. This solution was extracted with four 50-ml. portions of ether which were combined and then evaporated leaving a yellow residue, m.p. 102–108°, (0.19 g., 52%). An ether solution of this substance formed a white solid precipitate when saturated with dry hydrogen chloride. The amine was regenerated by adding 10% sodium carbonate solution to a water solution of the amine hydrochloride. Crystallization of the crude amine from petroleum ether, b.p. 60–70°, produced long, nearly colorless needles, m.p. 115–116°, of what is probably 3-benzamido-6-aminoacenaphthene.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.50. Found: C, 79.27; H, 6.05.

To a solution of 0.10 g. (0.00035 mole) of 3-benzamido-6-aminoacenaphthene, obtained as described above, in 5 ml. of dry pyridine was added 10 drops of benzoyl chloride. The

brown solution was allowed to stand for 15 min. and then poured into 400 ml. of cold water. The cream colored precipitate was removed by filtration, washed with water, and dried. The yield of the product, m.p. 270–275°, was quantitative. A mixture of this compound and the product obtained by rearranging the 3,6-dibenzoyldioxime melted without depression. The infrared spectra of these two substances were identical.

Hydrolysis of 3,6-dibenzamidoacenaphthene (VIII) *with 100% phosphoric acid.* The product from the Beckmann rearrangement of the dioxime of 3,6-dibenzoylacenaphthene (3.50 g., 1.00 mole) was added to 25 g. of 100% phosphoric acid and hydrolyzed as described by Berger and Oliver.[14] The yield of crude benzoic acid that sublimed from the reaction mixture was 1.58 g. which was dissolved in dilute sodium hydroxide and reprecipitated. The weight of the purified benzoic acid was 1.33 g. (1.22 mole). The phosphoric acid filtrate was made alkaline with 10% sodium hydroxide and extracted with five 50-ml. portions of ether. After drying, the combined ether solution was saturated with dry hydrogen chloride which precipitated the salt of the amine. The amine hydrochloride was converted into the amine by dissolving it in warm water and adding 10% sodium carbonate solution. The cream colored amine, m.p. 100–101° weighed 0.94 g. (0.37 equivalent).

3,6-Diacetylacenaphthene (X). To 400 ml. of dry carbon disulfide was added 75.0 g. (0.955 mole) of freshly distilled acetyl chloride and 60.0 g. (0.390 mole) of acenaphthene. The solution was cooled to 3° and 140 g. (1.05 mole) of powdered anhydrous aluminum chloride was added slowly so that the temperature did not rise above 5°. After packing the flask in ice, the solution was left to warm to room temperature overnight. During this time a tarry reddish brown mass separated which made stirring very difficult. The carbon disulfide was decanted and the residue was hydrolyzed with ice and hydrochloric acid producing a black solid. The solid was separated by filtration and partially dried on the suction filter, and then extracted with 400 ml. of boiling ethanol which deposited crude crystals on cooling. The extractions were continued until no crystals formed. The crude product was recrystallized from ethanol with decolorizing charcoal to yield 17.3 g. (19%) of a light tan crystalline product, m.p. 146–148°. Two additional recrystallizations from ethanol gave a white product, m.p. 148–149° (lit. 146°,[16] reported[10] as 5,6-diacetylacenaphthene, m.p. 149°).[17]

3,6-Acenaphthenedicarboxylic acid (XII). To a solution of 500 ml. of Chlorox (5.25% sodium hypochlorite) and 50 ml. of 10% sodium hydroxide was added 10.0 g. (0.042 mole) of 3,6-diacetylacenaphthene (X). The mixture was warmed for 3 hr. after which an additional 100 ml. of Chlorox was added. Two hours at reflux gave a clear pale yellow solution which was cooled and the excess sodium hypochlorite destroyed by adding sodium bisulfite. Acidification with concentrated hydrochloric acid to *p*H 2 caused precipitation of a cream colored solid which was removed by filtration, washed with water, and dried. The crude product, 10.1 g. (97%) which did not melt below 340° was crystallized from glacial acetic acid.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 68.63; H, 4.04.

3,6-Diacetylacenaphthene dioxime. This compound was prepared in 84% yield by the method of Dziewonski and Spirer,[10] m.p. 206–208° (lit.[10] reported as 5,6-diacetylacenaphthene dioxime, m.p. 196–197°). The product was crystallized from benzene.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: N, 10.20.

(17) An improved procedure for the preparation of this compound was described by A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, 22, 1197 (1957) after completion of this work. These authors assumed the formation of the 5,6-isomer.

3,6-Diacetamidoacenaphthene (XI). A solution was prepared of 2.0 g. (0.0075 mole) of 3,6-diacetylacenaphthene dioxime in 10 ml. of glacial acetic acid and 15 ml. of acetic anhydride. Hydrogen chloride was passed through the pale orange solution for 2 hr. After the first 15 min., precipitation of a cream colored solid began. The flask was stoppered and allowed to stand for 3 hr. The solid was removed by filtration and washed with water. The crude product, m.p. 185–204°, amounted to 0.93 g. Several crystallizations from ethanol with decolorizing charcoal gave colorless crystals, m.p. 208–210°. Analyses indicate an acetate intermediate probably 6-acetamido-3-acetylacenaphthene oxime acetate.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.54; H, 5.92; N, 9.20.

The filtrate from the above separation was poured into 400 ml. of cold water. A tan solid separated which was removed by filtration and washed with water. This substance (0.56 g.) melted at 295–299°. Two crystallizations from ethanol with decolorizing charcoal gave colorless needles, m.p. 299–301° (block). The analysis indicates a diacetamidoacenaphthene.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: N, 10.46.

The oxime acetate was dissolved in 50 ml. of a cold solution of equal volumes of glacial acetic acid and acetic anhydride. Hydrogen chloride was passed through the brown solution for 5 hr. The solution became warm and within 20 min. a cream colored solid began to precipitate. The flask was stoppered and allowed to stand overnight. The mixture was poured into a liter of water and filtration of the aqueous mixture separated the product. The yield of crude product, m.p. 295–299°, was quantitative. Crystallization from ethanol and from toluene with decolorizing charcoal gave fine white needles of 3,6-diacetamidoacenaphthene (XI), m.p. 299–300°.

3-Nitroacenaphthene. Morgan and Harrison[15] reported two methods for preparing this compound. Our attempt with the benzoyl nitrate method gave only 5-nitroacenaphthene. By using the diacetylorthonitric acid the yellow-green solid, m.p. 140–145° was prepared in 17% yield (lit.[15] 151.5°).

3,6-Dinitroacenaphthene. This compound was prepared from 3-nitroacenaphthene as described in the literature. The crude yellow solid, m.p. 196–202°, was produced in 94% yield. Crystallization from glacial acetic acid gave yellow needles, m.p. 205–207° (lit.[15] 205–206°).

3,6-Diaminoacenaphthene (VII). Four grams (0.016 mole) of 3,6-dinitroacenaphthene, 200 mg. of 10% palladium-on-charcoal, and 75 ml. of ethanol were placed in a Parr hydrogenation bottle. A hydrogen pressure of 2.82 atm. was applied for 1 hr. The initially yellow mixture changed to a gray colored solution which was filtered to remove the catalyst. The filtrate exhibited a strong blue fluorescence. The ethanol was removed by warming the solution under reduced pressure and the gray residue, (2.92 g., 98%) m.p. 95–99°, crystallized from petroleum ether, b.p. 60–70°, formed very pale yellow needles, m.p. 99–100°. This diamine did not depress the melting point of the diamine obtained by the hydrolysis of 3,6-dibenzamidoacenaphthene (VIII).

Anal. Calcd. for $C_{12}H_{12}N_2$: N, 15.21. Found: N, 15.17.

3,6-Dibenzamidoacenaphthene (VIII) *from the diamine* VII. To 1.82 g. (0.0100 mole) of VII in 15 ml. of dry pyridine was added 2.81 g. (0.0200 mole) of benzoyl chloride. The brown solution was allowed to stand for 30 min. When the solution was poured into a liter of cold water a cream colored precipitate separated. This was collected on a filter, washed well with water and dried. The crude product, m.p. 263–274°, 3.68 g. 94%, was crystallized several times from 1-butanol with decolorizing charcoal yielding colorless plates, m.p. 277–279°.

3,6-Diacetamidoacenaphthene (XI) *from the diamine* VII. A solution was prepared from 0.91 g. (0.0050 mole) of VII in 10 ml. of pyridine. To this solution was added dropwise 1.0 g. (0.010 mole) of acetic anhydride. After about 10 min., tan crystals began to deposit. After standing for 45 min., the mixture was poured into one liter of cold water. The

tan suspension was filtered and the resulting solid washed with water and dried. The crude product, m.p. 290–295°, 1.13 g. (84%), was crystallized from ethanol with decolorizing charcoal and again from toluene, m.p. 299–300°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: N, 10.61.

5,6-Dibenzamidoacenaphthene (V). To 1.1 g. (0.0060 mole) of III[6] in 20 ml. of dry pyridine was added 1.7 g. (0.12 mole) of benzoyl chloride. After 30 min. at room temperature, the solution was poured into 600 ml. of cold water causing the precipitation of a cream colored solid. The solid was removed by filtration, washed well with water, and dried. The crude product, m.p. 268–272°, weighed 1.95 g. (82%). It was crystallized from glacial acetic acid with decolorizing charcoal, forming very pale yellow needles, m.p. 275–276°.[6]

A mixture of this compound and the product from the Beckmann rearrangement of the dioxime of the dibenzoylacenaphthene obtained by the benzoylation of acenaphthene with the Friedel-Crafts reaction melted below 230°.

3,6-Acenaphthenedicarboxanilide. A mixture of 1.00 g. (0.00414 mole) of the 3,6-dicarboxylic acid XII and 15 ml. of thionyl chloride was heated at reflux for a total of 15 hr. During this period the solid dissolved forming a dark solution. The excess thionyl chloride was removed under reduced pressure and the acid chloride dissolved in dry benzene and 0.79 g. (0.0085 mole) of freshly distilled aniline in 25 ml. of benzene was added. A precipitate formed which was filtered off and washed well with water. The tan product, m.p. 287–294°, 1.15 g. (71%) was crystallized from 1-butanol and from chloroform with charcoal forming colorless crystals, m.p. 302–304°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: N, 7.14. Found: N, 7.27.

5-Acenaphthanilide. To 8.0 g. (0.040 mole) of 5-acenaphthoic acid there was added 50 ml. of dry benzene and 10 ml. of thionyl chloride. The mixture was warmed for 3 hr. on the steam bath, during which time the solid dissolved to form a dark solution. The solvent was removed by warming the solution under reduced pressure. The tan acid chloride was dissolved in 25 ml. of dry benzene and to this solution was added 7.5 g. (0.081 mole) of freshly distilled aniline dissolved in 25 ml. of dry benzene. Aniline hydrochloride separated as a white precipitate. The mixture was warmed on the steam bath for 5 min. and then filtered. The brown benzene solution deposited tan crystals on cooling. This product was separated by filtration, washed with a little benzene, and dried, m.p. 165–169°. The yield was 8.3 g. (74%). Further recrystallization from benzene and finally from cyclohexane gave fine colorless needles, m.p. 173–174°.

Anal. Calcd. for $C_{19}H_{15}NO$: N, 5.13. Found: N, 4.96.

Nitration of 5-acenaphthanilide. A mixture of 11.5 g. (0.0422 mole) of 5-acenaphthanilide and 100 ml. of glacial acetic acid was warmed on the steam bath to 80°. The solid was only slightly soluble at that temperature. After the mixture had cooled to 55°, concentrated nitric acid (23 ml., d. 1.42) was added rapidly with stirring. The temperature rose to 61° and the solid dissolved completely forming a brown solution. The solution was cooled to room temperature and then diluted with two liters of cold water. The yellow precipitate was collected on a filter, washed well with water, and dried. The crude product, 10.8 g., melted below 100°. Crystallization from benzene with decolorizing charcoal gave 2.70 g. (20%) of pale yellow needles melting at 250–253°. Several recrystallizations from the same solvent gave a product, m.p. 255–257°. The position of the nitro group has not been established and the compound is therefore designated 3(5)-nitro-6-acenaphthanilide.

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: N, 8.80. Found: N, 8.51.

Evaporation of the benzene filtrates gave 6.4 g. of a brown oil which could not be crystallized.

N-(o-Nitrophenyl)-5-acenaphthamide. A mixture, prepared from 10 ml. of thionyl chloride and 1.0 g. (0.0050 mole) of 5-acenaphthoic acid was heated under reflux for 2 hr. The solid dissolved during this period. After removing the excess thionyl chloride by warming under reduced pressure, the acid chloride was dissolved in 10 ml. of dry benzene. A solution of 1.38 g. (0.0100 mole) of *o*-nitroaniline in 30 ml. of dry benzene was added and the dark solution warmed on the steam bath for 10 min. The benzene was removed and the product crystallized from ethanol with decolorizing charcoal. The bright yellow needles, m.p. 198–200°, weighed 0.53 g. (33%). One recrystallization from ethanol raised the melting point to 199–200°.

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: N, 8.80. Found: N, 8.75.

N-(p-Nitrophenyl)-5-acenaphthamide. To 1.0 g. (0.0050 mole) of 5-acenaphthoic acid was added 10 ml. of thionyl chloride. This mixture was heated at reflux for 2 hr., during which time the solid dissolved to give a brown solution. The excess thionyl chloride was removed by warming the solution under reduced pressure. After dissolving the solid acid chloride in 10 ml. of dry benzene, *p*-nitroaniline (1.38 g., 0.00100 mole) dissolved in 50 ml. of dry benzene was added. The solution was warmed on the steam bath for 5 min. and then cooled. Since no product separated, the volume of the solution was reduced to about 20 ml. Brown crystals deposited slowly. These were removed by filtration, washed with a little benzene, and dried. The crude product, m.p. 230–238°, amounted to 0.87 g. (55%). Recrystallization from toluene and finally from benzene with decolorizing charcoal gave long, pale yellow needles, m.p. 236–238°.

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: N, 8.80. Found: N, 8.15.

A mixture of this compound and the product of the nitration of 5-acenapthanilide (m.p. 255–257°) melted at 208–220°.

3(5)-Amino-6-acenaphthanilide. The product from the nitration of 5-acenaphthanilide (1.60 g., 0.0050 mole) was suspended in 50 ml. of ethanol in a carefully cleaned hydrogenation bottle. About 200 mg. of 10% palladium-on-charcoal catalyst was added and the bottle was flushed three times with hydrogen. The hydrogen pressure was brought up to 3.1 atm. After shaking for 40 hr., the pressure had dropped to 2.7 atm. and the color had changed from yellow to green. The product was filtered off and dried. The yield of amine, m.p. 204–207°, was quantitative. Crystallization from cyclohexane with decolorizing charcoal gave colorless micro needles, m.p. 209–210°.

Anal. Calcd. for $C_{19}H_{16}N_2O$: N, 9.72. Found: N, 9.70.

3(5)-Benzamido-6-acenaphthanilide. To 0.72 g. (0.0025 mole) of 3(5)-amino-6-acenaphthanilide, obtained by reduction to the product of the nitration of 5-acenaphthanilide, dissolved in 10 ml. of dry pyridine was added 0.35 g. (0.0025 mole) of benzoyl chloride. The dark solution was allowed to stand for 30 min. and then poured into 400 ml. of cold water. A cream colored precipitate formed which was removed by filtration, washed with water, and dried. The yield of benzamide, m.p. 273–275° was quantitative. Three recrystallizations of the crude product from butanol with decolorizing charcoal gave nearly colorless plates, m.p. 276–277°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: N, 7.14. Found: N, 7.10.

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

Some Organosilicon Compounds Containing Long-Chained *n*-Alkyl Groups

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A series of tetra-*n*-alkyl-, tri-*n*-alkylaryl-, and *n*-alkyltriarylsilanes, as well as intermediate compounds, have been prepared for potential use as hydraulic fluids or lubricants. Each compound contains at least one long-chained *n*-alkyl group having from ten to eighteen carbon atoms. Some aspects of the various means of preparing these compounds are discussed.

In connection with a study on the preparation of potential hydraulic fluids and lubricating oils, the authors have prepared a series of tetra-*n*-alkyl-, tri-*n*-alkylaryl-, and *n*-alkyltriarylsilanes. For the most part, the *n*-alkyl groups are of the long-chained variety containing from ten to eighteen carbon atoms per group.[1] Other organosilicon compounds having long-chained *n*-alkyl groups have been prepared in this and other laboratories as part of a general synthetic program.[2,3]

The *n*-alkyltriarylsilanes were prepared by the four basic procedures illustrated in equations I, IIa, IIb, and III (R = an alkyl group, Ar = an aryl group and X = Br or Cl).

$$Ar_3SiH + RCH{=}CH_2 \longrightarrow Ar_3SiCH_2CH_2R \quad (I)$$

$$RLi + Ar_3SiCl \longrightarrow Ar_3SiR + LiCl \quad (IIa)$$

$$3\,ArLi + RSiCl_3 \longrightarrow Ar_3SiR + 3LiCl \quad (IIb)$$

$$RX + Ar_3SiK \longrightarrow Ar_3SiR + KX \quad (III)$$

Thus, *n*-decyltriphenylsilane was prepared by method I from *n*-decene-1 and triphenylsilane, by method IIa from *n*-decyllithium and chlorotriphenylsilane and by method III from triphenylsilylpotassium and *n*-decyl bromide. Other related compounds, namely, *n*-dodecyl-, *n*-tetradecyl-, *n*-hexadecyl-, and *n*-octadecyltriphenylsilane, have already been reported;[2b] these compounds were prepared by both methods I and IIa; *n*-heptadecyltriphenylsilane also was made by method IIa. Preparations of *n*-dodecyl- and *n*-octadecyltriphenylsilane, previously reported,[2b] have now been made by method III. The comparative yields obtained by methods I, IIa, and III are given in Table I. *n*-Dodecyltri-*m*-tolylsilane was made using method IIb, *i.e.*, from *m*-tolyllithium and trichloro-*n*-dodecylsilane. The yield was 49%.

TABLE I

PREPARATION OF *n*-ALKYLTRIPHENYLSILANES BY METHODS I, IIa, AND III[a]

R (in $RSiPh_3$)	Yield, % Method I	Method IIa	Method III
n-Decyl	25	75	6
n-Dodecyl	46[b]	67,[b] 67	33
n-Tetradecyl	52[b]	50[b]	..
n-Hexadecyl	45[b]	30[b]	..
n-Heptadecyl	..	43[b]	..
n-Octadecyl	40[b]	70,[b] 41	6

[a] See text for discussion of the methods. [b] See Ref. 2b for experimental data of these preparations.

The preparation of tri-*n*-alkylarylsilanes in the laboratory also may be carried out in a variety of ways. Methods analogous to I and III are not often, if ever, used because of the difficulty in adding more than one molecule of an olefin to a molecule of the $ArSiH_3$ type[4] and because of the lack of a good preparative method for pure trialkylsilyllithium compounds.[5] However, there are several preparative methods related to methods IIa and IIb; these are given as Equations IV and V (M and M′ = Li or MgBr; X = Cl, Br or H, the latter in Equation V when M′ = Li; R = an alkyl group and Ar = an aryl group). The choice between method IV or V will depend on the availability and reactivity of the various pairs of reagents.

$$3\,RM + ArSiX_3 \longrightarrow R_3SiAr + 3\,MX \quad (IV)$$

$$ArM' + R_3SiX \longrightarrow R_3SiAr + M'X \quad (V)$$

The organometallic compounds (RM and ArM′) are easily prepared in most cases, and the organic halides necessary for the preparations are usually commercially available. However, neither of the two types of silicon containing compounds, R_3SiX or $ArSiX_3$, is available commercially with the obvious exceptions of compounds containing short-

(1) See, however, R. H. Meen and H. Gilman, *J. Org. Chem.*, **23**, 314 (1958) for some organosilicon compounds containing intermediate-length alkyl groups.

(2) (a) H. Rosenberg, C. Tamborski, J. D. Groves, and E. J. Bartholomew, Wright Air Development Center Technical Report 54-613, Part I (1955), Part II (1956) and Part III (1957); (b) H. Merten and H. Gilman, *J. Am. Chem. Soc.*, **76**, 5798 (1954); (c) H. Gilman and R. K. Ingham, *J. Am. Chem. Soc.*, **77**, 1680 (1955); (d) H. Gilman and G. D. Lichtenwalter, *J. Org. Chem.*, **21**, 1307 (1956); (e) H. Gilman and D. Miles, *J. Org. Chem.*, **21**, 254 (1956); (f) H. Gilman and J. J. Goodman, *J. Org. Chem.*, **22**, 45 (1957).

(3) H. Gilman and D. H. Miles, unpublished studies.

(4) See, however, J. L. Speier, R. Zimmerman, and J. A. Webster, *J. Am. Chem. Soc.*, **78**, 2278 (1956) for compounds made by adding more than one equivalent of olefin to a silicon hydride compound.

(5) See, for instance, C. A. Eaborn, *J. Chem. Soc.*, 2755 (1949), and H. Gilman, R. K. Ingham, and A. G. Smith, *J. Org. Chem.*, **18**, 1743 (1953) for preparations and attempted preparations of trialkylsilylmetallic compounds and for references related thereto. See also, H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 607, 608 (1958) for related work.

chained alkyl or phenyl groups.[6] Thus, to prepare a series of tri-*n*-alkylarylsilanes one must either prepare a series of $ArSiX_3$ compounds or a few R_3SiX compounds. The latter choice was preferable to the authors, and they set out to prepare one such tri-*n*-alkylhalosilane, *i.e.*, chlorotri-*n*-hexadecylsilane. Several preparations of this compound were carried out by reaction VI (R = $C_{16}H_{33}$).

$$RSiCl_3 + 2\ RMgBr \longrightarrow R_3SiCl + Mg\ salts \quad (VI)$$

However, during repeated distillations of the product, significant decomposition into two lower boiling materials (in addition to the product) was detected. The lowest boiling material has been tentatively identified as *n*-hexadecene-1 as shown in Table II. The other by-product contained silicon and the infrared spectrum of this impure material indicated it to contain Si—H and Si—O—Si bonds. It is possible that a thermal decomposition such as depicted in Equation VII might have occurred. Such decompositions were observed somewhat earlier at the Wright Air Development Center[7]; Schmidt and Krimmel[8] also found a similar reaction of alkyl-*m*-terphenyl compounds, in which an *alhpa*-olefin was tentatively identified as a decomposition product.

$$(RCH_2CH_2)_3SiCl + \text{heat} \longrightarrow (RCH_2CH_2)_2SiH(Cl) + RCH{=}CH_2 \quad (VII)$$

$$\xrightarrow{O_2} \text{siloxanes, etc.}$$

The crude chlorotri-*n*-hexadecylsilane made by method VI was used in some preliminary experiments before the impurity was discovered. These experiments were repeated later with material prepared as illustrated in Equations VIII and IX

$$3\ RMgBr + HSiCl_3 \longrightarrow HSiR_3 + MgClBr \quad (VIII)$$

$$HSiR_3 + Cl_2 \longrightarrow ClSiR_3 + HCl \quad (IX)$$

(R = $C_{16}H_{33}$). This procedure for the preparation of chlorotrialkylsilanes was brought to the attention[7] of the authors during the course of this research and was found to be superior to the method formerly tried. The more recent procedure was used to prepare chlorotri-*n*-hexadecyl-, chlorotri-*n*-decyl-, and tri-*n*-butylchlorosilane with the only difficulty being incomplete chlorination during the first attempt to prepare the tri-*n*-decyl compound. There are several advantages of the two-step method. For instance, the silicon-hydride bond in silicochloroform is relatively unreactive toward a Grignard reagent; hence excess Grignard reagent may be used to assure complete conversion to a trialkylsilane. Since the silicon-hydrogen bond is only slightly effected during acid hydrolysis, the reaction mixture from method VIII may be hydrolyzed and the product extracted with ether (thus eliminating the difficult filtration of the magnesium salts under a nitrogen atmosphere such as is necessary in reaction VI). In many cases the chlorination step is not necessary since reaction V (X is H, M′ is Li) will take place[9] unless steric hindrance or other factors interfere. Thus, the authors prepared tri-*n*-butylphenyl- and tri-*n*-hexadecylphenylsilane from phenyllithium and the corresponding tri-*n*-alkylsilane; however, it was found that the sterically-hindered organolithium compounds, specifically 2-biphenylyllithium, would not react with tri-*n*-butyl-, tri-*n*-decyl-, nor tri-*n*-hexadecylsilane even under some forcing conditions.

The tri-*n*-alkylarylsilanes, prepared from the above reagents utilizing procedures IV and V, included 2-biphenylyltri-*n*-decyl-, 2-biphenylyltri-*n*-hexadecyl-, tri-*n*-hexadecylphenyl-, tri-*n*-dodecylphenyl-, *p*-chlorophenyltri-*n*-hexadecyl-, tri-*n*-hexadecyl-*p*-phenoxyphenyl-, and 4-biphenylyltri-*n*-hexadecylsilane. In addition, 1,1,1-triphenyl-2,2,2-tri-*n*-hexadecyldisilane was made by reaction of triphenylsilyllithium in tetrahydrofuran solution with chlorotri-*n*-hexadecylsilane. Tri-*n*-butylphenyl-

TABLE II

COMPARISON OF *n*-HEXADECENE-1 AND THE LOWEST BOILING FRACTION FROM DISTILLATIONS OF CHLOROTRI-*n*-HEXADECYLSILANE

Property	*n*-Hexadecene-1	Literature[a]	Fraction 1[b]	Redistilled Fraction 1[b]
Infrared Spectra	Nearly identical to fraction 1	...	Nearly identical to *n*-hexadecene-1	...
n_D^{20}	1.4410	1.4419	1.4395	1.4395[c]
B.p., °C.	150–160/15 mm.	157/15 mm.	100–110/0.05 mm.	150–153/13 mm.
Br_2/CCl_4	Decolorizes[d]	...	Decolorizes	Decolorizes
MnO_4^-/Me_2CO	Decolorizes when hot	...	Decolorizes when cold	Decolorizes when hot

[a] H. T. Waterman, P. Van't Spikjer, and H. A. Van Weston, *Rec. trav. chim.*, *48*, 1103 (1929). [b] Fraction 1 is the lowest boiling fraction from the original distillation, while "Redistilled Fraction 1" is the material collected in a third distillation of the highest boiling fraction from chlorotri-*n*-hexadecylsilane. [c] The refractive index at 25° of fraction 1 from the distillation of 20 g. of chlorotri-*n*-hexadecylsilane was 1.4395; an approximation to 20° would be 1.4410. [d] It requires 42 drops of 5% solution of bromine in carbon tetrachloride to react with 0.5 ml. of each of these compounds.

(6) Anderson Laboratories, Inc., Weston, Mich., have prepared small batches of chlorotri-*n*-dodecylsilane for the authors.

(7) Dr. H. Rosenberg, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, private communication. Also see K. Shiina and M. Kumada, *J. Org. Chem.*, **23**, 139 (1958), for a thermal rearrangement of some organosilicon compounds.

(8) J. J. E. Schmidt and J. A. Krimmel, Denver Research Institute, Wright Air Development Center Technical Report for period of January 15 to April 15, 1957, preprint copy.

(9) R. N. Meals, *J. Am. Chem. Soc.*, 68, 1880 (1946); H. Gilman and S. P. Massie, Jr., *J. Am. Chem. Soc.*, 68, 1128 (1946); and H. Gilman and H. W. Melvin, Jr., *J. Am. Chem. Soc.*, **71**, 4050 (1949).

silane was prepared, as mentioned earlier, mainly to serve as a model preparation for the long chain compounds made by method V (M′ = Li, X = H).

Five tetraalkylsilanes were prepared, namely, tetra-*n*-dodecyl-, tetra-*n*-tetradecyl-, dibenzyldi-*n*-octadecyl-, di-*n*-octadecylbis(γ-phenylpropyl)-, and *n*-butyltri-*n*-hexadecylsilane. The two tetra long-chained compounds were made from the alkylmagnesium bromide reagents and silicon tetrachloride, while the dialkyldialkyl compounds were made by reactions of benzylmagnesium chloride and γ-phenylpropylmagnesium bromide with dichlorodi-*n*-octadecylsilane. The *n*-butyltri-*n*-hexadecylsilane was made from *n*-butyllithium and chlorotri-*n*-hexadecylsilane.

In addition to making tri-*n*-hexadecylsilane (in 70% yield) by method VIII, it was made also by reaction of crude chlorotri-*n*-hexadecylsilane with lithium aluminum hydride (in 58% yield). Tri-*n*-dodecylphenylsilane was made from phenyllithium and chlorotri-*n*-hexadecylsilane (method V) and from *n*-dodecylmagnesium bromide and trichlorophenylsilane (method IV) in yields of 48 and 51%, respectively.

In preliminary thermal screening tests carried out by heating a small amount of the various compounds in a capillary tube mounted in a copper melting point block, none of the compounds containing long-chained *n*-alkyl groups was found to volatilize above 480°. Some of them showed significant decomposition below this temperature. It is possible that thermal decomposition such as that depicted in Equation VI occurs, and hence is a limiting factor in the thermal stability of organosilicon compounds containing long-chained *n*-alkyl groups.

EXPERIMENTAL[10]

Tri-n-butylsilane. Trichlorosilane (100 g., 0.738 mole), cooled in a Dry Ice–acetone bath, was allowed to react with 0.257 mole of *n*-butylmagnesium bromide in 1800 ml. of ether by addition of the Grignard reagent to the chlorosilane. After stirring for 3 hr., the mixture was hydrolyzed by pouring into a mixture of crushed ice and 100 ml. of hydrochloric acid. Work-up by extraction with 2 portions of ether, drying of the combined extracts and organic layer over sodium sulfate, filtration, and then distillation of the solvent was followed by distillation through a Widmer column: this afforded 110 g. (74%) of a colorless liquid, boiling at 215–220°, n_D^{20} 1.4380, d_4^{20} 0.7788.

Anal. Calcd. for $C_{12}H_{28}Si$: MR_D,[11] 67.88. Found: MR_D, 67.55.

Jenkins and Post[12] report the preparation (5% yield) of tri-*n*-butylsilane, b.p. 86–87°/2.5 mm., n_D^{20} 2.5 mm., n_D^{20} 1.4400, d_{25}^{25} 0.9312. Calculation of the MR_D value using the data of Jenkins and Post for the index of refraction and density gave a value of 56.4, which does not agree with the theoretical value of 67.55.[11]

Tri-n-decylsilane. *n*-Decylmagnesium bromide (0.89 mole, 89% yield) was prepared and added to 42 g. (0.28 mole) of trichlorosilane in the manner just described. Hydrolysis and work-up in the same manner as for tri-*n*-butylsilane, using a Claisen-type flask for the distillation, yielded 66.2 g. (61%) of colorless oil, boiling over the range of 206–210°/0.005 mm., n_D^{20} 1.4582.

Anal.[13] Calcd. for $C_{30}H_{64}Si$: Si, 6.20. Found: Si, 6.18.

Tri-n-hexadecylsilane. In a manner similar to the two previous experiments, 0.87 mole of *n*-hexadecylmagnesium bromide and 0.237 mole of trichlorosilane in 500 ml. of ether were allowed to react. Work-up yielded 117.8 g. (70.5%) of an oil, boiling at 300–305°/0.008 mm., which solidified to a white waxy solid, m.p. 34–36°.

Anal. Calcd. for $C_{48}H_{100}Si$: Si, 3.98. Found: Si, 4.08, 4.08.

An impure sample of the same compound was made by the reaction of 18.5 g. (0.025 mole) of chlorotri-*n*-hexadecylsilane with 0.7 g. (0.0185 mole) of lithium aluminum hydride in 40 ml. of ether. The yield was 10.4 g. (58%) of a white waxy material, m.p. 33–35°.

Chlorotri-n-butylsilane. A solution of 41.5 g. (0.206 mole) of tri-*n*-butylsilane in 100 ml. of carbon tetrachloride was allowed to react, using ice cooling, with 25 g. (0.35 mole) of chlorine gas. After the theoretical amount of chlorine had passed through the solution, the reaction mixture became yellow. Distillation of the solvent and then of the crude oil, avoiding contact with moisture, gave 33.5 g. (75%) of a colorless oil, boiling at 134–139°/16 mm.

Anal.[14] Calcd. for $C_{12}H_{27}ClSi$: Cl, 15.0. Found: Cl, 14.75, 14.75.

Chlorotri-*n*-butylsilane has been made by at least two other methods. Gilman and Marshall[15] made it in 51% yield by reaction of ethyl orthosilicate with *n*-butylmagnesium bromide to form ethoxytriethylsilane, acidification to give the disiloxane and finally treatment with ammonium chloride in sulfuric acid to give tri-*n*-butylchlorosilane. In 1952, Noller and Post[16] and Petrov and Chernyshev[17] prepared it by direct reaction of silicon tetrachloride with *n*-butylmagnesium bromide.

Chlorotri-n-decylsilane. As in the previous example, chlorine gas (a total of 0.7 mole) was allowed to react with 0.14 mole of tri-*n*-decylsilane. Distillation of the solvent and then of the residual oil yielded 35 g. (51.3%) of product, boiling over the range 240–250°/1.0 mm.

Anal. Calcd. for $C_{30}H_{63}ClSi$: Cl, 7.27. Found: Cl, 7.30, 7.35.

Chlorotri-n-hexadecylsilane. A. From tri-n-hexadecylsilane. As in the previous two examples, chlorine gas (0.2 mole) and 0.167 mole of tri-*n*-hexadecylsilane in 75 ml. of carbon tetrachloride were allowed to react. The yield of product was *ca.* 80% with a boiling range of 275–280°/0.005 mm.

(10) All melting points are uncorrected. Preparations utilizing reactive organometallic compounds or chlorosilanes were carried out under a dry, oxygen-free nitrogen atmosphere.

(11) Molecular refractions were calculated using the values reported by A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *Chem. & Ind. (London)*, 358 (1950); 376 (1951); *J. Chem. Soc.*, 514 (1952); W. T. Cresswell, J. Leicester, and A. I. Vogel, *Chem. & Ind. (London)*, 19 (1953); *J. Phys. Chem.*, **58**, 174 (1954).

(12) J. W. Jenkins and H. W. Post, *J. Org. Chem.*, **15**, 552 (1950).

(13) The silicon content was determined by the method of H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

(14) The hydrolyzable chlorine was determined by titrating *ca.* 0.1-g. samples dissolved in a mixture of 50 ml. of absolute ethanol and 50 ml. of ether, using 0.1*N* sodium hydroxide as the titrant.

(15) H. Gilman and F. J. Marshall, *J. Am. Chem. Soc.*, **71**, 2066 (1949).

(16) D. C. Noller and H. W. Post, *J. Am. Chem. Soc.*, **74**, 1361 (1952).

(17) A. D. Petrov and E. A. Chernyshev, *Doklady Akad. Nauk S.S.S.R.*, **86**, 737 (1952) [*Chem. Abstr.*, **47**, 8010 (1953)].

An infrared spectrum indicated that all the silane had reacted. No decomposition was noted as in the compound prepared by method B, possibly due to the slightly lower distillation temperature.

B. From trichloro-n-hexadecylsilane. Several different preparations from trichloro-*n*-hexadecylsilane and *n*-hexadecylmagnesium bromide gave yields of *ca.* 45%. A typical preparation is given.

n-Hexadecylmagnesium bromide (0.804 mole) in 400 ml. of ether was added to 130 g. (0.336 mole) of trichloro-*n*-hexadecylsilane in ether. The mixture was stirred at ether reflux for 3 days. The ether then was replaced by 400 ml. of xylene and the mixture refluxed overnight. The solution was filtered in a nitrogen pressure apparatus which had been thoroughly dried. The solvents were distilled from the filtrate leaving an oil. This was distilled at reduced pressure giving three fractions, 25 g., boiling at 100–110°/0.05 mm.; 25 g., boiling at 230–235°/0.1 mm.; and 150–200 g., boiling at 320°/0.1 mm. Redistillation of the last fraction again gave three fractions: 1, boiling over the range 92–107°/0.05 mm.; 2, boiling over the range 230–265°/0.05 mm.; and 3, 118 g., boiling at 295–300°/0.05 mm. Since it appeared that decomposition was taking place during the distillation, 20 g. of the product was redistilled and again three fractions of similar boiling ranges to those of the preceding distillations were obtained. The low boiling fraction tentatively was identified as an *alpha*-olefin, presumably 1-hexadecene (see Table II). The second fraction appears on the basis of infrared spectra to be an Si—H type compound, while the high boiling material is slightly impure product contaminated with Si—H and Si—O—Si components.

Anal. Calcd. for $C_{48}H_{99}ClSi$: Si, 3.80. Found: Si, 3.79, 3.59.

Tetra-n-dodecylsilane. n-Dodecylmagnesium bromide (1.7 moles, made in 85% yield) was prepared as usual in 1100 ml. of ether and then added slowly to 44 g. (0.26 mole) of silicon tetrachloride in 250 ml. of xylene. After stirring overnight at reflux, the ether was distilled as completely as possible and replaced by additional xylene. The resulting suspension was refluxed with stirring for 80 hr., cooled, and then hydrolyzed by the addition of saturated ammonium chloride solution. The layers were separated; the water layer was extracted with two large portions of ether; the combined organic layers were dried over sodium sulfate; and the solvent, after filtration of the sodium sulfate, was distilled. The resulting oil was distilled at reduced pressure to yield 150 g. (82%) of product boiling over the range of 240–250°/0.06 mm. This was redistilled in a Hickman molecular still using a sand-bath temperature of 370° at a pressure of 0.03 mm. This gave 145 g. (79%) of product, n_D^{27} 1.4633, d_{27}^{27} 0.8304.

Anal. Calcd. for $C_{48}H_{100}Si$: Si, 3.98; MR_D, 234.7. Found: Si, 4.39, 4.40; MR_D, 234.7.

Tetra-n-tetradecylsilane. In a method similar to the previous example, 0.149 mole of *n*-tetradecylmagnesium bromide in 250 ml. of ether was added to 0.037 mole of silicon tetrachloride. After stirring at reflux for 4 hr., most of the ether was distilled (not replaced by xylene as in the previous example) and the material was heated in the absence of any added solvent at 150–160° for 4 hr., cooled, the original ether added and the mixture refluxed overnight. Work-up as in the previous example (no molecular distillation) gave 12 g. (40%) of an oil, b.p. 253–255°/0.6 mm., n_D^{27} 1.4590, d_{27}^{27} 0.831.

Anal. Calcd. for $C_{56}H_{116}Si$: C, 82.26; H, 14.30; Si, 3.44; MR_D, 271.89. Found: C, 81.88, 82.01; H, 14.37, 14.47; Si, 3.56, 3.66; MR_D, 269.2.

Dibenzyldi-n-octadecylsilane. Benzylmagnesium chloride (0.068 mole) was prepared in the usual manner (96% yield) and then added to 12.1 g. (0.02 mole) of dichlorodi-*n*-octadecylsilane dissolved in 100 ml. of sodium-dried xylene. The ether (from the Grignard preparation) was distilled as completely as possible, and the reaction mixture was then refluxed for 7 hr. The cooled mixture was hydrolyzed by the addition of 100 ml. of 3*N* hydrochloric acid solution and then worked up by extractive procedures similar to those described previously and the product distilled under reduced pressure to yield 7.8 g. (54.5%) of an oil, boiling at 317–322° (0.9 mm.), n_D^{20} 1.5005.

Anal. Calcd. for $C_{50}H_{88}Si$: Si, 3.92. Found: Si, 3.92, 4.05.

Di-n-octadecylbis(γ-phenylpropyl)silane. Twelve and one-tenth grams (0.02 mole) of dichlorodi-*n*-octadecylsilane in 50 ml. of sodium-dried xylene was reacted with 0.05 mole of γ-phenylpropylmagnesium bromide in 70 ml. of ether (the Grignard reagent was prepared in the normal way in 71% yield). The reaction was carried out as in the previous experiment and worked up in the usual manner. Distillation under reduced pressure yielded 4.8 g. (31%) of an oil, boiling at 275–282° (0.001 mm.), n_D^{20} 1.4921, d_4^{20} 0.8872.

Anal. Calcd. for $C_{54}H_{96}Si$: Si, 3.63; MR_D,[11] 255.0. Found: Si, 3.83, 3.73; MR_D, 254.86.

n-Butyltri-n-hexadecylsilane. n-Butyllithium[18] (0.019 mole) was added with stirring to 14.0 g. (0.019 mole) of chlorotri-*n*-hexadecylsilane. After stirring the ethereal solution overnight, Color Test I[19] was still positive. After stirring for one more hour, the mixture was hydrolyzed by the addition of a saturated ammonium chloride solution. Work-up in the usual fashion left *ca.* 15.0 g. of white solid which could not be crystallized satisfactorily. After distilling the ethyl acetate–ethanol mixture used for the attempted crystallization, the residual material was distilled twice at reduced pressure to yield 4.4 g. (29.0%) of an oil, boiling at 270–280°/0.001 mm.

Anal. Calcd. for $C_{52}H_{108}Si$: Si, 3.69; MR_D, 253.75. Found: Si, 3.63, 3.64; MR_D, 251.58.

Tri-n-butylphenylsilane. Phenyllithium (0.038 mole) and 0.035 mole of tri-*n*-butylsilane were refluxed together for 6 hr. A white precipitate slowly formed during this period. When Color Test I[19] was negative, the mixture was hydrolyzed and worked up as usual. Reduced pressure distillation gave 3.2 g. (33.2%) of tri-*n*-butylphenylsilane, b.p. 163–166°, n_D^{20} 1.4940, d_4^{20} 0.8757. Reported values[15] are n_D^{20} 1.4891 and d_4^{20} 0.8719.

2-Biphenylyltri-n-alkylsilanes. A. From chlorotri-n-alkylsilanes. Two 2-biphenylyltri-*n*-alkylsilanes, 2-biphenylyltri-*n*-hexadecyl-, and 2-biphenylyltri-*n*-decylsilane were prepared by method A. The former preparation is here described; the other compound was prepared in a similar manner and the product (b.p. 235–238°/0.001 mm., n_D^{20} 1.5096, d_4^{20} 0.909) obtained in a 25% yield. The analyses for both compounds are given.

Chlorotri-*n*-hexadecylsilane (4.8 g., 0.02 mole) was allowed to react with 2-biphenylyllithium (0.015 mole, prepared by direct reaction of 2-bromobiphenyl with lithium metal) in ethereal solution. The mixture was refluxed overnight and then the ether was distilled and replaced by 100 ml. of toluene. After refluxing for 8 hr. Color Test I[19] was negative. Another 0.015 mole of 2-biphenylyllithium was added and reflux continued (with distillation of the ether) for 48 hr. Color Test I was again negative, so the mixture was hydrolyzed and worked up in the usual manner. The biphenyl present in the product was removed by vacuum sublimation at 5 mm., and the resulting oil distilled to yield 41% of product, b.p. 283–290°/0.001 mm., n_D^{20} 1.4840, d_4^{20} 0.870.

Anal. Calcd. for $C_{42}H_{72}Si$: (2-biphenylyltri-*n*-decylsilane): Si, 4.64; MR_D, 198.43. Found: Si, 4.66, 4.56; MR_D, 198.02.

Anal. Calcd. for $C_{60}H_{108}Si$ (2-biphenyltri-*n*-hexadecylsilane): Si, 3.27; MR_D, 283.40. Found: Si, 3.44, 3.48; MR_D, 282.8.

(18) Prepared by method of H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949) using a temperature of −40 to −30°.

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

2-Biphenylyltri-n-alkylsilanes. B. From tri-n-alkylsilanes (attempted). Using conditions similar to those described for the preparation of 2-biphenyltri-*n*-hexadecylsilane from the chlorosilane in the preceding experiment but refluxing in toluene for 9 days failed to yield any of the desired product when tri-*n*-butylsilane, tri-*n*-decylsilane, and tri-*n*-hexadecylsilane were reacted with 2-biphenylyllithium.

Tri-n-dodecylphenylsilane. A. From phenyllithium and chlorotri-n-dodecylsilane. Phenyllithium (0.01 mole) and 5.0 g. (0.0088 mole) of chlorotri-*n*-dodecylsilane[6] were allowed to react. After stirring overnight, Color Test I was negative, and the mixture was hydrolyzed with water and worked up in the usual way to yield 2.6 g. (48.2%) of product, b.p. 224–225°/0.001 mm., n_D^{20} 1.4673.

B. From n-dodecylmagnesium bromide and trichlorophenylsilane. *n*-Dodecylmagnesium bromide (0.16 mole) in 160 ml. of ether was reacted with 8.5 g. (0.04 mole) of trichlorophenylsilane in 20 ml. of toluene. The ether was distilled and an additional 130 ml. of toluene added. After refluxing overnight, the mixture was cooled, hydrolyzed, and worked up as usual. Reduced pressure distillation of the product afforded 12.5 g. (51%) of product, b.p. 250–253°/0.001 mm., n_D^{20} 1.4800, d_4^{20} 0.8595.

Anal. Calcd. for $C_{42}H_{58}Si$: Si, 4.58; MR_D, 202.89. Found: Si, 4.65, 4.77; MR_D, 201.3.

Tri-n-hexadecylphenylsilane. A. From trichlorophenylsilane. In essential accordance with the procedure just described, 0.1 mole of *n*-hexadecylmagnesium bromide and 0.0187 mole of trichlorophenylsilane were refluxed together in toluene-ether mixtures. Work-up yielded 6.0 g. (42%) of product, b.p. 279°/0.2 mm., n_D^{20} 1.4897, d_{27}^{27} 0.857.

Anal. Calcd. for $C_{54}H_{104}Si$: C, 82.99; H, 13.41; Si, 3.60. Found: C, 83.11, 83.27; H, 13.39, 13.39; Si, 3.66, 3.38.

B. From tri-n-hexadecylsilane. Phenyllithium (0.02 mole) and 0.014 mole of tri-*n*-hexadecylsilane were reacted together in the same manner as were phenyllithium and tri-*n*-butylsilane (described earlier) to yield 29% of an oil, boiling over the range 223–230°/0.003 mm., n_D^{20} 1.4804.

p-Chlorophenyltri-n-hexadecylsilane. *p*-Chlorophenyllithium[20] was prepared by the halogen-metal interconversion of 3.8 g. (0.02 mole) of *p*-bromochlorobenzene and 20 ml. (0.02 mole) of *n*-butyllithium at −10 to −20°. To this stirred mixture was added 11.1 g. (0.015 mole) of chlorotri-*n*-hexadecylsilane and stirring was continued until the mixture reached room temperature. Work-up in the usual manner afforded 10.1 g. (82%) of product, b.p. 295–300°/0.005 mm.; redistillation gave 7.5 g. (61%) of an oil, b.p. 250°/0.001 mm., n_D^{20} 1.4855, d_4^{20} 0.882.

Anal. Calcd. for $C_{54}H_{103}ClSi$: Si, 3.44; MR_D, 266.15. Found: Si, 3.48, 3.49; MR_D, 265.38.

Tri-n-hexadecyl-p-phenoxyphenylsilane. Using a method similar to that described for *p*-chlorophenyltri-*n*-hexadecylsilane, *p*-phenoxyphenyllithium[20] (0.045 mole prepared from *p*-bromophenyl phenyl ether and *n*-butyllithium) and 0.035 mole of chlorotri-*n*-hexadecylsilane were found to yield 58.5% of product, boiling at 305–315°/0.005 mm., n_D^{20} 1.4960, d_4^{20} 0.897.

4-Biphenylyltri-n-hexadecylsilane. 4-Biphenylyllithium (0.025 mole) and 13.3 g. (0.018 mole) of chlorotri-*n*-hexadecylsilane were stirred together for 15 min., hydrolyzed, and worked up in the usual manner to yield 6.2 g. (40.2%) of product, boiling at 310–323°/0.002 mm.; redistillation gave 4.15 g. (27%) of product, boiling at 300–310°/0.001 mm., n_D^{20} 1.5000, d_4^{20} 0.884.

Anal. Calcd. for $C_{60}H_{108}Si$: Si, 3.27; MR_D, 283.40. Found: Si, 3.36, 3.56; MR_D, 285.50.

1,1,1-Triphenyl-2,2,2-tri-n-hexadecyldisilane. Triphenylsilyllithium (*ca.* 0.05 mole) was prepared by the lithium metal cleavage[21] of 13.3 g. (0.025 mole) of hexaphenyldisilane using tetrahydrofuran as the solvent. The resulting solution was added in two portions to 17.2 g. (0.02 mole) of chlorotri-*n*-hexadecylsilane. Color Test I was negative after the first addition, but positive after the second addition. After refluxing for 24 hr., Color Test I was still weakly positive. The mixture was hydrolyzed and worked up as usual to yield, after chromatography on alumina to remove any silanol, 15 g. (78%) of a colorless oil, boiling at 320–325°/0.001 mm., n_D^{20} 1.5142, d_4^{20} 0.9081.

Anal. Calcd. for $C_{66}H_{114}Si$: Si, 5.83; MR_D, 320.04. Found: Si, 5.70, 5.66; MR_D, 320.99.

n-Decyltriphenylsilane. A. From decene-1 and triphenylsilane. By a method previously described[2b] for related compounds, 0.3 mole of triphenylsilane, and 0.05 mole of *n*-decene-1 in the presence of 0.5 g. of benzoyl peroxide were found to give 25% of product, m.p. 66–67°, which did not depress the melting point of samples made by methods B and C.

B. From n-decyllithium and chlorotriphenylsilane. Using the method described previously[2b] for related compounds, *n*-decyllithium (*ca.* 0.025 mole) and 0.025 mole of *n*-decyl bromide were allowed to react and work-up yielded 75% of the desired product, m.p. 68.5–69° (after recrystallization from 95% ethanol).

C. From triphenylsilylpotassium and n-decyl bromide. The triphenylsilylpotassium from the cleavage of 10 g. (0.0193 mole) of hexaphenyldisilane with sodium-potassium alloy was placed in a flask and 8.53 g. (0.0386 mole) of *n*-decyl bromide in 30 ml. of ether was added. After stirring for 1 hr., Color Test I[19] was negative, so 100 ml. of water was added to hydrolyze the mixture. After stirring for 10 min., the ether layer was separated and filtered to give 6.3 g. (62%) of hexaphenyldisilane, melting at 357–362°. The filtrate was dried over sodium sulfate and the solvent distilled to leave a residue which was recrystallized several times from ethanol and then methanol to finally give 0.1 g. of eicosane (m.p. 37.5–38.5°, mixed melting point undepressed) and 0.6 g. (6.32%) of triphenyl-*n*-decylsilane, m.p. 68–69°.

Anal. Calcd. for $C_{28}H_{36}Si$: Si, 7.00. Found: Si, 7.21, 6.87.

n-Dodecyltriphenylsilane. Triphenylsilylpotassium was prepared from 10 g. of hexaphenyldisilane as in the preceding experiment and reacted with 7.9 g. (0.0386 mole) of *n*-dodecyl chloride in 30 ml. of ether. Work-up of the mixture obtained after hydrolysis yielded 9% of hexaphenyldisilane melting at 359° and 33% of *n*-dodecyltriphenylsilane melting at 67.5–68°. A mixed melting point with authentic material prepared earlier[2b] was not depressed. Another sample of material (in 66.7% yield) was made by the *n*-dodecyllithium method described previously.[2b]

n-Octadecyltriphenylsilane. As in the preceding two experiments, triphenylsilylpotassium (from 10 g. of hexaphenyldisilane) was stirred with *n*-octadecyl bromide. Work-up gave 59% of hexaphenyldisilane melting at 356–360°, 35% of hexatricontane melting at 77.5–78°, and 6% of *n*-octadecyltriphenylsilane melting at 75.5–76.5°. Reported[2b] melting point is 72–73°. Another sample was made by the *n*-octadecyllithium method already described[2b] and found to melt at 78–79°. The yield in the latter case was 41%.

n-Dodecyltri-m-tolylsilane. To 15 g. (0.0495 mole) of trichloro-*n*-dodecylsilane was added 200 ml. (0.15 mole) of 0.8*N* *m*-tolyllithium in ether (the *m*-tolyllithium was prepared by direct reaction of lithium metal with *m*-bromotoluene). After stirring for 15 min., Color Test I[19] was negative, and the mixture was hydrolyzed with water and worked up as usual. Reduced pressure distillation of the crude product yielded 11.4 g. (49.0%) of product, boiling over the range of 196–206° (0.001 mm.), n_D^{20} 1.5488, d_4^{20} 0.9624.

Anal. Calcd. for $C_{33}H_{46}Si$: Si, 5.97; MR_D, 154.56. Found: Si, 6.08, 6.07; MR_D, 155.56.

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Oxidative Ring Cleavage of Some Substituted Nitronaphthalenes[1]

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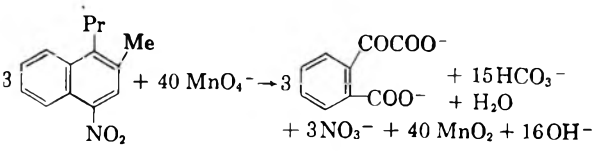
The oxidative ring cleavage of 2-methyl-1-propyl-4-nitronaphthalene, 1-bromo-5-nitronaphthalene, and 1,5-dinitronaphthalene by alkaline permanganate has been studied. The nitrated ring is cleaved preferentially by this reagent with the formation of substituted phthalonic acids. The hitherto unknown 3- and 6-bromophthalonic acids have been obtained in pure form and structures assigned. The data prove that 1-nitronaphthalenes are not cleaved by alkaline permanganate exclusively between carbons 1 and 2 or 3 and 4, but do not permit unequivocal designation of the point of ring cleavage.

As part of an investigation aimed at elucidation of satisfactory methods for selective ring cleavage of substituted naphthalenes, we became interested in the alkaline permanganate oxidation of naphthalene and certain of its derivatives. It is well known[2] that naphthalene is oxidized in good yield by that reagent to phthalonic acid. Under similar conditions alkylated naphthalenes are preferentially cleaved in the less-alkylated ring, but the degree of selectivity is not high.[3] An early report[4] states that 1-nitronaphthalene is slowly oxidized by permanganate but fails to specify conditions or products for the reaction. In view of the fact that 1-nitronaphthalene is cleaved by chromic anhydride to give 3-nitrophthalic acid,[4] it is interesting that Gardner[5] has reported the oxidation by alkaline permanganate of that compound to phthalonic acid in good yield. No further examples of this interesting oxidative cleavage have appeared. The high yield (74% as the aniline derivative), indicating a considerable degree of selectivity in this reaction, prompted a further investigation to determine its generality and hence utility for directed ring cleavage.

We have prepared and submitted to oxidation 1-bromo-5-nitronaphthalene and 2-methyl-1-propyl-4-nitronaphthalene. The results show that the nitro group does indeed direct the ring scission into the nitrated ring. In the case of 2-methyl-1-propyl-4-nitronaphthalene a mediocre yield of phthalic acid (36–40%) was obtained after isolation and purification. In this case no attempt was made to isolate the phthalonic acid undoubtedly formed in the alkaline medium, but the reaction mixture was acidified and permanganate added to a permanent color. The ether extraction employed for the isolation of phthalic acid permitted the recovery of substantially all of that substance from test solutions, but when phthalic acid was introduced in place of the naphthalene derivative only about 70% could be recovered under the normal oxidation conditions employed. However, no benzoic acid was found in such tests indicating probable destruction of the ring. For comparison purposes a sample of 2-methyl-1-propylnaphthalene was oxidized under identical conditions and only 13% of phthalic acid could be obtained. Thus the directive effect of the nitro group is indeed apparent but the presence of the alkyl groups reduced its effectiveness. The influence is also dependent on the alkalinity of the medium, for a run started in neutral solution produced only 20% phthalic acid despite the increasing *p*H of the medium as the reaction proceeds.



Oxidation of 1-bromo-5-nitronaphthalene under alkaline conditions gave a mixture of acidic products in good yield (76%). The crude product showed a wide melting range (*ca.* 125–165°), and contained no nitrogen as indicated by fusion tests and by Dumas analysis. That this mixture consisted substantially of the isomeric 3- and 6-bromophthalonic acids was denoted by its neutral equivalent

(1) This work was supported in part by the Atomic Energy Commission through contract AT(45-1)352 with Oregon State College. One of us, E. N. M., is indebted to E. I. du Pont de Nemours and Co., Inc., for a summer fellowship which aided this work. Published with the approval of the Monographs Publications Committee, Oregon State College, as Research Paper No. 347, School of Science, Department of Chemistry.

(2) (a) J. Tcherniac, *Ber.*, **31**, 139 (1898). (b) F. Ullmann and J. B. Uzbachian, *Ber.*, **36**, 1797 (1903).

(3) R. B. Randall, M. B. Benger, and C. M. Groocock, *Proc. Royal Soc. (London)* **165A**, 432 (1938).

(4) F. Beilstein and A. Kurbatow, *Ann.*, **202**, 213 (1880).

(5) J. H. Gardner, *J. Am. Chem. Soc.*, **49**, 1831 (1927).

(calcd. 136.5, found 136.4). The opportune discovery that 3-bromophthalic acid is nearly insoluble in cold nitroethane, an excellent solvent for the bromophthalonic acids, permitted the separation of the former in nearly quantitative manner. A negligible amount of 3-bromophthalic acid (2%) was obtained from the crude oxidation product. Since the oxidation product here was nitrogen-free, the directive influence of the nitro group was dominant. Previous work[6] showed, by comparison, that with nitric acid as the oxidant a bromine atom can exert an important directive effect on ring cleavage.

These results in conjunction with those of Gardner point to a relatively general ring activation by the nitro group in the case of alkaline permanganate cleavage. The *modus operandi* of this activation is then an open question. Intimately related to this latter problem is the question of the point at which cleavage of the nitrated ring occurs, a subject readily accessible to experimental study. Thus the unsymmetrical nitro substituted ring cleaves to give an unsymmetrical product, phthalonic acid, and if the other ring of the naphthalene were appropriately substituted the point of the ring opening should become apparent.

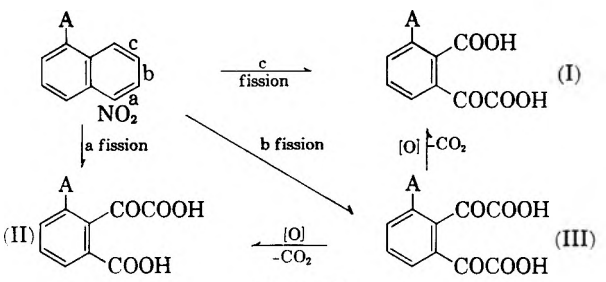


FIGURE I

As Figure I illustrates if a 5-substituted-1-nitronaphthalene is used, the isolation of only a 3-substituted phthalonic acid (I) denotes unequivocal cleavage at bond c, and similarly a 6-substituted phthalonic acid (II) cleavage at bond a. However, the isolation of a mixture of the two isomeric acids would not permit an *a priori* differentiation between oxidative scission at bond b or at both a and c. Two such cases have been studied in some detail as a part of this work, *i.e.* 5-bromo-1-nitronaphthalene and 1,5-dinitronaphthalene, these two being chosen because of their ease of preparation and the divergent electronic nature of the two labelling groups.

Oxidation of 1,5-dinitronaphthalene under the standard conditions employed gave rise to a good yield (75%) of a mixture of acids, m.p. 163–175°. Von Braun[7] has studied the 3- and 6-nitrophthalonic acids, developed a method of separation and assigned structures on the basis of isatin formation from 3-aminophthalonic acid, obtained from the corresponding nitro acid by reduction. Using the separation procedure of von Braun, we obtained 890 mg. of 6-nitrophthalonic acid, m.p. 185–186°, and 80 mg. of 3-nitrophthalonic acid, m.p. 192–193°, from 2 grams of the crude acidic mixture. The low recovery precludes any more certain conclusion than that the 6-nitrophthalonic acid is the more abundant product. Since the 6-nitrophthalonic acid is the less soluble isomer, it also seems safe to consider that the 11/1 ratio recovered constitutes a maximum and that the actual product contains a higher percentage of 3-nitrophthalonic acid.

As was noted above the oxidation of 1-bromo-5-nitronaphthalene also proceeds cleanly to give in good yield a mixture of acids which was shown to consist of the isomeric bromophthalonic acids. Though von Braun had in hand a sample of a similar mixture, he had failed to isolate the pure materials and no assignment of structure has been achieved. Partition chromatography on acidified silicic acid[8] failed to resolve the mixture using either 5% *n*-butanol in chloroform or pure chloroform as the eluant. All attempts to use the keto group for separation *via* preferential derivative formation at the less hindered position also proved fruitless. Although von Braun had found that Fischer esterification of the mixed bromophthalonic acids gave both acid and neutral esters, it was anticipated that the reaction product would be complex in view of the possibility for both normal and pseudoester formation.[9] Despite anticipated difficulties, the procedure offered the possibility of isolation of a pure substance from the acid ester so it was repeated.

Under the conditions employed (12 hr. at room temperature and one hr. at reflux) the mixed acids were readily esterified to give almost exactly half acid ester and half neutral ester. The results of four separate oxidations and esterifications were remarkably consistent showing less than 5% deviation from the 50–50 ratio in all cases. The neutral ester was a viscous yellow oil which was never induced to crystallize. Saponification gave a solid glassy material which when recrystallized from nitroethane gave a nicely crystalline pure white acid, m.p. 191.5–192.5°.

The basic extract of the esterification product yielded an acid ester which eventually crystallized. The solid acid ester, m.p. 111–119°, was repeatedly recrystallized from benzene but no improvement in the melting point was achieved. This material was saponified and the resultant acid recrystallized from nitroethane to give a light yellow crystalline acid, m.p. 185–186°. The melting point of a mixture of this acid and 3-bromophthalic acid, m.p. 186–186.5°, was 157–160°. A mixture of

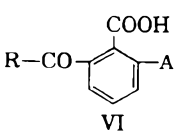
(6) V. Merz and W. Weith, *Ber.*, **15**, 2708 (1882).
(7) J. von Braun *et al.*, *Ber.*, **56**, 2332 (1923).
(8) C. S. Marvel and R. D. Rands, *J. Am. Chem. Soc.*, **72**, 2642 (1950).
(9) A. Cornillot, *Ann. Chim.* [10] **7**, 275 and [10] **8**, 120 (1927).

the two bromophthalonic acids melted at 141–143°.

There remains then the problem of assigning structures to the two isolated acids, not a simple problem in view of the keto acid–lactol tautomerism superimposed on the problem of determining the position of the bromine atom with respect to the other substituents. Interestingly enough, however, this double problem ultimately proved to simplify the situation considerably. It was considered originally, in view of the well-established tendency of keto acids to form normal esters by the Fischer method,[9,10] that the acid derived from the neutral ester must be the 6-bromophthalonic acid (II). However, a study of the infrared spectra of the esters and their derived acids indicated that such could not be the case.

The infrared spectrum of the neutral ester shows peaks in the carbonyl region at 1790 cm.$^{-1}$ and 1730 cm.$^{-1}$ both showing up as part of a broad general absorption in the region from 1800–1720 cm.$^{-1}$. The crystalline acid derived from this ester shows two nicely resolved sharp absorption bands at 1790 and 1720 cm.$^{-1}$ along with a weaker broad band between 3480 and 3500 cm.$^{-1}$ (OH). The excellent paper of Grove and Willis[11] shows that the high frequency band at 1790 cm.$^{-1}$ can be attributed to the carbonyl of the five-membered ring lactol or pseudo-ester, whereas the 1720 and 1730 bands may be assigned to normal acid and ester groups respectively. The appearance of a normal hydroxyl absorption in the 3480 cm.$^{-1}$ region is also characteristic of lactols. Conversely the acid ester shows absorption in the carbonyl region at 1730 cm.$^{-1}$ and two inflections, one at 1715 cm.$^{-1}$, the other at 1690 cm.$^{-1}$. The acid derived thereform absorbs at 1730 cm.$^{-1}$, and 1685 cm.$^{-1}$. The latter pair thus show only infrared bands characteristic of normal ester or acid groups and a ketone conjugated with an aromatic ring.[11] It is thus apparent that the neutral ester is a pseudo ester-normal ester and the acid obtained from it exists predominantly in the lactol form, whereas the acid ester is a normal ester and the acid it produced exists in the keto acid form.

The studies of Newman[10] on pseudo ester formation show that in acids of the type VI pseudo esters are formed only when A is a substituent other than H. Though that study involved mainly a methyl



VI

substituent, if it is assumed that this is a steric effect then the case in hand should be comparable because there is reasonable evidence that bromine is at least as bulky a group as methyl.[12] These data in combination with the infrared spectra reported above permit the unequivocal assignment of structure II (A = Br) to the acid melting at 185–186° and structure I(A = Br) to the acid melting at 191.5–192.5°. This assignment is also in accord with the fact that the low melting acid exhibits the characteristic yellow color of keto acids, whereas the high melting acid is pure white.

The failure of 6-bromophthalonic acid to undergo more than monoesterification is interesting, and also raises the question of which carboxyl undergoes esterification. It is our opinion that the α-keto carboxyl group undergoes esterification and that the failure of the aromatic carboxyl to form an ester is merely a rate effect. Cornillot[9] has stated that phthalonic acid forms a diester in good yield only when the Fischer esterification utilizes alcoholic hydrochloric acid saturated in the cold. He also assigned the α-ketoester structure to the monoester in view of the pK_a of the free acid group. Effects of single ortho substituents on esterification rates cannot be correlated simply by steric considerations.[12] Thus an ortho hydroxyl decreases the rate by a factor of 21.9, nitro 32.2, but a bromine only 3.33, and a CH_3CO group increases the rate 27 times! If the effect in this last case is attributed to chelation, the similarity to the present case is removed because the added bromine ortho to the keto acid group would hinder the coplanarity appropriate for chelation.

The results show that in both cases studied a mixture of 3- and 6-substituted phthalonic acids is obtained from the oxidation. Thus the nitro group does not direct cleavage exclusively to either position a or c. This leaves three alternatives for consideration, fission at both bonds a and c in appropriate ratio, fission at bond b alone or some combination of these first two. No unequivocal decision can be reached on the basis of the evidence now available. However the rather considerable difference in proportions of the 3- and 6-substituted phthalonic acids obtained when the marking group is varied from nitro to bromine indicates a considerable influence of the substituent in the other ring on the nature of the product. This influence would not appear to be due to steric factors but rather to the difference of nitro and bromine in electronic character. The step or steps in this multistage process where this influence is exerted are not yet apparent.

Although any really significant discussion of this reaction process must await a more comprehensive study, the data accumulated here have limited in some degree the number of possibilities. There is, however, one simple assumption which provides a

(10) M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **73**, 4627 (1951) and preceding papers.

(11) J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(12) *Cf.* M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, N. Y., 1956, p. 215.

coherent explanation of the results. The activation of the nitrated ring can be accounted for by assuming addition of the hydroxyl ion to that ring with consequent formation of a 1,4-dihydronaphthalene derivative.[13] Addition products have been isolated[14] when polynitroaromatic compounds are treated with alkoxides. Thus the equilibrium formation of a minute quantity of the addition product cannot be *a priori* excluded here even though no adduct has been isolated from a mononitro compound. Oxidation of the isolated double bond in the dihydro form may be expected to be rapid and could lead to direct cleavage of the double bond.[15] This is cleavage at point b exclusively and would lead to the diketo dicarboxylic acid (III). Thus the ratio of 3- and 6-substituted phthalonic acids would be determined exclusively by the oxidative decarboxylation step, and thus, *via* the influence of the substituents on the other ring on this reaction.

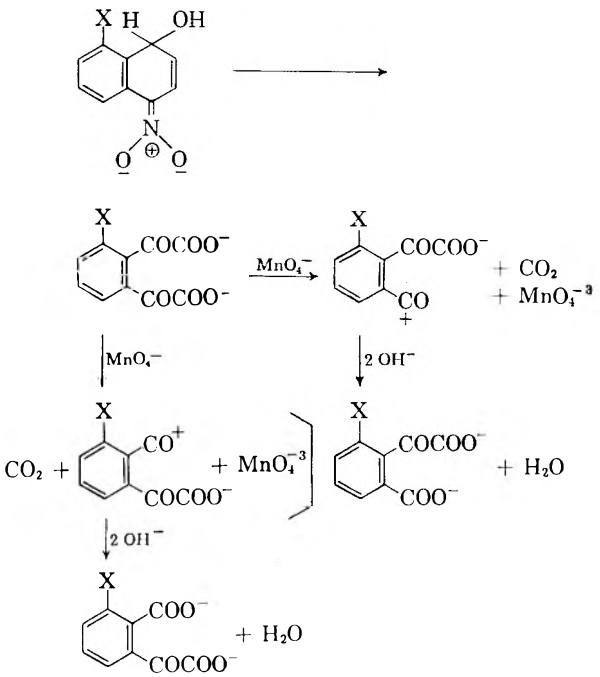


FIGURE II

If oxidative decarboxylation occurs by the simultaneous transfer of two electrons to MnO_4^- and loss of CO_2, a mechanism analogous to one considered by Wiberg and Stewart[16] for oxidation of formate ion, the reaction should be favored by electron releasing and hindered by electron attracting groups. Thus since the nitro group attracts electrons more effectively from the ortho and para positions the nitro substituted diacid should react more rapidly at the meta position and give a predominance of 6-nitrophthalonic acid. The experimental observations accord with this result. The bromo diacid should conversely produce a predominance of the 3-bromophthalonic acid since bromine attracts electrons more effectively from the meta position. However, the data show that the bromine has little influence on the reaction. This may be explained in two ways. Either the steric effect favors reaction at the meta position in both cases augmenting the electronic influence in the nitro case and masking it in the bromo, or the strong electron attraction of the two alpha keto groups swamps the weaker electronic effect of the bromine and only a powerful attracting force such as the nitro group supplies can influence the course of the reaction.

(13) A 1,2-dihydro form is also conceivable, but since it is eliminated as the sole form by the experimental results whereas the 1,4-dihydro derivative as a single entity is permitted by the present data, we have chosen to simplify the discussion by reference to the latter derivative only.

(14) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

(15) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 2822 (1957).

(16) K. B. Wiberg and R. Stewart, *J. Am. Chem. Soc.*, **78**, 1213 (1956).

EXPERIMENTAL

1-Allyl-2-methylnaphthalene. This substance was prepared from 1-bromo-2-methylnaphthalene[17] essentially according to the directions of Fieser and Hershberg[18] for the preparation of 1-allylnaphthalene. The product, b.p. 129–130° (6 mm.), n_D^{20} 1.6133, was obtained in 76% yield after distillation through a 30 in. Vigreux column.

Anal. Calcd. for $C_{14}H_{14}$: C, 92.31; H, 7.69. Found: C, 92.00; H, 7.60.

The *picrate* of the product was isolated from methanol and recrystallized from that solvent, m.p. 95.5–96.5°.

Anal. Calcd. for $C_{20}H_{17}N_3O_7$: C, 58.39; H, 4.13. Found: C, 58.25; H, 4.12.

2-Methyl-1-propylnaphthalene. Ten grams (0.055 mole) of 1-allyl-2-methylnaphthalene was dissolved in 30 ml. of absolute ethanol, mixed with approximately one gram of Raney nickel and shaken with hydrogen at two atmospheres pressure for 2 hr. The reduction product was isolated by distillation after removal of the catalyst and solvent, b.p. 138–139° (9 mm.), n_D^{20} 1.5960. Smith and Lo[19] have reported this compound to boil at 102–105° (5 mm.) and to have n_D^{20} 1.5961. The picrate prepared in ethanol melted at 118–119°, which agrees with the melting point previously reported.[19]

2-Methyl-1-propyl-4-nitronaphthalene. A solution of 3 ml. of nitric acid (*d* 1.42) in 2 ml. of nitromethane was added dropwise to a cold, well stirred solution of 2.0 g. (0.001 mole) of 2-methyl-1-propylnaphthalene in 2 ml. of nitromethane. During the course of the reaction the temperature was maintained below −10° by the addition of Dry Ice directly to the reaction mixture. As the nitration progresses a yellow precipitate of the nitration product is formed. After all the acid had been added the mixture was stirred for 1 hr., and the product isolated then by filtration. After recrystallization from methanol the product melted at 69.5–70.5°, yield 51%.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.41; H, 6.55. Found: C, 73.25; H, 6.50.

General oxidation procedure. The aromatic compound was suspended in sufficient 0.5*N* NaOH to make the initial concentration after addition of permanganate solution approximately 0.1*N* NaOH. The calculated amount of potassium

(17) R. Adams and L. O. Binder, *J. Am. Chem. Soc.*, **63**, 2773 (1941).

(18) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 1658 (1938).

(19) L. I. Smith and C. P. Lo, *J. Am. Chem. Soc.*, **70**, 2209 (1948).

permanganate was dissolved in enough hot water to adjust the total reaction mixture concentration to 5–6%. The permanganate solution was added to the reaction flask in one batch and the reaction heated under reflux with vigorous stirring until the oxidation was effectively complete as indicated by color. Enough ethanol was added to reduce any remaining permanganate and the manganese dioxide removed by filtration. The dioxide was washed with 0.1*N* NaOH and water, and the combined filtrates then concentrated to about 1/7 the volume of the reaction mixture. After having been acidified the concentrate was repeatedly extracted with ether. The crude oxidation product was obtained upon evaporation of the ether.

Oxidation of 2-methyl-1-propyl-4-nitronaphthalene was carried out as described above. Under these conditions 10 hr. was required to effect complete reaction. The isolation procedure was modified slightly in that the acidified concentrate was cooled in an ice bath and treated dropwise with 5% permanganate until the color persisted. This solution was extracted with ether for 40 hr., and the ethereal solution evaporated to dryness. The residue was triturated with a small amount of ice water and the insoluble phthalic acid collected on a Buchner funnel, m.p. 203–205°, yield 35–40%. The *p*-bromophenacyl ester was prepared and recrystallized from acetone, m.p. 154.5–155.5.[20] The *p*-phenylphenacyl ester was also prepared and, after recrystallization from ethanol, melted at 168–169°.[21]

Oxidation of 1-propyl-2-methylnaphthalene was effected as described above except that 4% permanganate was employed. Phthalic acid was isolated in 13% yield as crude acid, m.p. 196–200°. It was identified by derivative formation as noted above.

3- and 6-Nitrophthalonic acids. Oxidation of 1,5-dinitronaphthalene[22] by the general procedure required 2 hr. and gave 75.5% of crude acids, m.p. 163–175°. Two grams of the mixed acids were separated according to the procedure of von Braun[7] giving 890 mg. of 6-nitrophthalonie acid, m.p. 185–186°, and 80 mg. of 3-nitrophthalonic acid, m.p. 192–193°. The melting points are in excellent agreement with those reported by von Braun.

3- and 6-Bromophthalonic acids. When 1-bromo-5-nitronaphthalene is oxidized under the general conditions herein employed a mixture of acids, m.p. 124–164°, was obtained in 65% yield. Neutral equivalent: calcd. for $C_9H_5BrO_5$, 136.5; found, 136.4. This acid mixture was dissolved in a minimum amount of nitroethane, and a small amount (2%) of insoluble 3-bromophthalic acid, m.p. 186–186.5° (lit.[7] 188°), was recovered.

The acid mixture, 8.1 g. (3.0 mmol.), was dissolved in 50 ml. of ethanol containing approximately 12 g. of HCl. This solution was allowed to stand at room temperature for 12 hr. and heated then to boiling for 1 hr. The solvent and hydrogen chloride were removed under reduced pressure and the oily residue taken up in ether. The ether solution was extracted with 5% sodium bicarbonate solution. The ether solution was dried over anhydrous sodium sulfate, and the ether removed *in vacuo*. A pale yellow viscous oil remained, 4.10 g. (44%), which was not further purified. The ester shows broad absorption at 1725–1800 cm.$^{-1}$ with a strong peak at 1800 cm.$^{-1}$ (five membered lactone) and a weaker peak at 1730 cm.$^{-1}$ (normal ester.)

The bicarbonate solution was made acid to Congo Red and extracted several times with ether. The ether solution was dried and the ether removed leaving a pale yellow oil which slowly crystallized. The light tan crystalline acid ester, 4.22 g. (46%), melted at 111–119° and repeated crystallization failed to improve the melting range.

Anal. Calcd. for $C_{11}H_9BrO_5$: C, 43.87; H, 3.08; neut. equiv., 301. Found: C, 44.27; H, 3.25; neut. equiv., 297.

This ester shows absorption in the infrared at 3100–3300 cm.$^{-1}$ (COOH) and 1730 cm.$^{-1}$ (COOEt) with shoulders at 1715 cm.$^{-1}$ (aromatic COOH) and 1690 cm.$^{-1}$ (aromatic ketone).

The neutral ester, 3.2 g. (10 mmol.), was stirred for 10 hr. then heated for 0.5 hr. at reflux with 60 ml. of aqueous sodium hydroxide solution containing 1.0 g. (25 mmol.) of the base. After acidification the solution was extracted with ether, the combined extracts dried over anhydrous sodium sulfate, and the ether removed *in vacuo*. The white crystals of 3-bromophthalonic acid melted at 191.5–192.5° after recrystallization from nitroethane. Yield 2.12 g. (80%).

Anal. Calcd. for $C_9H_5BrO_5$: C, 39.42; H, 1.85; Br, 29.3; neut. equiv., 136.5. Found: C, 39.60; H, 2.03; Br, 29.3; neut. equiv., 136.9.

This acid absorbs at 1790 cm.$^{-1}$ (five membered lactone) and 1720 cm.$^{-1}$ (COOH) with broad general absorption between 3480–3520 cm.$^{-1}$ (OH) and 2500–3200 cm.$^{-1}$ (COOH).

The acid ester was hydrolyzed in similar fashion. The 6-bromophthalonic acid was obtained as light yellow crystals, m.p. 185.0–186.0° (from nitroethane), in 69% yield.

Anal. Calcd. for $C_9H_5BrO_5$: Br, 29.3; neut. equiv., 136.5. Found: Br, 28.9; neut. equiv., 136.8.

3-Bromophthalonic acid shows infrared peaks at 1730 cm.$^{-1}$ (COOH), 1685 cm.$^{-1}$ (ketone conjugated with aromatic ring), and 3200 cm.$^{-1}$ (COOH).

CORVALLIS, ORE.

(20) T. L. Kelly and P. A. Kleff, *J. Am. Chem. Soc.*, **54**, 4444 (1932).

(21) N. L. Drake and J. P. Sweeney, *J. Am. Chem. Soc.*, **54**, 2059 (1932).

(22) C. C. Price and S. T. Voong, *J. Org. Chem.*, **14**, 111 (1949).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Chemistry of Trityllithium. Direct Preparation and Some Reactions[1,2]

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Received September 8, 1958

The preparation of trityllithium by the reaction of lithium with trityl chloride has been studied under a variety of conditions. The highest yield (70%) of the carbonation product, triphenylacetic acid, was obtained with 1,2-dimethoxyethane as solvent, although the reaction proceeded more readily in tetrahydrofuran. Triphenylmethane and *p*-benzhydryltetraphenylmethane are formed as side products in the preparation of trityllithium. The carbanion character of this reagent has been demonstrated by reactions with several carbonyl compounds.

Although a number of organometallic compounds containing the triphenylmethyl (trityl) group have been prepared, tritylsodium and the trityl Grignard reagent are by far the most common. Bachmann demonstrated that tritylmagnesium bromide underwent a number of reactions typical of organomagnesium compounds, such as addition to phenyl benzoate to give benzopinacolone in 46% yield.[3] Yields near 90% were obtained in coupling reactions with alkyl halides,[3,4] and carbonation gave 83% of the theoretical amount of triphenylacetic acid.[5]

A study of the reactions of tritylsodium was made by Schlenk and Bergmann in 1928, who found addition to take place with triphenylacetyl chloride and phenyl isocyanate.[6] Compounds with acidic hydrogen atoms gave triphenylmethane. The yields in these conversions, however, were not indicated. The strong basic properties of tritylsodium have found use in the catalysis of ester condensations,[7,8] and in the determination of active hydrogen atoms.[9] The nucleophilic properties of tritylsodium have been demonstrated by its reaction with diphenyl ether to give tetraphenylmethane,[10] and by conjugate addition observed with ethyl crotonate and ethyl cinnamate.[11]

The direct preparation of trityllithium was first reported in 1929 by Grosse who treated trityl chloride with lithium amalgam in ethyl ether.[12] Based on analytical data, a structure has been proposed for the orange dietherate formed in this reaction.[13] The lithium amalgam method has been reported to give a 16–20% yield of the reagent,[14] but reaction does occur with lithium metal alone in diethyl ether[15] or in tetrahydrofuran.[16] An attempt to prepare trityllithium by the action of lithium amide on triphenylmethane appeared to be successful until ether was added to replace the liquid ammonia solvent, whereupon the color of the reagent disappeared and only starting material was recovered.[17] Also, no reaction was observed when triphenylmethane was treated with lithium in tetrahydrofuran.[18] Metalation of triphenylmethane has been carried out by use of *n*-butyl- or *n*-propyllithium in ethyl ether.[19–21] Carbonation of trityllithium produced by exchange gave triphenylacetic acid in 82% yield.[19]

As a result of the present work, a number of solvents have been found suitable for the preparation of trityllithium by the action of lithium on trityl chloride. Among these are: tetrahydrofuran

$$(C_6H_5)_3CCl + 2Li \longrightarrow (C_6H_5)_3CLi + LiCl$$

(THF), 1,2-dimethoxyethane (DME), ethyl ether, benzene, and toluene. The reaction failed in cyclohexane. The ease of preparation differs markedly, however, mainly due to variations in the initiation period. The superior solvating properties of tetrahydrofuran and 1,2-dimethoxyethane in many organometallic reactions also are evidenced here. In the solvent of choice, tetrahydrofuran, consist-

(1) Presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, April 1958; Abstracts, p. 7N.

(2) This work was supported by a research grant from the University of Minnesota.

(3) W. E. Bachmann and R. F. Cockerill, *J. Am. Chem. Soc.*, **55**, 2932 (1933).

(4) W. E. Bachmann, *J. Am. Chem. Soc.*, **55**, 2135 (1933).

(5) J. Schmidlin, *Ber.*, **39**, 628 (1906).

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(18) H. Gilman and R. D. Gorsich, *J. Org. Chem.*, **23**, 550 (1958).

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ently reproducible results were obtained. In the hydrocarbon solvents, the initiation requires a considerable period and occasionally the reaction cannot be started. The course of the reaction can be followed by observing the color changes and the disappearance of the lithium. The first evidence of reaction is the appearance of the red color of the reagent on the surface of the lithium. This may be hastened by vigorous stirring with a Teflon paddle which is adjusted to scrape the surface of the metal. After a few minutes to a few hours, depending on the solvent, the yellow solution suddenly acquires a red color. This change is usually very abrupt and requires about 10 min. In tetrahydrofuran, the induction period is about 15–30 min.; in benzene, the period is about 24 hr. Once the red color appears, the mixture darkens rapidly as the concentration of the lithium reagent increases; the reaction is usually complete within 4 hr. In hydrocarbon solvents and ethyl ether, tritylllithium is not very soluble and forms an orange suspension. The red or orange color, however, is not always indicative of the reagent; in several experiments which employed long reflux periods, the color was present at the time of carbonation but no acidic compounds were isolated. Apparently various by-products of the reaction are also colored but do not react with carbon dioxide.

The yields of tritylllithium were determined by isolation of triphenylacetic acid following carbonation with Dry Ice. The benzyl chloride double titration method has been found unsatisfactory for this analysis.[19] The compositions of the neutral organic residues were determined by quantitative infrared methods and by chromatographic analysis. The yields obtained and the various reaction conditions are outlined in Table I.

TABLE I

YIELDS OF TRIPHENYLACETIC ACID

Solvent	Temp.	Time, hr.	Yield, %
C_6H_6	80	24	49
C_6H_6	80	49	0
C_7H_8	110	27	16
C_6H_{12}	80	46	..[a]
Et_2O	25	23	68
DME	[b]	24	70
DME	84	18	10
DME	84	23	0
THF	25[c]	3	55
THF	−10[d]	2	57
THF	−60[d]	4	43

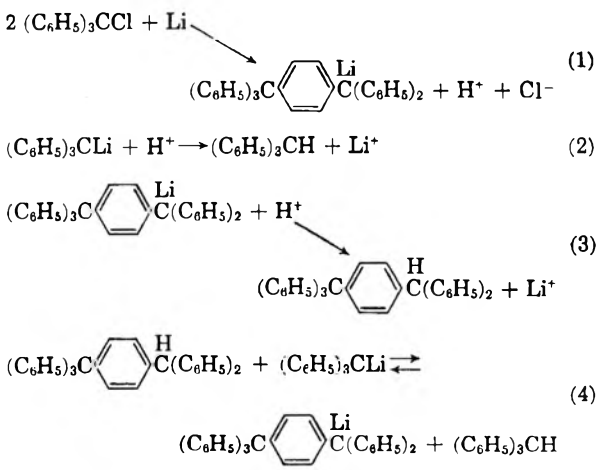
[a] Reaction could not be initiated. [b] Reflux for 5 hr.; 25° for 19 hr. [c] Reaction is exothermic; temperature depends on rate of addition of trityl chloride. [d] Bath temperature.

That all the trityl chloride reacts was demonstrated by an experiment in which hydrolysis was effected by a sodium azide solution. Because of the very strong nucleophilic character of the azide ion, any unchanged trityl chloride would react preferentially with the azide ion rather than with water[22]; however, no trace of trityl azide was observed.

The presence of small amounts of triphenylcarbinol in the reaction product may be explained by (1) contamination of the trityl chloride with about 1.5% of triphenylcarbinol (as shown by infrared analysis) or (2) reaction of tritylllithium with traces of oxygen present. In an experiment in which the lithium reagent was treated with oxygen, the major product was triphenylcarbinol, with only a small amount of trityl peroxide indicated.[23] In no experiment which employed freshly distilled solvent was an appreciable amount of trityl peroxide observed. A sample of tetrahydrofuran which had been purified but allowed to stand in a partially filled bottle for three weeks gave a 63% yield of trityl peroxide when treated with trityl chloride and lithium.

Recovery of excess lithium metal from reactions run in 1,2-dimethoxyethane and tetrahydrofuran indicated that 70–80% of the theoretical amount of lithium reacts. This is consistent with the observed quantities of triphenylacetic acid and *p*-benzhydryltetraphenylmethane.

The formation of the two hydrocarbon by-products may be explained by the equations given below.



Equation (1) represents the "dimerization" of trityl chloride, probably a Friedel-Crafts type reaction. A similar type of coupling has been observed by several workers who treated acetic acid solutions of trityl chloride with zinc and silver.[24] The hydrogen ion produced may react with tritylllithium (Equation 2) or with the lithium derivative of *p*-benzhydryltetraphenylmethane (Equation 3). In the tritylllithium reaction mixture, the equilibrium (4) lies to the right (see below). During

(22) C. G. Swain, C. B. Scott, and K. H. Lohmann, *J. Am. Chem. Soc.*, 75, 136 (1953).

(23) Bachmann and Cockerill (ref. 3) reported a similar behavior when the trityl Grignard reagent was treated with oxygen. They reported a 54% yield of triphenylcarbinol and a 10% yield of trityl peroxide.

(24) (a) F. Ullman and W. Borsum, *Ber.*, 35, 2877 (1902); (b) M. Gomberg, *Ber.*, 35, 3915 (1902).

carbonation, however, this equilibrium is shifted to the left since the tritylllithium reacts with carbon dioxide, whereas the lithium derivative of *p*-benzhydryltetraphenylmethane apparently does not react, since no acid corresponding to this anion was isolated.

Other sources of triphenylmethane may be from the reaction of tritylllithium with: (1) triphenylcarbinol, (2) traces of hydrochloric acid occluded in the trityl chloride, and (3) the solvent. Reaction with the solvent is probably responsible for the low yields observed in the experiments with high reaction temperatures or long reaction periods.

Information on the equation (4) was obtained from the reaction of tritylllithium with deuterium oxide. Assuming equation (4) to be a rapid reversible equilibrium and assuming that no loss of deuterium occurred during the work-up, then the total "labile" hydrogen in the system was either in the triphenylmethane (39.8%) or the *p*-benzhydryltetraphenylmethane (7.4%). This hydrogen came from reaction (1) and from the other sources listed above. The results of the deuteration analyses give the relative amounts of the two lithium derivatives prior to reaction with deuterium oxide: 60.2% triphenylmethane and 92.6% *p*-benzhydryltetraphenylmethane. Thus, the equilibrium constant for (4) is approximately 8, which indicates that the more stable lithium reagent is that derived from *p*-benzhydryltetraphenylmethane. This stability may result from the inductive effect of the *p*-trityl group.

The reaction of tritylllithium with acetone demonstrates the strong basic nature of the reagent.[25]

$$(C_6H_5)_3CLi + CH_3COCH_3 \longrightarrow (C_6H_5)_3CH + [CH_2COCH_3]^- + Li^+$$

$$[CH_2COCH_3]^- + CH_3COCH_3 \xrightarrow{H^+} (CH_3)_2C{=}CHCOCH_3$$

The reagent is decomposed rapidly to triphenylmethane; the acetone enolate condenses with another mole of acetone to give (after acidification) mesityl oxide, which was isolated as the 2,4-dinitrophenylhydrazone.

Similar results were observed in the reaction of tritylllithium with cyclohexanone. No adduct was obtained and the products were not investigated further.

The action of tritylllithium on benzaldehyde did yield the expected adduct, 1,2,2,2-tetraphenylethanol, in 12.5% yield. Difficulty in isolation of the alcohol was partly responsible for the low yield.

$$(C_6H_5)_3CLi + C_6H_5CHO \xrightarrow{H^+} (C_6H_5)_3CCHC_6H_5 \quad (OH)$$

When benzaldehyde was added to a solution of the reagent containing excess lithium, tetraphenylethanol was not formed. Instead, a complex mixture of substances was obtained which could not be separated by any of the usual procedures. The presence of lithium apparently was responsible for the formation of the mixture of compounds.[26]

The action of the tritylllithium reaction mixture on benzoyl chloride was also investigated. A chromatographic separation of the reaction products furnished a 27% yield of benzopinacolone and a small amount of a ketone whose structure was shown to be α-benzoyl-$\alpha,\alpha,\alpha',\alpha',\alpha'$-pentaphenyl-*p*-xylene. Reaction of ethyl benzoate with the tritylllithium reaction mixture gave essentially the same results. The formation of these two adducts again demonstrates the presence of the two lithium derivatives in the mixture formed by the reaction of trityl chloride with lithium.

$$\left[(C_6H_5)_3CLi + (C_6H_5)_2C(Li)C_6H_4C(C_6H_5)_2\right] + C_6H_5COOC_2H_5 \text{ or } C_6H_5COCl \longrightarrow$$

$$\left[(C_6H_5)_3CCOC_6H_5 + (C_6H_5)_2C(CO{-}C_6H_5)C_6H_4C(C_6H_5)_3\right]$$

The structure of α-benzoyl-$\alpha,\alpha,\alpha',\alpha',\alpha'$-pentaphenyl-*p*-xylene was established by base catalyzed cleavage of the ketone to form *p*-benzhydryltetraphenylmethane and benzoic acid.

$$(C_6H_5)_2C(CO{-}C_6H_5)C_6H_4C(C_6H_5)_3 \xrightarrow[270^\circ]{NaOH} \xrightarrow{H^+} (C_6H_5)_2C(H)C_6H_4C(C_6H_5)_3 + C_6H_5COOH$$

EXPERIMENTAL[27]

Trityl chloride was prepared[28] from triphenylcarbinol or obtained from commercial sources. Crystallization from ether or an acetyl chloride–hexane mixture, followed by heating the sample at 70° and 0.3 mm. pressure for several hours, furnished large pale yellow prisms, m.p. 112–114° after sintering near 109°. The commercial samples of triphenylcarbinol yielded products with slightly lower melting points, presumably due to traces of dichlorodiphenylmethane present. Analysis for triphenylcarbinol in the trityl chloride was accomplished by quantitative infrared methods. Under actual working conditions, the amount of triphenylcarbinol was found to be 1.5–2.0%. The presence of greater amounts

(25) Tritylmagnesium chloride is reported to be completely "passive" toward acetone, acetaldehyde, and acetyl chloride; J. Schmidlin and H. H. Hodgson, *Ber.*, **41**, 430 (1908).

(26) The action of trityl Grignard reagent on benzaldehyde is reported to give a mixture of 1,2,2,2-tetraphenylethanol and *p*-benzhydrylbenzhydrol; A. E. Tschitschibabin, *Ber.*, **42**, 3469 (1909), and J. Schmidlin and A. Garcia-Banus, *Ber.*, **45**, 3193 (1912).

(27) All melting points are corrected. The microanalyses were performed by Mrs. Olga Hamerston.

(28) W. E. Bachmann, *Org. Syntheses*, Coll. Vol. III, 841 (1955).

of triphenylcarbinol seemed to have no effect on the course of the reaction. Hydrolysis of the trityl chloride gave triphenylcarbinol free from any detectable contaminant.

Solvents. The hydrocarbon solvents used were dried over sodium and distilled before use. The ethers were dried over potassium hydroxide and/or sodium and distilled from lithium aluminum hydride directly into the reaction system. Tetrahydrofuran and 1,2-dimethoxyethane rapidly form peroxides or hydroperoxides which react with tritylllithium.

Atmosphere. The use of an inert oxygen-free atmosphere was necessary in order to obtain consistent results and prevent formation of triphenylcarbinol. For this purpose, argon purified by passage through Fieser's solution and dried with magnesium perchlorate was employed. In reactions employing freshly purified solvents and an argon atmosphere, no trityl peroxide was found; triphenylcarbinol was usually present in about the same amount as in the trityl chloride (1.5–2.0%).

Lithium wire or lithium sand was equally effective in the reaction, although the wire was more convenient to use and permitted easy removal of excess lithium. Also, initiation by exposure of a fresh metal surface of the wire was easy to accomplish by means of a Teflon stirring paddle.

Infrared analyses were performed by standard techniques. The spectra were usually measured in carbon disulfide solution in 0.5-mm. thick cells at concentrations of about 5%. Solvent compensation was made by use of a 0.5-mm. cell containing the solvent in the reference beam. The spectra were obtained from a Perkin-Elmer model 21 spectrophotometer equipped with sodium chloride optics. The following absorption bands were used in the quantitative analysis of mixtures: triphenylmethane—2880, 1076, 725 $cm.^{-1}$; deuterotriphenylmethane (carbon tetrachloride solution)—2110, 985, 902 $cm.^{-1}$; *p*-benzhydryltetraphenylmethane—1020, 725 $cm.^{-1}$; triphenylcarbinol—3610, 1325, 1158, 1030, 1010, 887 $cm.^{-1}$; trityl peroxide—975, 758 $cm.^{-1}$ The analyses were checked against known mixtures and the relative error in the determination of any component was found to be less than 20%.

Techniques for the transferral of tritylllithium. The following methods were found satisfactory: (1) a pipet flushed with argon, (2) a glass tube inserted below the surface of the reagent and leading to another flask, and (3) an inverse Grignard flask (a flask fitted with a stopcock on the bottom). The reagent reacts very rapidly with air, as evidenced by disappearance of the deep red color.

Work-up of carbonation mixtures. After the reagent had been added to Dry Ice and sufficient time had been allowed for complete reaction, methylene chloride and 5% sodium carbonate solution were added. The layers were shaken well and the aqueous layer was separated. Extraction with base was repeated until no more precipitate was observed when a portion of the extract was acidified. The basic extracts were combined, filtered, and acidified. The precipitated triphenylacetic acid was collected on a filter, washed with water, and dried; the melting point (with decomposition) was 264–267°. A mixture with an authentic sample melted at 265–268°, with decomposition. The infrared spectrum was identical with that of a known sample of triphenylacetic acid. The neutralization equivalent was 293 (theoretical 288). All the experiments gave acid of essentially this purity. The organic layer from the basic extraction was filtered to remove any insoluble material and then the solvent was evaporated under reduced pressure. Repeated attempts to crystallize the residue did not effect a satisfactory fractionation of the neutral components.

Each of the procedures below describes one experiment taken usually from a group of three to eight similar experiments which all gave essentially the same results. Some of the data mentioned in the discussion were taken from experiments which are not included.

Preparation of tritylllithium in benzene; (A) *24-hour reaction period.* In a 100-ml. flask, 3.33 g. (0.0120 mole) of trityl chloride, 0.44 g. (0.063 g. atom) of lithium sand, and 30 ml. of benzene were stirred at the reflux temperature. The mixture gradually turned to an opaque brown. After 22 hr., the dark mixture suddenly assumed a pasty consistency and the color changed to orange. Two hours after this change occurred, the contents of the flask were cooled and transferred to a Dry Ice–ether slurry. The color of the mixture changed immediately to grey-green. After the work-up, 1.69 g. (49% yield) of triphenylacetic acid was isolated. One tenth of a gram of neutral organic solid was obtained by filtration of the basic extracts. This material had no definite melting point. Evaporation of the solvent from the neutral organic fraction left 0.97 g. of orange-brown semisolid. An infrared analysis of this mixture indicated the following components: triphenylcarbinol (27%), triphenylmethane (35%), *p*-benzhydryltetraphenylmethane (20%), and unidentified material (10%).

Preparation of tritylllithium in benzene; (B) *49-hour reaction period.* Trityl chloride (3.45 g., 0.0124 mole) and lithium (0.49 g., 0.071 g. atom) were placed in a flask containing about 30 ml. of benzene. The mixture was stirred under reflux. The orange color of tritylllithium was noted after about 25 hr. The color deepened slightly during the next 8 hr. After a total of 49 hr., 60 ml. of ether was added, and the reaction mixture was poured into a Dry Ice–ether slurry. The orange color persisted even after hydrolysis. No acid was obtained; the infrared spectrum showed the red-brown semisolid product to be a complex mixture of compounds including triphenylcarbinol, triphenylmethane, *p*-benzhydryltetraphenylmethane, and several alcoholic components. No separation was attempted.

Preparation of tritylllithium in toluene. A mixture of 3.76 g. (0.0135 mole) of trityl chloride, 0.43 g. (0.062 g. atom) of lithium sand and 35 ml. of toluene was stirred under gentle reflux. After 21 hr., the solution was clear red. During the next 6 hr., the color deepened gradually and the mixture became opaque. One third of the reaction mixture then was added to Dry Ice and allowed to stand. Following the usual work-up, 0.21 g. (16%) of triphenylacetic acid was isolated. Infrared analysis of the neutral fraction of the product indicated the presence of 15% triphenylcarbinol, 40% triphenylmethane, and 35% *p*-benzhydryltetraphenylmethane.

Attempted preparation of tritylllithium in cyclohexane. A mixture of 2.04 g. (0.0073 mole) of trityl chloride, 0.24 g. (0.035 g. atom) of lithium sand, and 35 ml. of cyclohexane was stirred under reflux. The grey-green color of the initial mixture was unchanged after 46 hr., when the attempt was stopped. Attempts to initiate the reaction by extensive crushing of the lithium particles had no effect.

Preparation of tritylllithium in ether. A mixture of 0.99 g. (0.143 g. atom) of lithium wire, 4.35 g. (0.0156 mole) of trityl chloride, and 30 ml. of ethyl ether was stirred at room temperature. After 5 hrs. the pasty yellow mixture began to darken; the solution was red and the precipitate (probably the lithium reagent) was orange. Eighteen hr. later, the mixture was poured onto Dry Ice. After the usual work-up, 3.08 g. (68%) of triphenylacetic acid was found. The neutral organic residue weighed 0.73 g.

Preparation of tritylllithium in 1,2-dimethoxyethane; (A) *24-hour reaction period.* To 0.42 g. (0.061 g. atom) of finely cut lithium wire in 20 ml. of 1,2-dimethoxyethane, 3.23 g. (0.0116 mole) of trityl chloride was added. The red color of the lithium reagent soon appeared on the surface of the lithium, and then gradually in the solution. After being stirred for 5 hr. under gentle reflux, the mixture was stirred for an additional 19 hr. at room temperature before carbonation. The deep red color faded immediately to a pale pink when the reagent came in contact with carbon dioxide. Hydrolysis was effected with 20 ml. of an aqueous solution containing 3.2 g. (0.049 mole) of sodium azide and 0.4 g. of ammonium chloride. The *p*H of this solution was about 6. After addition of the organic mixture, the *p*H was 7–8. A total of 2.34 g. (70%) of triphenylacetic acid was obtained. By infrared analysis the neutral fraction of the product (0.57 g.) was found to contain: 30% triphenylmethane,

57% *p*-benzhydryltetraphenylmethane, and 7% triphenylcarbinol. The characteristic absorption band of the azide group (2130 $cm.^{-1}$) was absent.

Preparation of trityllithium in 1,2-dimethoxyethane; (B) *23-hour reaction period at reflux temperature.* A solution of trityllithium was prepared by treating 0.54 g. (0.078 g. atom) of lithium sand with 2.23 g. (0.0080 mole) of trityl chloride in 20 ml. of refluxing 1,2-dimethoxyethane. Within 1 hr. the mixture became a deep opaque red. At the end of 3 hr., the color had deepened to red-purple. After a total reflux period of 23 hr., the reaction mixture, which was then an orange-red, was poured onto Dry Ice. The color remained until dilute hydrochloric acid was added, whereupon the mixture turned yellow. No acid was obtained from base extraction of the reddish oily product, which contained at least five compounds according to spectral analysis.

Preparation of trityllithium in tetrahydrofuran; (A) *3-hour reaction period at room temperature.* To a well stirred mixture of 0.252 g. (0.0364 g. atom) of finely cut lithium wire in 5 ml. of tetrahydrofuran, a solution of 3.05 g. (0.0110 mole) of trityl chloride in 40 ml. of tetrahydrofuran was added during 40 min. The reaction began almost as soon as a fresh surface of lithium was exposed by the stirrer blade. The red color of trityllithium appeared on the metal and the solution darkened rapidly. The mildly exothermic reaction subsided after all the trityl chloride had been added. After two more hours of stirring at room temperature, the mixture was carbonated with Dry Ice. After the work-up, 1.72 g. (55%) of triphenylacetic acid was obtained. The organic residue (0.97 g.) was shown by infrared analysis to contain: 30% triphenylmethane, 50% *p*-benzhydryltetraphenylmethane, 8% triphenylcarbinol, and an unidentified alcoholic component.

Preparation of trityllithium in tetrahydrofuran; (B) *4-hour reaction period at −60°.* A solution of trityllithium was prepared by addition of 5.20 g. (0.0187 mole) of trityl chloride in 30 ml. of tetrahydrofuran to 0.96 g. (0.138 g. atom) of lithium wire. The reaction flask was kept in a Dry Ice–chloroform bath at $-60 \pm 5°$. The addition required 1 hr. and the mixture was stirred for an additional 3 hr. The normal color changes were observed. After carbonation and workup, a 43% yield (2.31 g.) of triphenylacetic acid was isolated. The neutral residue amounted to 2.36 g. No trityl peroxide was found.

Preparation of trityllithium in three-week-old tetrahydrofuran; (C). To 0.399 g. (0.058 g. atom) of lithium in a flask cooled in a Dry Ice–chloroform bath at $-60 \pm 5°$, a solution of 6.43 g. (0.0232 mole) of trityl chloride in 50 ml. of *three-week-old* tetrahydrofuran was added during 90 min. After an additional 90 min. of stirring, the mixture was carbonated. After hydrolysis, the organic layer was filtered to remove the insoluble trityl peroxide. A total of 3.80 g. (63% yield) of trityl peroxide (m.p. with decomposition 179–181°) was obtained. By basic extraction of the organic layer, 0.36 g. (5.4% yield) of triphenylacetic acid was obtained.

Reaction of trityllithium with oxygen. A solution of trityllithium was prepared from 0.33 g. (0.048 g. atom) of lithium wire and 3.07 g. (0.0110 mole) of trityl chloride in 30 ml. of 1,2-dimethoxyethane. The mixture was stirred at the reflux temperature for 5 hr. before a stream of dry oxygen was passed through the solution. The red-purple color changed to a yellow-orange. After hydrolysis, a partial separation of the reaction products was effected by chromatography on alumina[29] since fractional crystallization was not effective in separating the components. From 2.64 g. of crude product, 0.56 g. (21%) of triphenylmethane and 0.30 g. (11%) of *p*-benzhydryltetraphenylmethane were obtained. By infrared analyses, the other components were found to be: triphenylcarbinol (55%) and trityl peroxide (15%).

Reaction of trityllithium with deuterium oxide. To a stirred mixture of 0.99 g. (0.143 g. atom) of lithium wire and 5 ml. of tetrahydrofuran was added a solution of 5.93 g. (0.0213 mole) of trityl chloride in 45 ml. of tetrahydrofuran during 90 min. The reagent was stirred for an additional 30 min. before it was added to 3 ml. of Stuart 99.5+% deuterium oxide in 15 ml. of tetrahydrofuran. This mixture was stirred for 30 min., then allowed to stand overnight. After addition of dilute hydrochloric acid and benzene, the organic layer was removed, dried, and the solvent was distilled to yield 4.92 g. of yellow semisolid. This crude product was subjected to chromatography on a column packed with freshly activated alumina. Elution with a benzene-hexane mixture (1:19) furnished 3.34 g. (64.5% yield) of triphenylmethane and elution with a 3:7 mixture afforded 1.36 g. (24% yield) of *p*-benzhydryltetraphenylmethane. The deuterium content[30] of these two hydrocarbons was determined by (1) combustion of the samples, (2) followed by reduction to hydrogen, deuterium, and hydrogen deuteride, and (3) determination of the DH/H_2 ratio by mass spectrometry. The observed DH/H_2 ratios were: triphenylmethane, 0.0782; *p*-benzhydryltetraphenylmethane, 0.0622. This is equivalent to 58.7% and 90.3% deuteration, respectively. After correction for the water in the deuterium oxide, the numbers of millimoles of the various products are: triphenylmethane, 5.44; deuterotriphenylmethane, 8.23; *p*-benzhydryltetraphenylmethane, 0.21; and deutero-*p*-benzhydryltetraphenylmethane, 2.58.

A sample of the partially deuterated triphenylmethane was allowed to stand for 3 hr. in a tetrahydrofuran-water mixture containing lithium hydroxide. Infrared analysis of the recovered triphenylmethane indicated no appreciable loss of deuterium.

Action of trityllithium on acetone. A solution containing about 0.015 mole of trityllithium was added through a filter to an excess (3.5 g., 0.060 mole) of acetone in 20 ml. of tetrahydrofuran. The deep red color of the reagent was discharged immediately, leaving a pink solution. After 30 min. of stirring, the contents of the reaction flask were added to a mixture of 50 ml. of saturated sodium bisulfite solution and 50 ml. of methylene chloride. After the organic layer had been shaken well with the bisulfite solution, the aqueous layer was removed and the extraction was repeated three times. (This method was found to be the most convenient for removing the acetone from the organic layer.) The last aqueous extract gave no precipitate when treated with the 2,4-dinitrophenylhydrazine reagent. The organic layer then was stirred overnight with 1200 ml. of a saturated solution of 2,4-dinitrophenylhydrazine (about 4 g.) in 3*N* hydrochloric acid. The deep red organic layer was then removed and the solvent was evaporated. The semisolid red residue was washed well with hot hexane, and then crystallized twice from a benzene-ethanol mixture. The 2,4-dinitrophenylhydrazine derivative melted with decomposition at 201–203° and the mixture melting point with an authentic sample of mesityl oxide 2,4-dinitrophenylhydrazone was also 201–203°. The hexane washes were concentrated to yield mainly triphenylmethane. An infrared analysis indicated the absence of any carbonyl or alcohol compounds other than a small amount of triphenylcarbinol.

Action of trityllithium on cyclohexanone. To the lithium reagent prepared from 4.11 g. (0.0148 mole) of trityl chloride, 2.0 g. (0.020 mole) of cyclohexanone was added. The color of the reagent disappeared immediately. Following hydrolysis, the volatile components of the mixture were removed by vacuum distillation leaving 4.11 g. of a yellow semisolid oil which was subjected to chromatography on alumina. Only triphenylmethane (2.33 g.) and *p*-benzhydryltetraphenylmethane (about 1.0 g.) were isolated as crystalline com-

(29) Alcoa F-20 Grade alumina was used for most of the chromatograms. A more active adsorbent could be made by heating the alumina at 200° for 5 hr. under reduced pressure. Matheson Reagent Grade aluminum oxide which had been treated similarly was employed when an adsorbent less active than Alcoa alumina was required.

(30) Deuterium analyses were performed by Dr. C. B. Koons.

pounds. No evidence for any adduct was observed and no attempt was made to isolate the cyclohexanone self-condensation product.

Action of trityllithium on benzaldehyde in the absence of lithium. Tritylithium was prepared from 3.05 g. (0.0110 mole) of trityl chloride, 0.297 g. (0.0428 g. atom) of lithium wire, and 30 ml. of tetrahydrofuran. After a total reaction period of 5 hr., the lithium was removed and 0.85 g. (0.0080 mole) of benzaldehyde in 9 ml. of tetrahydrofuran was added. The color faded to amber and did not change during the next 5 hr., after which time the reaction mixture was added to Dry Ice. Following hydrolysis and work-up, a yellow semisolid was obtained. No triphenylacetic acid was isolated. The infrared spectrum of the crude product exhibited bands characteristic of 1,2,2,2-tetraphenylethanol (778, 1182, 1380, 3620 cm.$^{-1}$) as well as absorption assigned to triphenylmethane and a weak carbonyl band at 1700 cm.$^{-1}$ (probably benzaldehyde). The mixture was subjected to chromatography on alumina. By combination and crystallization of various fractions, the following compounds were obtained: triphenylmethane (0.55 g.), *p*-benzhydryltetraphenylmethane (0.25 g.) and 1,2,2,2-tetraphenylethanol (0.48 g., 12.5%). Most of the later fractions did not yield crystalline material. The tetraphenylethanol melted at 152–153° and did not depress the melting point of a mixture with an authentic sample.

Action of trityllithium on benzaldehyde in the presence of lithium. A solution of trityllithium was prepared from 3.60 g. (0.0130 mole) of trityl chloride, 0.291 g. (0.042 g. atom) of lithium, and 40 ml. of tetrahydrofuran. After a total reaction period of 5 hr., 1.3 g. (0.013 mole) of benzaldehyde in 8 ml. of tetrahydrofuran was added. The deep red color of the reagent faded to amber, then gradually the deep red color returned during the next 6 hr. The mixture was hydrolyzed with water, and acid was added until the *p*H reached 7. The organic layer was separated and the solvent was evaporated to yield 4.38 g. of yellow oil. The infrared spectrum of this material showed absorption bands assignable to triphenylmethane, *p*-benzhydryltetraphenylmethane, and a hydrogen-bonded alcohol. The only carbonyl absorption was a weak band at 1677 cm.$^{-1}$ None of the characteristic bands of 1,2,2,2-tetraphenylethanol was present. Fractional crystallization of this mixture was unsuccessful. Chromatography of the mixture on alumina yielded the following results: 1.78 g. triphenylmethane, 0.79 g. of *p*-benzhydryltetraphenylmethane, several fractions which had melting point ranges from 145–200°, and a number of fractions which did not crystallize. Attempted crystallization of these fractions also did not yield any discrete compounds.

Action of trityllithium on benzoyl chloride. The tritylithium reagent was prepared in the usual manner from 6.19 g. (0.0222 mole) of trityl chloride and 0.901 g. (0.130 g. atom) of lithium in 50 ml. of tetrahydrofuran. The reagent was added through a filter to 2.3 g. (0.017 mole) of benzoyl chloride in 10 ml. of tetrahydrofuran. The deep opaque red-purple mixture turned to a clear red-amber within a few seconds. This reaction mixture was stirred for 3 hr. before hydrolysis. After removal of the solvent from the organic layer, the yellow solid (7.31 g.) was subjected to chromatography on a deactivated alumina column. A total of 6.38 g. of solid was obtained; elution with benzene and chloroform gave 0.73 g. of yellow oil which did not crystallize and was discarded. A second chromatographic separation on activated alumina yielded: 1.15 g. of triphenylmethane, 0.25 g. of impure *p*-benzhydryltetraphenylmethane, and a number of fractions with wide melting point ranges. Some of these fractions were combined and subjected to a third chromatographic separation. By combination and crystallization of fractions from the second and third chromatographic analyses, 2.09 g. (27% yield) of benzopinacolone and 0.69 g. of α-benzoyl-$\alpha,\alpha,\alpha',\alpha',\alpha'$-pentaphenyl-*p*-xylene (m.p. 239–245°) were obtained. The benzopinacolone was identified by its infrared spectrum, melting point (180–182°), and mixture melting point with an authentic sample (181–183°).

The *α-benzoyl-$\alpha,\alpha,\alpha',\alpha',\alpha'$-pentaphenyl-p-xylene* was identified as follows: Three crystallizations from a benzene-hexane mixture furnished an analytical sample; m.p. 246–247°.

Anal. Calcd. for $C_{45}H_{34}O$: C, 91.49; H, 5.80. Found: C, 91.16; H, 5.91.

The infrared spectrum was very similar to that of benzopinacolone. Conjugated ketone bands occur at 1675 and 1212 cm.$^{-1}$; absorption assigned to a *para*-disubstituted benzene ring occurs at 808 cm.$^{-1}$ Fusion of 180 mg. of this ketone with 400 mg. of sodium hydroxide at 270° for one hour gave 31 mg. of benzoic acid (m.p. 122–122.5°) and 180 mg. of impure *p*-benzhydryltetraphenylmethane (m.p. 212–220°). The hydrocarbon was purified by chromatography; 155 mg. of reasonably pure hydrocarbon was obtained. Identity with an authentic sample was proved by comparison of infrared spectra and by the fact that no melting point depression was observed upon admixture of the two. A purified sample melted at 226–229°.

Action of trityllithium on ethyl benzoate. A mixture of 6.02 g. (0.0216 mole) of trityl chloride, 0.933 g. (0.134 g. atom) of lithium wire, and 50 ml. of tetrahydrofuran were used to prepare the lithium reagent, which was then added to 2.6 g. (0.0175 mole) of ethyl benzoate. The color changed to a clear red-brown. After being stirred for 20 hr. at room temperature, the reaction mixture was hydrolyzed. The 6.55 g. of organic material obtained was subjected to chromatography on alumina. From the early fractions, 1.20 g. of triphenylmethane and about 0.20 g. of *p*-benzhydryltetraphenylmethane were obtained. Some of the later fractions were combined and a second chromatographic separation was attempted. By combination and crystallization of various fractions from the first and second separations, 2.44 g. (32% yield) of benzopinacolone (m.p. 180–182°) and 0.61 g. of α-benzoyl-$\alpha,\alpha,\alpha',\alpha',\alpha'$-pentaphenyl-*p*-xylene (m.p. 243–246°) were obtained.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD.]

Reactions of Hexachlorobenzene with Mercaptides

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In the reaction of hexachlorobenzene with alkyl mercaptides the chlorine atoms were replaced by alkylmercapto groups two at a time to form either bis(alkylmercapto)tetrachlorobenzene (II) or tetrakis(alkylmercapto)dichlorobenzene (III) depending on conditions used. The orientation in the disubstituted product II was established by degradation to tetrachloro-*p*-benzoquinone (IX). 1,4-Bis(alkylmercapto)-2,3,5,6-tetrachlorobenzenes (II) underwent partial dealkylation to the thiol VI in boiling alcoholic sodium hydrosulfide. One (VII) was converted to the phenol VIII in the presence of alkali.

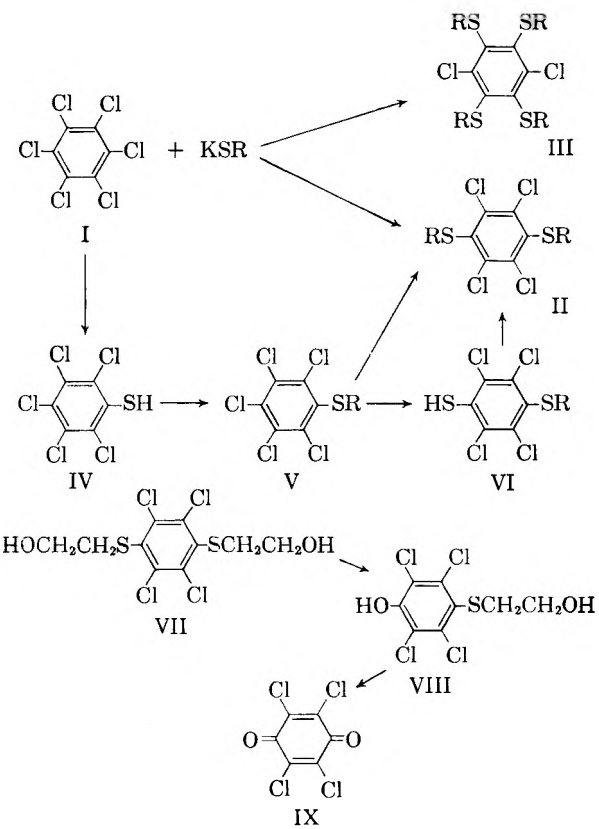
Hexachlorobenzene (I) though regarded as an inert substance does undergo substitution reactions under relatively moderate conditions. It has been pointed out recently that nucleophilic reagents such as alcoholic alkali,[1] alkali alkoxides,[2–4] sodium hydrosulfide or disulfide,[4–6] and amines[4] attack I replacing one chlorine atom.

The thiophenoxide ion is a powerful nucleophilic reagent[7] and therefore would be expected to attack I. Rocklin[4] stated that mercaptides react readily with I in pyridine solution but did not report the isolation of any reaction products.

In this investigation it was found that two chlorine atoms of hexachlorobenzene (I) are attacked by alcoholic alkali mercaptides to form 1,4-bis-(alkylmercapto)tetrachlorobenzenes (II). The reaction was exothermic and when allowed to proceed with excess mercaptide, resulted in further substitution to form tetrakis(alkylmercapto)dichlorobenzene (III). With ethyl mercaptan and 2-mercaptoethanol the conditions of the reaction with I could be controlled so that either the disubstituted product II or the tetrasubstituted product III could be obtained. With amyl mercaptan and *p*-chlorobenzyl mercaptan, although there was evidence for the formation of both substitution products, only the disubstituted compound II was isolated in pure form.

In the case where equimolecular quantities of I and amyl mercaptide were allowed to react the main product was still the disubstituted II. Though none of the monosubstituted compound V could be isolated its formation cannot be excluded.

Some polyhalobenzenes refused to react with mercaptides. Thus *p*-dichlorobenzene, 1,2,4,5-tetrachlorobenzene, pentachlorophenol, pentachloroanisole, and pentachlorobenzenethiol remained unchanged after prolonged heating with butanolic sodium hydrosulfide or with the potassium salt of 2-mercaptoethanol. However, the blocking of the highly nucleophilic mercapto group of pentachlorobenzenethiol (IV) activated the para chlorine atom so that pentachlorophenyl ethyl sulfide (V) reacted readily with sodium hydrosulfide to form 4-ethylmercapto-2,3,5,6-tetrachlorobenzenethiol (VI). This on ethylation with diethyl sulfate yielded the same 1,4-bis(ethylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = ethyl) as was obtained by the direct reaction I→II. 1,4-bis(Methylmercapto)-2,3,5,6-tetrachlorobenzene (II) did not undergo



further substitution reaction when treated with butanolic sodium hydrosulfide. Instead demethylation occurred to form 4-methylmercapto-2,3,5,6-

(1) P. D. Bartlett, U.S. Patent 2,644,015 (1953); *Chem. Abstr.*, 48, 5216 (1954).

(2) E. A. Kryuger and M. S. Bednova, *J. Gen. Chem. (U.S.S.R.)*, 3, 67 (1933); *Chem. Abstr.*, 28, 1593 (1934).

(3) T. Van der Linden, *Rec. trav. chim.*, 57, 781 (1938); *Chem. Abstr.*, 32, 6628 (1938).

(4) A. L. Rocklin, *J. Org. Chem.*, 21, 1478 (1956).

(5) J. Pikl, U.S. Patent 2,765,345 (1956); *Chem. Abstr.*, 51, 5828 (1957).

(6) F. Lober, O. Bayer, and M. Bögemann, U.S. Patent 2,695,898 (1954); *Chem. Abstr.*, 49, 3572 (1955).

(7) J. F. Bunnett and W. D. Merritt, *J. Am. Chem. Soc.*, 79, 5967 (1957).

tetrachlorobenzenethiol (VI). Pentachloroanisole behaved similarly to form pentachlorophenol.

Of the two routes to 1,4-bis(alkylmercapto)-2,3,5,6-tetrachlorobenzenes (II) the direct one (I→II) is more convenient for preparative purposes. However, the indirect route (I→IV→V→II) has the advantage of introducing the sulfur substituents one at a time and therefore lends itself to the preparation of II with mixed alkylmercapto groups.

In order to show that the sulfur substituents of II were located para to each other, an attempt was made to synthesize 2,3,5,6-tetrachlorobenzene-1,4-dithiol by an independent method. Accordingly 1,2,4,5-tetrachlorobenzene was treated with chlorosulfonic acid. The product of the reaction was sulfur free and proved to be hexachlorobenzene. The orientation of the substituents in II was finally demonstrated by degradation and oxidation. 1,4-bis(2-Hydroxyethylmercapto)-2,3,5,6-tetrachlorobenzene (VII) was heated under reflux with potassium hydroxide in ethylene glycol. The resulting product which was obtained in 80% yield, was soluble in alkali, methylated readily with dimethyl sulfate or diazomethane but refused to react with ethylene dichloride in the presence of alkali. This showed that the compound was a phenol and not a thiol. Analytical examination indicated that the product was 4-(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol (VIII). This was presumably formed from VII by replacement of one 2-hydroxyethylmercapto group by a hydroxyl. Finally, the oxidation of VIII with hydrogen peroxide and chromic oxide yielded chloranil (IX), thus proving that the two sulfur substituents are located para to each other. An attempt to replace both the 2-hydroxyethylmercapto groups of VII with hydroxyl groups to form tetrachlorohydroquinone was not successful. Prolonged heating of VII or VIII with alkali in ethylene glycol gave only tars. Methylation of VIII first to the anisole followed by the alkali and ethylene glycol treatment resulted in demethylation and the formation of VIII.

EXPERIMENTAL[8]

1,4-Bis(ethylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = ethyl). (a) *Directly from hexachlorobenzene.* To a cooled solution of potassium hydroxide (18 g.) in ethanol (75 ml.) was added ethyl mercaptan (18 g.) in methyl ethyl ketone (200 ml.). Then hexachlorobenzene (40 g.) was added and the reaction mixture gently warmed until the exothermic reaction commenced. When the reaction became too violent a cooling bath was applied. The exothermic reaction subsided in a few minutes and then the reaction mixture was heated under reflux for 2 hr. The precipitated potassium chloride was filtered from the hot reaction mixture and washed with methyl ethyl ketone. The combined filtrate and washings were concentrated to about 100 ml., a little methanol was added to the concentrate and the solution allowed to cool. The precipitate after filtration and drying melted at 87–89° and weighed 32 g. or 68%. A portion on recrystallization from benzene-methanol yielded white needles melting at 88–89°.

Anal. Calcd. for $C_{10}H_{10}Cl_4S_2$: C, 35.72; H, 2.97. Found: C, 35.26, H, 2.99.

(b) *From 4-ethylmercapto-2,3,5,6-tetrachlorobenzenethiol* (VI). The thiol VI (see below) was dissolved in excess aqueous alkali and the solution warmed on a steam bath and treated with diethyl sulfate. The reaction mixture was cooled and the precipitate filtered, washed, and dried. It melted at 88–89° alone or in admixture with the product obtained in (a).

1,4-Dichloro-2,3,5,6-tetrakis(ethylmercapto)benzene (III, R = ethyl). To a cooled solution of potassium hydroxide (50 g.) in ethanol (150 ml.) was added a solution of ethyl mercaptan (53 g.) in methyl ethyl ketone (350 ml.). Then hexachlorobenzene (40 g.) was added. After the exothermic reaction subsided, the reaction mixture was heated under reflux for 40 hr. The precipitated potassium chloride (48 g.) was filtered off and the filtrate taken to dryness. The residue distilled at 183–185° (0.5 mm.) and the yellow distillate (49 g.) solidified on standing. It was crystallized from petroleum ether (b.p. 30–60°) twice yielding light yellow prisms (31 g. or 50%) melting at 48–49°.

Anal. Calcd. for $C_{14}H_{20}Cl_2S_4$: C, 43.41; H, 5.16. Found: C, 42.79; H, 5.01.

1,4-Bis(n-amylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = n-amyl) was prepared in 89% from two moles of *n*-amyl mercaptan and hexachlorobenzene in the same manner as was the ethyl analog II (R = ethyl) above. The colorless liquid boiled at 245–255° (12 mm.) or 170–175° (0.5 mm.), $n_D^{20} = 1.5922$.

Anal. Calcd. for $C_{16}H_{22}S_2Cl_4$: C, 45.71; H, 5.24. Found: C, 45.62; H, 5.44.

1,4-Bis(p-chlorobenzylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = p-$ClC_6H_4CH_2$). This was prepared in 50% yield from two moles of *p*-chlorobenzyl mercaptan and hexachlorobenzene in the same manner as was II (R = ethyl) above except that reaction time was extended to 7 hr. It crystallized from benzene-ethanol yielding white needles melting at 147–148°.

Anal. Calcd. for $C_{20}H_{12}Cl_6S_2$: C, 45.29; H, 2.26. Found: C, 45.18; H, 2.48.

1,4-Bis(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = CH_2CH_2OH). To a stirred suspension of hexachlorobenzene (285 g.), pyridine (1 l.), and methanol (200 ml.) was added dropwise a solution of potassium hydroxide (118 g.), 2-mercaptoethanol (160 ml.) and methanol (100 ml.) over a period of 2.5 hr. The temperature was maintained at 65 to 68° by occasional cooling. The reaction mixture was stirred for an additional hour, let stand overnight, and then filtered. The filtrate was concentrated to a volume of about 350 ml., boiling methanol (350 ml.) added, and the solution allowed to cool. The white precipitate was filtered, washed with methanol, with water, and with methanol and dried. It weighed 265 g. or 72% and melted at 145–147°. Recrystallization from methanol raised the melting point to 151–153°.

Anal. Calcd. for $C_{10}H_{10}O_2Cl_4S_2$: C, 32.62; H, 2.72. Found: C, 32.45; H, 2.94.

1,4-Bis(2-chloroethylmercapto)-2,3,5,6-tetrachlorobenzene. A reaction mixture of 1,4-bis(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorobenzene (II, R = CH_2CH_2OH) (10 g.) and thionyl chloride (25 ml.) was heated under reflux for 0.5 hr. The excess thionyl chloride was distilled off and the residue treated with water. The white solid was filtered, washed, dried, and crystallized twice from benzene, yielding (8.5 g.) microscopic prisms melting at 175–179°.

Anal. Calcd. for $C_{10}H_8Cl_6S_2$: C, 29.63; H, 1.98. Found: C, 29.72; H, 2.02.

1,4-Dichloro-2,3,5,6-tetrakis(2-hydroxyethylmercapto)benzene. To a solution of potassium hydroxide (37 g.) in ethanol (400 ml.) was added hexachlorobenzene (28 g.) and 2-mercaptoethanol (50 ml.) and the reaction mixture was heated

(8) All melting points are corrected.

under reflux for three days. The potassium chloride (30 g.) was filtered off and the filtrate was taken to dryness *in vacuo*. The residue was crystallized twice from aqueous ethanol yielding (7 g.) of white solid melting at 184–186°.

Anal. Calcd. for $C_{14}H_{20}O_4Cl_2S_4$: C, 37.15; H, 4.44. Found: C, 37.49; H, 4.49.

1,4-Dichloro-2,3,5,6-tetrakis(2-chloroethylmercapto)benzene. A reaction mixture of 1,4-dichloro-2,3,5,6-tetrakis (2-hydroxyethylmercapto)benzene (5 g.) and thionyl chloride (20 ml.) was heated under reflux for 0.5 hr. The excess thionyl chloride was removed *in vacuo* and the residue crystallized from benzene. This yielded 5 g. of white needles melting at 184–185°.

Anal. Calcd. for $C_{14}H_{16}Cl_6S_4$: C, 32.00; H, 3.05. Found: C, 32.30; H, 2.95.

Methyl pentachlorophenyl sulfide. Pentachlorobenzenethiol (60 g.) [4–6] was dissolved in a solution of sodium hydroxide (20 g.) and water (300 ml.), heated on a steam bath and treated with excess dimethyl sulfate. The reaction mixture was cooled, the white solid (60 g.) filtered, washed, and crystallized from benzene-methanol, m.p. 93–94°.

Anal. Calcd. for $C_7H_3Cl_5S$: C, 28.33; H, 1.01. Found: C, 28.25; H, 1.00.

Ethyl pentachlorophenyl sulfide. This was prepared in 90% yield by ethylation of pentachlorobenzenethiol with diethyl sulfate and alkali as above. It crystallized from methanol in the form of white needles melting at 51–52°. Tadros and Saad[9] give a melting point of 42–44°.

Anal. Calcd. for $C_8H_5Cl_5S$: C, 30.92; H, 1.61. Found: C, 30.96; H, 1.50.

2-Chloroethyl pentachlorophenyl sulfide. To a solution of potassium hydroxide (4 g.) in methanol (50 ml.) was added pentachlorobenzenethiol (14 g.) and ethylene dichloride (250 ml.) and the reaction mixture was heated under reflux for one hour. This was cooled, washed with water, and the residue crystallized from benzene. The white prisms (13 g.) melted at 132–134°.

Anal. Calcd. for $C_8H_4Cl_6S$: C, 27.83; H, 1.16. Found: C, 28.25; H, 1.25.

4-Methylmercapto-2,3,5,6-tetrachlorobenzenethiol (VI, R = CH_3). A reaction mixture of technical sodium hydrosulfide (36 g.), methyl pentachlorophenyl sulfide (55 g.), and butanol (300 ml.) was heated under reflux for 16 hr. The butanol was distilled off *in vacuo*, the residue treated with water and the aqueous solution was extracted with benzene in order to remove unreacted material. The aqueous solution was acidified, extracted with benzene, and the organic solvent removed. The residue distilled at 150–155° (0.5 mm.) and the distillate on crystallization from acetone-methanol yielded 36 g. or 65% of almost white plates melting at 82–84°.

Anal. Calcd. for $C_7H_4Cl_4S_2$: C, 28.57; H, 1.36. Found: C, 28.73; H, 1.58.

4-Ethylmercapto-2,3,5,6-tetrachlorobenzenethiol (VI, R = C_2H_5). This was prepared in 60% yield from ethyl pentachlorophenyl sulfide and sodium hydrosulfide as described above for 4-methylmercapto-2,3,5,6-tetrachlorobenzenethiol. The yellow prisms melted at 58–59°. An aqueous alkaline solution of this when treated with diethyl sulfate yielded a product melting at 88–89° alone or in admixture with 1,4-bis(ethylmercapto)-2,3,5,6-tetrachlorobenzene (see above).

1,4-Bis(methylmercapto)-2,3,5,6-tetrachlorobenzene. This was prepared in 90% yield by the methylation of 4-methylmercapto-2,3,5,6-tetrachlorobenzenethiol with dimethyl sulfate and alkali. The white needles melted at 132–134°.

Anal. Calcd. for $C_8H_6Cl_4S_2$: C, 31.17; H, 1.95. Found: 30.90; H, 2.12.

1-(Methylmercapto)-4-(2-chloroethylmercapto)-2,3,5,6-tetrachlorobenzene. This was prepared in 90% yield from 4-methylmercapto-2,3,5,6-tetrachlorobenzenethiol and ethylene dichloride in the same manner as was 2-chloroethyl pentachlorophenyl sulfide (above). The white product after crystallization from acetone-methanol melted at 104–106°.

Anal. Calcd. for $C_9H_7Cl_5S_2$: C, 30.30; H, 1.96. Found: C, 30.04; H, 1.81.

1-(Ethylmercapto)-4-(2-chloroethylmercapto)-2,3,5,6-tetrachlorobenzene. This was prepared in 90% yield from 4-ethylmercapto-2,3,5,6-tetrachlorobenzenethiol and ethylene dichloride in the same manner as described above. It crystallized as white needles and melted at 102–103°.

Anal. Calcd. for $C_{10}H_9Cl_5S_2$: C, 32.39; H, 2.43. Found: C, 31.91; H, 2.55.

Reaction of 1,2,4,5-tetrachlorobenzene with chlorosulfonic acid. A reaction mixture of 1,2,4,5-tetrachlorobenzene (35 g.) and chlorosulfonic acid (150 ml.) was heated at 140–145° for 20 hr. The cooled reaction mixture was cautiously added to cracked ice. The precipitate was filtered, washed with cold water, dried, and crystallized from benzene. The product (35 g.) melted at 231–233° and did not depress the melting point of *hexachlorobenzene*.

4-(2-Hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol (VIII). A solution of potassium hydroxide (25 g.) in ethylene glycol (150 ml.) and 1,4-bis(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorobenzene (VII) (25 g.) was heated under reflux for 3 hr. The amber solution was concentrated *in vacuo* until most of the glycol was removed. The residue was dissolved in water, filtered, and the filtrate acidified. The precipitate was filtered, washed, dried, and then distilled from a large Späthe bulb, b.p. (1 mm.) 180–220°. The distillate on crystallization from benzene-methanol yielded 17 g. or 80% of white prisms which melted at 168–169°.

Anal. Calcd. for $C_8H_6O_2Cl_4S$: C, 31.17; H, 1.95; S, 10.4. Found: C, 31.13; H, 2.00; S, 11.1.

This compound did not react with ethylene dichloride in the presence of alkali showing that it is not a thiol.

4-(2-Hydroxyethylmercapto)-2,3,5,6-tetrachloroanisole. This was prepared in almost quantitative yield by methylation of 4-(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol with diazomethane. Methylation with dimethyl sulfate gave poor yields because the alkyl hydroxyl group was also attacked. The product crystallized from benzene as white needles and melted at 100–101°.

Anal. Calcd. for $C_9H_8O_2Cl_4S$: C, 33.54; H, 2.49. Found: C, 33.99; H, 2.93.

4-(2-Chloroethylmercapto)-2,3,5,6-tetrachloroanisole. 4-(2-Hydroxyethylmercapto)-2,3,5,6-tetrachloroanisole (4 g.) and thionyl chloride (20 ml.) were heated under reflux for 0.5 hr. and then the excess thionyl chloride was removed *in vacuo*. The residue on crystallization from methanol yielded white prisms (2.5 g.) melting at 107–108°.

Anal. Calcd. for $C_9H_7OCl_5S$: C, 31.76; H, 2.06. Found: C, 31.81; H, 2.34.

4-(2-Chloroethylmercapto)-2,3,5,6-tetrachlorophenol. This was prepared in 70% yield from 4-(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol (VIII) and thionyl chloride in the usual manner. After crystallization from benzene the white prisms melted at 134–135°.

Anal. Calcd. for $C_8H_5Cl_5OS$: C, 29.41; H, 1.53. Found: C, 29.21; H, 1.69.

Oxidation of 4-(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol (VIII) *to 2,3,5,6-tetrachloro-1,4-benzoquinone* (IX). To 4-(2-hydroxyethylmercapto)-2,3,5,6-tetrachlorophenol (VIII) (1 g.) in acetic acid (20 ml.) was added 30% hydrogen peroxide (5 ml.) and the resulting solution was heated on the steam bath for 1 hr. To this was added dropwise with stirring a solution of chromic oxide (3 g.) in water (2 ml.) and acetic acid (20 ml.) over about 5 min. The dark solution was diluted with water, the yellow precipitate filtered, washed, dried, and crystallized from benzene. The yellow crystals (0.18 g. or 20%) melted at 290–292° alone or in admixture with 2,3,5,6-tetrachloro-1,4-benzoquinone.

(9) W. Tadros and E. Saad, *J. Chem. Soc.*, 1155 (1954).

GUELPH, ONT.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF FLORIDA]

Fluoroolefins. VI.[1] The Synthesis of Some α-Trifluoromethylstyrenes

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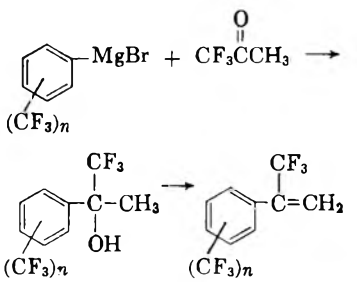
Three new α-trifluoromethylstyrenes were prepared in a two-step synthesis involving the dehydration of the carbinols made from trifluoroacetone and Grignard reagents. The effect of hydrogen bonding in the carbinols is discussed.

According to the patent literature[2] α-difluoromethyl- and α-trifluoromethylstyrene have been made from the corresponding phenylpropanols. However, neither physical constants nor yields were given. Furthermore, the use of mild dehydrating agents such as oxalic acid, zinc chloride, *etc.*, indicated an ease of dehydration not normally associated with carbinols containing the trifluoromethyl group.[3] It thus seemed of some interest to prepare some α-trifluoromethylstyrenes and to observe any unusual behavior exhibited.

In the present study phenyl-, 3-trifluoromethylphenyl-, and 3,5-bis(trifluoromethyl)phenylmagnesium bromide were allowed to react with trifluoroacetone to give a carbinol which was dehydrated to the desired olefin. This method has



previously been employed[4-6] to give styrenes containing substituents on the benzene ring. McBee and Sanford synthesized some bis-trifluoromethyl- and trifluoromethylchlorostyrenes. Renoll prepared *m*-trifluoromethylstyrene by dehydrating *m*-trifluoromethylphenylmethylcarbinol, and Bachman and Lewis prepared some styrenes and α-methylstyrenes substituted by fluorine and trifluoromethyl groups on the ring by a similar method.

It was found that decreased yields of carbinol resulted when the highly substituted Grignard reagent was used. Furthermore, the dehydration of the resulting carbinols required heating with phosphoric oxide at atmospheric pressure at temperatures above 150°. The 3,5-bistrifluoromethylcarbinol was particularly difficult to convert to the styrene and low yields were obtained.

The compounds were characterized by physical properties, infrared spectra, and elemental analysis.

It is of interest to note that the boiling points of the three intermediate carbinols are not in line for materials of increasing molecular weight in a homologous series. This may be readily seen in Table I. Evidence has been presented[7] to show that an unassociated hydroxyl group exhibits an absorption band at approximately 2.75μ, while an associated hydroxyl absorbs near 3.00μ. As is readily seen in the above table, the absorption peak at 2.79μ increases in strength as the aromatic ring becomes increasingly electronegative due to the presence of trifluoromethyl groups. On the other hand, the absorption band at 2.89μ constantly decreases in intensity. If the 2.79μ and 2.89μ bands are assigned to unassociated and associated hydroxyl groups, respectively, it becomes apparent that the degree of association is being constantly decreased as the ring becomes more electronegative.

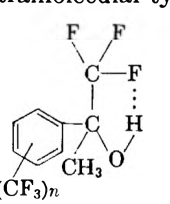
TABLE I

BOILING POINTS AND INFRARED ABSORPTION OF CARBINOLS

Carbinol	Boiling Point/°C.	Infrared Absorption[a] 2.79μ	2.89μ
$C_6H_5C(CF_3)(OH)CH_3$	62–66/4.5 mm	...	s
3-$(CF_3)C_6H_4C(CF_3)(OH)CH_3$	87.5–88.0/4 mm	w	m-s
3,5-$(CF_3)_2C_6H_3C(CF_3)(OH)CH$	59.0–60.0/3 mm	m	m

[a] s = strong. w = weak. m-s = medium strong. m = medium.

Two types of association are possible in this case. The first is of the intramolecular type:



(1) Paper V: Paul Tarrant, John Attaway, and A. M. Lovelace, *J. Am. Chem. Soc.*, 76, 2343 (1954).

(2) J. B. Dickey and T. E. Stanin, U.S. Patent 2,475,423 (July 5, 1949).

(3) K. A. Campbell, J. O. Knoblock, and B. K. Campbell, *J. Am. Chem. Soc.*, 72, 4380 (1950).

(4) M. W. Renoll, *J. Am. Chem. Soc.*, 68, 1159 (1946); U.S. Patent 2,580,504 (January 1, 1952).

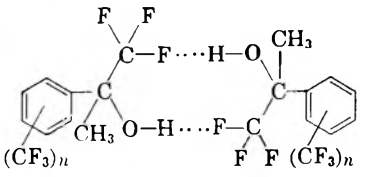
(5) G. B. Bachman and L. L. Lewis, *J. Am. Chem. Soc.*, 69, 2022 (1947); U.S. Patent 2,414,330 (January 14, 1947).

(6) E. T. McBee and R. A. Sanford, *J. Am. Chem. Soc.*, 72, 4053 (1950).

(7) Ferguson A. Smith and E. C. Creitz, *J. Research Nat. Bur. Standards*, 46, (2), 145 (1951).

J. J. Fox and A. E. Martin, *Trans. Faraday Soc.*, 36, 897 (1940).

Association of this type would decrease the boiling point of the material as the degree of association increased. The second possible type of association is of the intermolecular type:



Association of this type would increase the boiling point by increasing the effective molecular weight of the carbinol. As the degree of association decreased the boiling point would decrease. Since this is the observed result, it becomes apparent that this is the actual type of association occurring in the above carbinols.

EXPERIMENTAL

Formation of the carbinols. A one-liter, three-neck flask equipped with a stirrer, pressure equalized addition funnel, and ice water reflux condenser topped with a drying tube was charged with 0.5 mole (12.2 g.) of magnesium turnings and flame-dried under an atmosphere of dry nitrogen. The nitrogen was supplied from a cylinder, dried by passing through concentrated sulfuric acid and a tube containing Drierite, and admitted to the system through the top of the addition funnel. Dry ether (400 ml.) was added to cover the magnesium and a small portion of bromobenzene added to initiate the reaction. Cooling was often required to control the reaction once it had commenced. After the initial reaction had subsided, the remainder of 0.5 mole (78.5 g.) of bromobenzene was added at such a rate as to cause gentle boiling of the solvent. An hour was allowed after completion of the addition to ensure complete reaction. The Grignard reagent was then treated with 0.6 mole (67 g.) of trifluoroacetone *via* a gas inlet which replaced the addition funnel and the mixture left overnight. Hydrolysis was accomplished by pouring the ether solution onto 100 ml. of hydrochloric acid and 1 kg. of cracked ice. The ether layer was separated and the water extracted several times with small portions of ether. The combined extracts were dried and fractionated to give 71 g. (74.7%) of $C_6H_5C(CF_3)(OH)CH_3$, b.p. 62–6°/4.5 mm, n_D^{22} 1.4656, d_4^{22} 1.2511.

Anal. Calcd. for $C_6H_5C(CF_3)(OH)CH_3$: C, 56.8; H, 4.78; MR_D, 41.70. Found: C, 57.01; H, 4.87; MR_D, 42.07.

The Grignard reagent prepared from *m*-bromobenzotrifluoride (73 g., 0.325 mole) reacted with trifluoroacetone (36.4 g., 0.325 mole) to give a 70% yield of *m*-$CF_3C_6H_4C(CF_3)(OH)CH_3$. The constants for this compound are b.p. 87.5–88.0° at 4 mm., n_D^{24} 1.4148, d_4^{24} 1.4267.

Anal. Calcd. for $C_{10}H_8F_6O$: C, 46.6; H, 3.13. Found: C, 46.7; H, 3.04.

This Grignard reagent was also reacted with formaldehyde and gave a 33% yield of *m-trifluoromethylbenzyl alcohol*, b.p. 68° at 2 mm., n_D^{21} 1.4606, d_4^{21} 1.2949.

Anal. Calcd. for $C_8H_7F_3O$: C, 54.6; H, 4.01. Found: C, 54.5; H, 3.89.

The Grignard reagent from 3,5-bis(trifluoromethyl)-bromobenzene (189 g., 0.645 mole) reacted with trifluoroacetone (78.5 g., 0.7 mole) to give 3,5-$(CF_3)_2C_6H_3C(CF_3)(OH)CH_3$ in 40.2% yield. A center fraction of the distilled product had the following physical constants: b.p. 59–60° at 3 mm., n_D^{22} 1.3966, d_4^{22} 1.5118.

Anal. Calcd. for $C_{11}H_7F_9O$: C, 40.6; H, 2.17. Found: C, 40.4; H, 2.51.

Preparation of the α-trifluoromethylstyrenes. (*a*) A 500-ml. flask fitted with a stirrer, addition funnel, and short fractionation column topped with a variable take-off distilling head was charged with 15.0 g. of phosphoric oxide and cooled in ice water. One tenth mole (19 g.) of α-methyl-α-trifluoromethylbenzyl alcohol was added and the mixture stirred until an even paste formed. The ice bath was then replaced by a heating mantle and the mixture slowly heated until the desired product distilled at 148–157°. Fractionation of this crude distillate gave 11.6 g. (66.9%) of $C_6H_5C(CF_3)=CH_2$, b.p. 148.0–151.0°. A center fraction of 9.1 g. had the physical constants: b.p. 148.0–148.5°C., n_D^{21} 1.4603, d_4^{21} 1.167.

Anal. Calcd. for $C_9H_7F_3$: C, 62.7; H, 4.09; MR_D, 41.39. Found: C, 62.57; H, 4.16; MR_D, 40.42.

(*b*) Preparation of 3-trifluoromethyl-α-trifluoromethylstyrene: The above procedure was repeated using 0.2 mole (28.4 g.) of phosphoric oxide and 0.194 mole (50 g.) of 3-trifluoromethyl-α-methyl-α-trifluoromethylbenzyl alcohol to give crude material boiling up to 151°. Fractionation gave 23 g. (47.7%) of 3-$(CF_3)C_6H_4C(CF_3)=CH_2$, b.p. 151–159° with a center cut taken at 157–158°, n_D^{22} 1.4151, d_3^{22} 1.346.

Anal. Calcd. for $C_{10}H_6F_6$: C, 50.01; H, 2.52; MR_D, 46.00. Found: C, 49.89; H, 2.89; MR_D, 44.68.

(*c*) Preparation of 3,5-bis(trifluoromethyl)-α-trifluoromethylstyrene: The procedure above was repeated in the following two sections to give the results described below.

(1) The flask was charged with 0.2 mole (28.4 g.) of phosphoric oxide and 0.237 mole (77 g.) of 3,5-bis(trifluoromethyl)-α-methyl-α-trifluoromethylbenzyl alcohol added as described. The mixture was heated until material distilled between 170–180°. Redistillation gave 47 g. of recovered carbinol and 18.5 g. of lower boiling material whose infrared spectrum indicated it to be the desired styrene. The conversion was 9.3%.

(2) The procedure was repeated using 0.1 mole (14.2 g.) of phosphoric oxide and 0.144 mole (47 g.) of 3,5-bis(trifluoromethyl)-α-methyl-α-trifluoromethylbenzyl alcohol to give the crude distillate from which 9.5 g. of product boiling from 158° to 178° was obtained.

The olefin fractions from the two runs were combined and refractionated to give 14.8 g. of 3,5-bis(trifluoromethyl)-α-trifluoromethyl styrene, b.p. 59.5–60.0°/14 mm., n_D^{22} 1.3921, d_4^{22} 1.456.

Anal. Calcd. for $C_{11}H_6F_9$: C, 42.8; H, 1.63; MR_D, 51.63. Found: C, 42.41; H, 1.92; MR_D, 40.43.

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[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER AND GOODRICH-GULF CHEMICALS, INC.]

Isoprene-d_8 and Other Intermediates for the Synthesis of Deuterio-SN Rubber

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Perdeuterio isoprene was synthesized from acetone-d_6 and acetylene-d_2. 2-Methyl-3-butyn-2-ol-d_8 and 2,5-dimethyl-3-hexyn-2,5-diol-d_{14} were isolated and the latter decomposed to acetone and the ynol. The ynol was deuteriumated to 2-methyl-3-buten-2-ol-d_{10} over the Lindlar catalyst and the enol then dehydrated to isoprene. The maleic anhydride adduct as well as the α- and β-sulfones of isoprene-d_8 were prepared. The D compounds were more dense, less refractive, and had lower boiling points than the corresponding H compounds.

The synthesis[1] of perdeuterio SN rubber (all *cis*, all head-to-tail, all 1,5-diene polyisoprene), a preliminary report of which appeared recently, was possible as the result of the availability of D_2, D_2O, and geometrically specific polymerization techniques.[2] The present paper describes the preparation and properties of the required isoprene-d_8 and other intermediates.

The Favorskiĭ-Bergmann isoprene synthesis. Of the many possible routes to isoprene-d_8 from various simple compounds, the one chosen for adapting to the D series involves the Favorskiĭ[3] synthesis from acetone and acetylene as modified by Bergmann.[4] The following reactions are involved:

$$DC{\equiv}CD + KOD \rightleftharpoons DC{\equiv}CK + D_2O \quad (1)$$

$$DC{\equiv}CK + CD_3C(O)CD_3 \rightleftharpoons (CD_3)_2C(OK)C{\equiv}CD \quad (2)$$

$$KC{\equiv}CK + 2CD_3C(O)CD_3 \rightleftharpoons (CD_3)_2C(OK)C{\equiv}CC(OK)(CD_3)_2 \quad (3)$$

$$DC{\equiv}CD + CD_3C(O)CD_3 \xrightarrow{KOD} CD_3C(O)CD_2CD{=}CD_2 \quad (4)$$

$$(CD_3)_2C(OD)C{\equiv}CD + D_2 \xrightarrow[40°]{Pd} (CD_3)_2C(OD)CD{=}CD_2 \quad (5)$$

$$(CD_3)_2C(OD)CD{=}CD_2 \xrightarrow[300°]{Al_2O_3} D_2O + D_2C{=}C(CD_3)CD{=}CD_2 \quad (6)$$

Each intermediate was confirmed in the protium series before being tried as a deuterio intermediate. In addition to D_2 and D_2O, the starting materials include potassium, calcium carbide, and acetone-h_6. In two of the steps diethylene glycol dimethyl ether (diglyme) and ethyl ether were used as the solvents. Catalysts needed were potassium carbonate, Lindlar palladium, and alumina. Of these materials, only acetone and the ethers contain protium, the protium of the latter not being exchangeable. Acetone-h_6 was converted to acetone-d_6 by a standard technique[5] with potassium carbonate as catalyst. Other intermediates were acetylene-d_2, 85% KOD, DC≡CK, 2-methyl-3-butyn-2-ol-d_8, and 2-methyl-3-butene-2-ol-d_{10}. A rather special intermediate of the synthesis was 2,5-dimethyl-3-hexyl-2,5-diol-d_{14} which was found to cleave smoothly at 150–160° in the presence of potassium carbonate to form acetone, acetylene, and 2-methyl-3-butyn-2-ol. A similar cleavage in the presence of sodium methylate was reported by Mauge.[6]

The work of Bergmann and associates[4] showed that, in 100% excess, 85% potassium hydroxide reacts with acetylene to form a mono potassium salt and that a diether of appropriate boiling point is almost essential. The excess potassium hydroxide acts as a water acceptor in aiding the neutralization. In the presence of the diether a reactive voluminous precipitate is secured. They reported that yields of over 90% of the ynol were feasible when an excess of potassium acetylide and also excess acetylene were contacted with acetone at about −12°. We believe their work to be authentic although our yields of deuterio as well as of protio acetylenic alcohols were only 65–73% ynol and 17.5% yndiol. Acetylene-h_2 and -d_2 were generated by adding H_2O or D_2O to calcium carbide covered with diglyme. Actually Bergmann and others reported a yield of 67% ynol and 27% yndiol when ethylene glycol ethyl butyl ether was used in place of their preferred diether which was an aldehyde acetal. We avoided the use of an acetal because of its instability and presumed tendency to undergo H to D interchange.

The most troublesome feature of the isoprene-d_8 synthesis was the preparation of 85 to 87% KOD. This was successful when D_2O and potassium were added alternately to diglyme and when the amount of D_2O was great enough so that the potassium droplets (m.p. 62°) did not coat over with solid KOD. Infrared spectra of recovered diglyme were superposable over the spectrum of the starting

(1) W. L. Semon and others, *Science*, **128**, 359 (1958).

(2) S. E. Horne and others, *Ind. Eng. Chem.*, **48**, 784 (1956); *Rubber Chem. and Technol.*, **29**, 687 (1956).

(3) A. E. Favorskiĭ, *Bull. acad. sci. U.R.S.S. Classe. sci. chim.*, 1940, 181; *Chem. Abstr.*, **37**, 3046 (1943).

(4) E. D. Bergmann, M. Sulzbacher, and D. F. Herman, *J. Appl. Chem.*, **3**, 39 (1953) and previous articles.

(5) J. R. McNesby, T. W. Davis, and A. S. Gordon, *J. Am. Chem. Soc.*, **76**, 823 (1954); F. E. Condon, *J. Am. Chem. Soc.*, **73**, 4675 (1951).

(6) R. Mauge, C. Malen, and J. R. Boissier, *Bull. soc. chim. France*, 1956, 425.

diether. This showed that H did not interchange with D during this or any subsequent stage of the synthesis.

The Lindlar[7] palladium catalyst was important though not essential for Reaction 5 of the synthesis. Quinoline was found not to be needed as a poison in addition to the usual lead acetate added during the catalyst preparation. Deuterium absorption in the absence of a solvent does not slow down appreciably during deuteriumation, but if the reaction is stopped when the ynol has disappeared it will be found that almost no reduction of the enol will have occurred. In contrast, in the presence of a solvent, reduction did slow down when the ynol was nearly used up. The complete removal of ynol by deuteriumation is obviously most essential. Its presence in the enol led during dehydration to acetone (reversal of the Favorskiĭ reaction) and to 2-methyl-1-butene-3-yn in the isoprene. These are specific poisons in the polymerization of isoprene.

The dehydration (Reaction 6) of 2-methyl-3-buten-2-ol (isoprene alcohol) at 300° over alumina was straightforward. Purification of isoprene-d_8 so produced was gaged by various techniques, including infrared and mass spectroscopy, diene analysis, vapor phase chromatography, and polymerization. Impurities detected include acetone, *n*-pentane and *n*-pentenes, 2-methylbutane, 2-methyl-1-butene, 2-methyl-2-butene, and 2-methyl-1-butene-3-yn. More or less obvious reactions account for the impurities including the straight chain hydrocarbons which no doubt result from the vinylation of acetone (Reaction 4). Fractionation through an efficient column was effective but for the removal of traces of acetone, acetylenes, peroxides, water, and alcohols, as well as of unknown impurities, it was necessary to treat with sodium in order to secure polymerization-grade isoprene. The h_8 and isoprene-d_8 hydrocarbons, as finally isolated, gave single-peak vapor-phase chromatograms. The positions of these peaks were not changed by "purification" through the sulfones.[8]

Physical properties of protio and deuterio compounds. Data are given in Tabels I and II for eleven isotopic pairs of compounds. The data for benzene and cyclohexane were taken from the literature. The other data, except for water, are for "best" samples (mostly heart cuts). The deuterio derivatives are more dense and less refractive than the corresponding protio compounds. All the data, especially the boiling points, are of interest in the study of molecular interaction in rubbers, liquids, and solids. Thus, for all six of the pairs of easily volatile organic compounds (Table I) the deuterio derivative has the lower boiling point. Even for water above 221°, the crossover temperature,[9] it is noted

TABLE I

PERPROTIO AND PERDEUTERIO COMPOUNDS AND AZEOTROPIC MIXTURES

Compound or Azeotrope	Perprotio Derivatives of Compounds and Mixtures					Perdeuterio Derivatives of Compounds and Mixtures				
	B.P., °C., 740 mm.	M.P., °C.	Wt. % Water	n_D^{20}	d_4^{20}	B.P., °C., 740 mm.	M.P., °C.	Wt. % Water	n_D^{20}	d_4^{20} Found	d_4^{20} Calcd.
2-Methyl-3-butyn-2-ol	104	3.2	...	1.4215	0.8609	102	1.9	...	1.4188	0.9423	0.9435
	103–104[a]	2.6[a]		1.4211[a]	0.8623[a]						
2-Methyl-3-butyn-2-ol water azeotrope	80.0	−10.5	27	1.4050	...	89.5	...	27	1.4034	...	...
	90.7[a]		28.4[a]								
2-Methyl-3-buten-2-ol	96.5	−28.0	...	1.4172	0.8231	96.0	−28.8	...	1.4134	0.9185	0.9194
	96–97.5[a]	−30.5[a]		1.4163[a]	0.8249[a,b]						
2-Methyl-3-buten-2-ol water azeotrope	85.3	−9.0	23.2	1.4078	...	86.0	...	20.0	1.4053	...	...
Acetone	55.3	...	...	1.3592	0.7895	54.3	...	...	1.3565	0.8719	0.8700
Cyclohexane	80.6[c], 80.738[c]	...	...	...	0.7787[a]	78.0,[c] 78.43[c]	...	...	...	0.8927[d]	0.8901
Benzene[e]	80.099	5.5	...	1.4998	0.8760	79.31	6.8	...	1.4978	0.9456	0.9435
Isoprene	33.3	...	...	1.4219	0.6802	31.8	...	...	1.4189	0.7604	0.7605
Water	99.2	0.0	100	1.333	0.99823	100.6	3.8	100	1.3286	1.1075	1.1100

[a] Value from data sheet of Air Reduction Chemical Co., New York 17, N. Y. [b] d_{20}^{20}. [c] Value from A. Langseth and B. Bak. *J. Chem. Phys.*, **8**, 406 (1956). [d] Value from Ref. 10; b.p. at 760 mm. [e] Values from Ref. 15; b.p. is for 760 mm., density is d_{25}^{25}, and *n* is n_D^{25}.

(7) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).
(8) D. Craig, *J. Am. Chem. Soc.*, **65**, 1010 (1943).
(9) G. O. Oliver and J. W. Grisard, *J. Am. Chem. Soc.*, **78**, 561 (1956).

TABLE II

PERPROTIO AND PERDEUTERIO DERIVATIVES

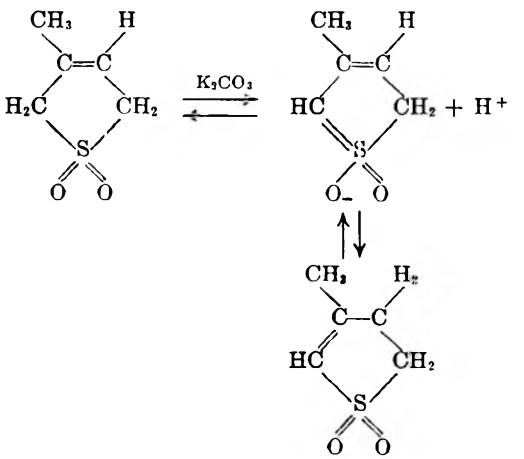
Compound	Perprotio Derivative M.P., °C.	n_D^{25}	d, g./ml. at 25°C.	Perdeuterio Derivative M.P., °C.	n_D^{25}	d, g./ml. at 25°C.
SN rubber[a]	...	1.5190	0.901	...	1.5147	1.005
Isoprene sulfone	63.5	...	...	65.5	...	...
2,5-Dimethyl-3-hexyn-2,5-diol	96.5	...	...	95	...	...
Isoprene–maleic anhydride adduct	63.2	...	...	62.2[b]	...	...

[a] The SN rubbers will be described in a later paper. [b] Two of the ten hydrogen atoms in this derivative are protium.

that D_2O has the higher vapor pressure. Hydrogen-bridge bonding probably makes a greater contribution below 221° than above. Deuterium seems to contribute more to hydrogen-bridge bonding and less to van der Waals forces than protium. The weaker interaction revealed for deuterio molecules suggests that deuterio rubber segments should be faster acting (show greater escaping tendency) than corresponding protio segments. This is to say that D-SN rubber should be faster acting than H-SN rubber. The dynamics and other properties of the two rubbers are under study and will be reported separately.

It is noted that isoprene-d_8 of formula weight 76.17 boils 1.5° lower than isoprene-h_8 of formula weight 68.12. The ratio of the formula weights is 1.118 and this multiplied by the density of isoprene-h_8 gives 0.7605 g./ml. as the calculated density of isoprene-d_8. This value, within experimental error of the found value, is given in Table I along with similarly calculated densities for D_2O, acetone-d_6, benzene-d_6, cyclohexane-d_{12}, methyl butynol-d_8, and methyl butenol-d_{10}. The method is seen to give slightly low values for the densities of acetone, cyclohexane, and benzene, and slightly high values for water and the two alcohols. For D-SN rubber a value, 1.007, in good agreement with the actual value of 1.005, Table II, was also found using this method. The molecular volumes of five of the deuterio compounds thus are shown to be nearly equal, and in the case of isoprene exactly equal, to those of the corresponding protio compounds. Recently, Dixon and Schiessler[10] reported the molar volumes of perdeuterio benzene and cyclohexane to be nearly equal to those of the corresponding perprotio derivatives.

The melting points of the two deuterio alcohols (Table I and II), the yndiol-d_{14} and the deuterio isoprene-MA adduct, are lower than those of the protio derivatives. This also appears to indicate weaker intermolecular action for the D compounds. Understandably, for water in which hydrogen bonds are strong, D_2O melts 3.8° above H_2O. This rather consistent behavior is disturbed by the melting point of C_6D_6 being 1.3° higher than the melting point of C_6H_6 and by the melting points of perdeuterio isoprene sulfone (65.6°) and perprotio isoprene sulfone (63.5°). The reason for the higher melting points for the D members of the two pairs of compounds is obscure. However, the hydrogen atoms in the 2- and 5-positions of the sulfone ring no doubt contribute significantly to the rather unique physical and chemical properties[11] of the diene sulfones. The rise in melting point here resulting from replacement of H with D suggests that the bonds connecting hydrogen atoms to the 2- and 5-positions are in reality hydrogen-bridge bonds between carbon and oxygen in different molecules. Jeffrey[12] recalculated the previously reported x-ray diffraction data[11] and found them to show all of the bonds in the five-membered ring to be of abnormal length. The O—S and C—CH_3 bonds, however, appeared to be of normal length. Koch[13] summarized the properties of the sulfone and concluded that extensive conjugation accounted for both the abnormal bond lengths and the α-methylenic nature of the molecule. We have found that isoprene-d_8 sulfone does not react with H_2O at 50 to 60° but that it rearranges at this temperature in the presence of 1% potassium carbonate to the α-sulfone, m.p. 79–80°, with simultaneous replacement of four of the D atoms with H, the replacement being established by the mass spectrum of the recovered α-sulfone.[14] Thus the "loosening" of the 2- and 5-position hydrogen atoms appears to be confirmed. The rearrangement probably occurs as follows:



(10) J. A. Dixon and R. W. Schiessler, *J. Am. Chem. Soc.*, **76**, 2197 (1954); R. T. Davis, Jr., and R. W. Schiessler, *J. Phys. Chem.*, **57**, 966 (1953).

(11) E. G. Cox and G. A. Jeffrey, *Trans. Faraday Soc.*, **38**, 241 (1943); *Rubber Chem. and Technol.*, 16, 486 (1943).

Finally, with respect to the effect on melting and boiling points of replacing H with D, it is noted that Ingold, Raisin, and Wilson[15] who found benzene-d_6 to melt higher (m.p. 6.8°) but to boil lower (b.p. 79.3°) than benzene-h_6 (m.p. 5.5° and b.p. 80.1°) also found H to D interchange in benzene to be catalyzed by acids.

EXPERIMENTAL

Source and purity of reagents. Deuterium oxide, 99.5% D_2O, and 99.5% deuterium gas were purchased from the Stuart Oxygen Co., San Francisco, Calif. Acetone was a commercial grade with properties given in Table I. Diethylene glycol dimethyl ether, or diglyme, was purchased from the Ansul Chemical Co. under the label Ansul Ether 141. Potassium metal, Code 2080, came from the General Chemical Co., and calcium carbide from Fisher Scientific Co. Alumina was catalyst grade, Harshaw Scientific Co., Al-0104T 1/8 inch.

Potassium deuteroxide, 87%. A 300 g. quantity of diglyme was added to a 2-liter, 3-necked Pyrex flask. One neck was fitted with a glass paddle stirrer driven by a compressed air motor. The other necks accommodated a thermometer, nitrogen inlet, dropping funnel, and water-cooled reflux condenser. A gas vent led from the top of the condenser through a Dry Ice trap to the hood. Evolved D_2 was not recovered. Diglyme is miscible with D_2O or H_2O, is readily salted out by potassium hydroxide or carbonate, but not by sodium chloride. A solution of 300 g. (15 moles) of D_2O in 150 g. of diglyme was dropped in and pieces of potassium (m.p. 62°) added from time to time so that the temperature remained at 60–70°. As the reaction proceeded it became necessary to heat the flask with a mantle. At first the potassium reacted vigorously to form a turbid mixture, but soon a white solid precipitate appeared and the liquid became blue. The blue color, not fully understood, disappeared when the rate of water-diglyme addition was increased in relation to the rate of potassium addition. A total of 248 g. (6.36 g.-atoms) of potassium was added during approximately 9 hr. after which a 120-g. quantity (6 moles) of D_2O was added during 2 hr. In this way a solid-free, two-liquid phase mixture at 60° was secured. It weighed 1100 g. and was transferred to a five-liter stainless steel flask, capped with a three-necked Pyrex head. The three necks accommodated a stainless steel thermometer well, stainless steel loop stirrer, nitrogen inlet, and connection to a condenser. The flask was heated with a glass mantle and the diglyme-water mixture distilled until the pot temperature reached 280–290°. The remaining product weighed 410 g. and by titration with standard acid was found to be 87.4% KOD. Assuming complete recovery from 6.36 g.-atoms of potassium, the 410 g. of product should contain 88.5% KOD.

Potassium deuterio acetylide, 2-methyl-3-butyn-2-ol-d_8, and 2,5-dihydroxy-2,5-dimethyl-3-hexyne-d_{14}. A 900-g. portion of diglyme was added to the 87.4% KOD which had crystallized on cooling. As soon as possible the temperature was raised to 150° after which it was allowed to fall while stirring vigorously. Crystallization occurred at 100–105° to form a slurry. The temperature was allowed to fall to 65–70° and finally brought to −5° by use of an ice salt bath. Acetylene-d_2, prepared by adding 176 g. of D_2O to a mixture of 675 g. diglyme and 433 g. (6.8 moles) of 20–30 mesh calcium carbide at 42–47° was then passed in for 4 hr. During this time the nitrogen stream was stopped. The rate of acetylene was easily controlled by rate of D_2O addition. The potassium acetylide was a fluffy solid.

Acetone-d_8, 204 g. (3.19 moles), was next added during 2.7 hr. while continuing the stream of acetylene. The acetylene absorbed amounted to a minimum of 90 g. (3.2 moles) as determined by increase in weight. Actually the weights of acetone and diglyme swept from the mixture are unknown but they are believed to be small. The reaction mixture was stored at −14° for 14 hr. during which time it thickened. The mixture was returned to a salt ice bath and the nitrogen stream turned on. A 733 g. (36.7 moles) quantity of D_2O was dropped in during 2.7 hr. while maintaining the temperature at −4 to −6°. After stirring 1.3 hr., the oil layer was separated and treated with carbon dioxide to neutralize any KOD present. The lower KOD layer was extracted with three 150-ml. portions of ethyl ether to recover dissolved product. The extracts were also treated with carbon dioxide. The dilute KOD was concentrated and the D_2O and KOD used in subsequent runs.

The D_2O-diglyme-ynol-yndiol mixture was fractionated through a one-inch glass helices filled column 24 inches high. This column was fitted with a small-holdup, water-cooled, total-reflux, variable-takeoff stillhead. The butynol-d_8-D_2O azeotrope (see Table I) fraction came over at 86–99°, and anhydrous diglyme at about 161°. A residue of yndiol remained. The ynol-D_2O azeotrope was dehydrated by alternate distillation through a 0.25-inch coil column 24 inches high and salting out of the ynol with NaCl previously dried in an oven at 120°. Fractions of 181 g., collected at 101.8–102.2° at 730 mm., m.p. + 1.9°, and 34 g. at 101.2–102.4°, m.p. 1.7°, were secured, the latter from foreruns and the ether extract of the KOD layer. The total yield, 215 g., was 73%. The residue was distilled to give 43.5 g. (17.5%) of nearly pure yndiol, m.p. 89° or at 94.5–95.0° after recrystallization from benzene. The perprotio yndiol melted at 95.5–96.6° (Lit.[4] 94.5°) or at 95–96° mixed with the perdeuterio derivative.

Cleavage of 2,5-dimethyl-3-hexyn-2,5-diol-d_{14} and 2-methyl-3-butyn-3-ol-d_8. A 125-ml. flask fitted with a mantle heater and a short, punched-in side-arm was charged with 40.0 g. yndiol-d_{14} 6.0 g. acetone-d_6, and 0.003 g. potassium carbonate. It was connected to a Dry Ice-cooled receiver. The liquid mixture was heated to 150°–160° for 1 hr. during which time distillate (44.2 g.) came over at 55°–93° leaving a distilland (1.3 g.) of nearly pure yndiol. A total of 245 g. (1.57 moles, 3.14 acetone equivalents) of yndiol was decomposed in this way in six runs. The distillates were united and fractionated through the 0.25 × 24 inch coil column to give 121 g. (1.89 moles) of acetone-d_6 and 101.4 g. (1.10 moles, 70%) of pure 2-methyl-3-butyn-3-ol-d_8, m.p. 1.9°, $n_D^{20°}$ 1.4188. Material lost during the decompositions and fractionation amounted to 23 g. (9.5%) consisted mostly of acetylene and acetone.

A mixture of 2.5 g. acetone-h_6, 25.0 g. 2-methyl-3-butyn-2-ol-h_8, and 0.10 g. potassium carbonate was distilled during 7 hr. through the 0.25 × 24 inch coil column. A gas, presumably acetylene and acetone, was lost through the water-cooled (10°) reflux condenser, the loss amounting to 8.7 g. Nearly pure acetone (15.9 g.), $n_D^{20°}$ 1.3598 (lit. 1.3592) was collected at 55–57°, while the liquid temperature remained at 103°. The final distilland, mostly ynol, weighed 3.0 g.

2-Methyl-3-buten-2-ol-d_{10} (isoprene alcohol-d_{10}). The Lindlar catalyst was prepared exactly as described by him. All reductions with H_2 and later with D_2 were conducted with catalyst from a single preparation. In the first few experiments quinoline was added to the ethinyl carbinol in accordance with Lindlar's procedure. This was discontinued when it was found that the presence of quinoline did not cause the hydrogenation either to slow down or to stop at the desired stage and that the amount of overhydrogenation was about the same with or without quinoline present provided the reaction was stopped at the theoretical hydrogen uptake.

A Parr Instrument Company hydrogenation apparatus model CA, consisting of gas reservoir, pressure gage, shaker,

(12) G. A. Jeffrey, *Acta Cryst.*, 4, 58 (1951).

(13) H. P. Koch, *J. Chem. Soc.*, 1949, 412.

(14) A study of this rearrangement will be reported separately.

(15) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 915 (1936).

TABLE III

PERDEUTERIOISOPRENE FRACTIONATION AND CHROMATOGRAPHIC ANALYSIS

Fraction	B.P., °C.	Pressure, Mm. Hg	Amount, G.	$n_D^{20°}$	Gas Chromatographic Analysis		
					Isoprene	2-Me-2-butene	2-Me-1-butene
1	31.5–31.8	731	23.2	1.4151	...	...	...
2[a]	31.8–31.9	731	51.0	1.4165	97.1	0.5	2.4
3	32.2–32.3	740	64.5	1.4184	98.9	0.6	0.5
4[a]	32.0–32.1	731	55.0	1.4186	98.5	1.3	0.2

[a] The mass spectra for fractions 2 and 4 revealed the presence of about 20 mole % C_5D_7H and 80 mole % C_5D_8, corresponding to one H per 39 D or to 97.5% deuteration.

and 0.5 l. stainless steel pressure flask was used for the hydrogenations. A second gas reservoir for the deuteriumations was constructed from a small breathing oxygen cylinder. The gas volumes of the systems were measured with a wet gas flow meter and were also determined by reduction of pure cinnamic acid. The hydrogen (and deuterium) consumption was calculated from the pressure drop and the gas volume. To avoid deuterium-hydrogen exchange in the deuteriumation runs the reactions were run solvent-free. The heat of reaction was controlled by blowing an air jet onto the reaction flask. The reductions were carried out with gas pressures between 40 and 2 p.s.i. For all runs this necessitated repressurizing with H_2 or D_2 while the run was in progress. Some runs were repressurized as many as twelve times. Thus a considerable error in gas measurement occurred. Most runs were, therefore, stopped short of the theoretical H_2 or D_2 uptake and were run to completion after determination of the α-acetylene content. A typical deuteriumation run will be described.

184.2 g. (2.0 moles) of 3-methyl-1-butyne-3-ol-d_8 and 2.0 g. Lindlar catalyst were charged to the reaction flask. The flask was closed with a calcium chloride tube and chilled in Dry Ice. It was then fastened to the shaker, rapidly evacuated to about 0.2 mm., and the vacuum broken with deuterium. The flask was allowed to warm to room temperature before pressurizing with deuterium to about 40 lb. After starting the shaker, the temperature rose rapidly but was kept below 50°C. by a strong air jet directed at the flask. The pressure was allowed to drop to 2 lb., the shaker stopped, and the system repressurized to 40 lb. This was repeated until the sum of pressure drops was 314.5 lb. (theory 316 lb.). The elapsed reaction time was 242 min. The rates of deuterium uptake for two similar pressures at the beginning and toward the end of the reaction were identical: After about 10% deuteriumation the rate was 0.85 lb. per minute for a pressure drop from 5.5 lb. to 2.0 lb. and after about 90% deuteriumation the rate was 0.83 lb. per minute for a pressure drop from 6.0 to 1.0 lb.

The flask was allowed to cool to room temperature and the reaction mixture filtered through a bed of activated charcoal on a sintered glass filter. Product recovered: 189.1 g. or 98.5% of theory. The reaction flask, the filter, and the receiver were rinsed with pentane and the rinses combined with those from other runs to be worked up separately. The filtrate contained 5.46% α-acetylene calculated as C_5D_8O. It was combined with a previous run of similar α-acetylene content for deuteriumation to completion. As a rule the isoprene alcohol was not purified prior to dehydration. A sample was distilled through the 0.25 × 24 in. coil column (see Table I).

Isoprene-d_8. A stainless steel tube 36 in. long with an ID of $^5/_8$ in., fitted with a thermocouple well extending through the length of the tube, was filled with 133 g. alumina, $^1/_8$ in. tablets. Two furnaces of 750 watts each were used to heat the tube over its entire length. Additional heaters were provided at the upper end and at the joining point of the two furnaces, by wrapping with Nichrome resistance wire. The tube was inclined about 25° to the horizontal. The inlet end was fitted with a glass adapter accommodating a dropping funnel, gas inlet, and the thermocouple well. The lower exit end was connected to a glass elbow ending in a 24/40 ⅀ joint. Sauereisen cement, glazed with water glass, was used to join the glass parts to the tube. The alumina was heated *in situ* to 300° for 12 hr. in a nitrogen stream saturated hot with steam from 10 ml. D_2O and then dried at 300° for 36 hr. in a nitrogen stream. The temperature was maintained at 300° ± 10°. With the exit end connected to a 0.5 l. two-necked flask carrying a Dry Ice–acetone cold finger type condenser which in turn was connected to a Dry Ice–acetone trap. The stream of dry nitrogen was adjusted to a rate of about five bubbles per second. When the catalyst packing had reached equilibrium the addition of 321.0 g. (3.34 moles) isoprene alcohol-d_{10} was started from a dropping funnel and adjusted to a rate of about 2.0 g. per min. The material collected in the receiver flask separated into a D_2O layer (54.5 g., 2.72 moles) and an organic layer of 245.3 g. (The material loss of 21.2 g. was due to a leak at a glass-to-steel connection which was corrected later.) The organic layer was dried with sodium sulfate and fractionated through a vacuum-jacketed column $^5/_{16}$ × 36 in. filled with stainless steel No. 2917 HeliPak packing (Podbielniak, Inc., Chicago, Ill.). Methanol at −30 to −20° was circulated through the condenser. The reflux ratios varied from 80 to 100:1. A forerun was collected at 26–31.3° at 740 mm. The main fraction (164.7 g.) distilled at 31.3–32.0° at about 740 mm. The residue (50 g.) was recycled through the dehydration tube. The combined main fractions (226 g.) from two runs of this type were rectified through a 1 × 24 in., 20-plate, improved Oldershaw bubble plate column[16] at a reflux ratio of about 70:1. A series of four fractions totaling 194 g. was obtained and analyzed with results given in Table III. Polymerization-grade isoprene was secured by addition of sodium dispersed in petrolatum, refluxing for 30 min., and flash distilling.

Yields. A total of 1367 g. of dimethylethinylcarbinol-d_8 was catalytically deuteriumated in nine runs, yielding 1398 g. of crude isoprene alcohol-d_{10} or 98.0% of the theoretical yield.

From 1237 g. of isoprene alcohol-d_{10}, dehydrated in five runs (of which two runs were recycles), 924 g. of crude dehydration product was recovered. Purification of this gave 509 g. isoprene-d_8 of a chemical purity of at least 96% and 281 g. of product containing a minimum of 87% isoprene-d_8. Based on the minimum concentrations the yield of pure isoprene-d_8 was at least 75% of theory for the dehydration step and the over-all yield for deuteriumation and dehydration thus was at least 74%.

BRECKSVILLE, OHIO

(16) F. C. Collins and Vernon Lantz, *Ind. Eng. Chem. Anal. Ed.*, **18**, 673 (1946).

Notes

A department for short papers of immediate interest.

A Simplified Procedure for Synthesis of Oleic-1-C^{14} Acid[1]

SUSANNE VON SCHUCHING AND ERNEST STUTZMAN

Received February 14, 1958

It became of interest to prepare oleic-1-C^{14} acid in the course of metabolic studies. Bergström *et al.*[2] have published a short report describing the introduction of a C^{14}-atom in the carboxyl position by means of the nitrile synthesis. During attempts to follow their procedure, certain steps were found difficult to carry out on a small scale and were modified as described in this note. For example, the silver salt degradation method[3] for the preparation of 1-bromo-8,9-diacetoxyheptadecane was improved through exposure of the reactants to ultraviolet light; in addition, the temperature was kept low during the degradation step and the product was purified over a column of Celite mixed with silicic acid. Furthermore, a purer product was obtained when the addition of cyanide was carried out in a sealed tube. The preparation of ethyl 9,10-dibromostearate-1-C^{14} and the debromination[4] of this compound were modified to give a better recovery of radioactive material. It was found also that when the intermediates are prepared in pure form as described later, the ethyl 9,10-dibromostearate-1-C^{14} does not require micro distillation; its purification over a column of aluminum oxide is sufficient. The synthetic steps up to the nitrile addition were carried out on a semimicro scale. The yield of radioactivity at this point was calculated to be in excess of experimental requirements, and enough inactive dihydroxystearic acid was added to give a total of 5 g.

EXPERIMENTAL

Merck U.S.P. oleic acid was used as the starting material. Melting points were determined on a Fisher-Johns melting point apparatus and are reported as uncorrected. Double bonds were determined by the Wijs method. Bromine determinations were made by the procedure of Stepanow.[5]

The 9,10-dihydroxystearic acid (I) was prepared according to the method of Coleman *et al.*,[6] modified through the use of 2.5 times the recommended amount of potassium hydroxide. The yield of dihydroxystearic acid was 50%.

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.3; H, 11.4. Found: C, 68.0; H, 11.3.

Neutralization equivalent, calculated 324, and found, 315; m.p. 127.5°.

9,10-Diacetoxyoctadecanoic acid (II). Dihydroxystearic acid, 13.5 g., was acetylated with 15 ml. of acetic anhydride in 30 ml. of purified pyridine. The yield of II, obtained as a light colored oil, was 16.1 g. (94%).

Silver salt of 9,10-diacetoxyoctadecanoic acid (III). Of II, 16.1 g. were taken up in 150 ml. of ethanol and neutralized to a phenolphthalein end point with sodium hydroxide. With vigorous stirring, 6 g. of silver nitrate in 90 ml. of 60% ethanol were added, light being carefully excluded. The heavy precipitate was collected, washed with water and acetone, and thoroughly dried. The white sticky product was obtained in 80% yield.

1-Bromo-8,9-diacetoxyheptadecane (IV). Degradation of 16.4 g. of silver salt (III) was carried out after suspending the material in 300 ml. of dry carbon tetrachloride and 16 ml. of methylene chloride. With magnetic stirring, 150 ml. of the solvent mixture were distilled off. After the residual material was cooled, 3 g. of dry silver acetate was added followed by 3.6 ml. of dry bromine dissolved in 9 ml. of carbon tetrachloride. An ultraviolet light[7] was placed close to the flask and the mixture was heated gradually under reflux. Carbon dioxide started to evolve at 40° and the reaction was brought to completion by raising the temperature and heating at 80° for 1 hr. Silver bromide was removed from the cooled mixture and the filtrate was washed with 2*N* potassium iodide, 2*N* sodium thiosulfate, and finally water and then was dried. This washing procedure averted troublesome emulsions. For further purification, the product was passed over a column of a mixture of 125 g. of silicic acid and 125 g. of Celite. The mixture of Celite and silicic acid had been prepared by being washed with acetone, ether, and carbon tetrachloride. Since the filtration is very slow, two chromatographic tubes, 40 × 600 mm., were employed. Adsorption was carried out in carbon tetrachloride solution and followed by elution with petroleum ether. The petroleum ether was dried down and yielded 8.9 g. (64%) of a light yellow oil. It was hydrolyzed without further purification to V.

1-Bromo-8,9-dihydroxyheptadecane (V). In a solution of 300 mg. of dry hydrogen chloride in 45 ml. of dry methanol, 8.9 g. of IV was refluxed for 3 hr. Water was added and V was dissolved in ether. The solution was washed with water, dried over sodium sulfate, and gave, after evaporation, 6.9 g. of V. On recrystallization from hexane, there resulted 3.5 g. (48%) of V; m.p. 101–102°.

Anal. Calcd. for $C_{17}H_{35}O_2Br$: C, 58.4; H, 10.0; Br, 22.3. Found: C, 58.7; H, 10.1; Br, 22.3.

9,10-Dihydroxystearic-1-C^{14} acid (VI) was prepared under conditions to give a pure product and a high recovery of radioactivity. Potassium cyanide (3 mmoles) containing 4 mc. of carbon^{14} were dissolved in 1 ml. of water and 10 ml. of ethanol in a 100 ml. Kjeldahl flask. A small excess, 1.1 g., of V was added to the flask. The flask was sealed and heated at 100° for 48 hr. The resulting nitrile was transferred to an

(1) Supported in part by grants from the United States Public Health Service (H-1897) and The American Heart Association to C. R. Treadwell and L. Swell.

(2) S. Bergström, K. Pääbo, and M. Rottenberg, *Acta Chem. Scand.*, 6, 1127 (1952).

(3) H. Hunsdiecker and C. Hunsdiecker, *Ber.*, 75, 291 (1942).

(4) D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 1079 (1951).

(5) A. Stepanow, *Ber.*, 39, 4056 (1906).

(6) J. E. Coleman, C. Ricciuti, and D. Swern, *J. Am. Chem. Soc.*, 78, 5342 (1956).

(7) 6 Amp. "Mineralight," Ultra-Violet Products, Inc.

alkali-resistant flask[8] and 2 g. of potassium hydroxide dissolved in 3 ml. of ethanol was added. Hydrolysis of the nitrile was carried out by refluxing for 48 hr. The mixture was acidified with 2*N* hydrochloric acid and washed with water. After being dried, VI was recrystallized from methanol. The yield was 730 mg. (82%), m.p. 127°. In order to increase the recovery of dihydroxystearic acid, the mother liquors were reextracted with 3 g. of unlabeled dihydroxystearic acid. The total recovery of radioactivity was 3.552 mc. (88.8%).

Ethyl 9,10-dibromostearate-1-C^{14} (VII). Enough inactive dihydroxystearic acid was added to VI to make a total of 5 g. Conversion to the dibromo-compound was carried out according to Ames and Bowman[4] with the use of hydrogen bromide–acetic acid and sulfuric acid. The yield of the crude dibromide ester was 6.5 g. (88.6%). The product was esterified by refluxing in a device diagrammed in Fig. 1 with 4

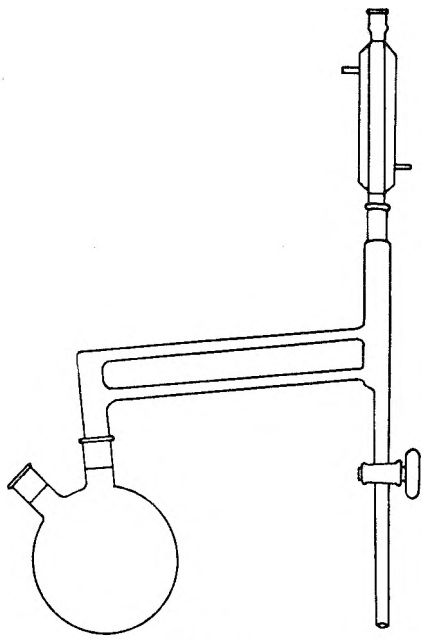


Figure 1

ml. of absolute alcohol, 10 ml. of benzene, and 0.17 ml. of concentrated sulfuric acid, water being removed azeotropically. The ester VII was run over a short column of activated alumina which retained most of the impurities. A sample had a b.p. of 235° at 1 mm.; bromine content calculated for $C_{20}H_{38}O_2Br_2$: Br, 34%. Found: 34.5%. The ester was a pale yellow oil. The yield was 5.1 g. (85%). It was used for the preparation of oleic-1-C^{14} acid without further purification.

Oleic-1-C^{14} *acid* (VIII). Of zinc, 3 g. were activated by being boiled 5 min. with 15 ml. of ethanol and 1 ml. of 60% aqueous hydrobromic acid. The ethyl ester of VII was added to the zinc and the mixture refluxed under nitrogen for 2 hr. The zinc was removed by filtration and extracted with 1 g. of carrier ethyl oleate in petroleum ether for a more complete recovery of radioactive material. The combined filtrates were washed with 5% sulfuric acid and water and the solution was dried. Product VIII can be saponified directly without distillation. Saponification of the ethyl oleate was carried out with sodium ethoxide in absolute alcohol, followed by acidification with 2*N* hydrochloric acid. The yield of oleic-1-C^{14} acid was 3.7 g., m.p. 12°; iodine number calculated, 89.9. Found: 91.6. Radioactivity was determined by counting an infinitely thick sample after diluting with cold oleic acid in a gas-flow chamber.[9] The total activity was 2.4 mc. (60%) based on C^{14}-cyanide. The specific activity of the final product was 0.65 μc. per mg.

(8) Corning "Boron Free."

(9) RCL Nucleometer, Scaler Type, Mark 9, Model 4.

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Derivatives of Piperazine. XXXI. Salts of Piperazine and *N*-Phenylpiperazine for Utilization in Identification of Perfluoro-Organic Acids

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In research work involving the syntheses of fluorine organic compounds, the rapid identification of perfluoro-organic acids presented a problem as suitable derivatives have not been reported. Pollard *et al.*[1–5] have found the piperazine and *N*-phenylpiperazine salts of organic acids to be easily prepared and useful for identification. Haszeldine[6] reported the preparation of the piperazinium salt of perfluorobutyric acid.

It has been found that piperazine and *N*-phenylpiperazine react readily with perfluoro acids to form stable crystalline salts which can be readily purified. The monocarboxylic acids form piperazinium salts having a molecular ratio of 2 acid to 1 base. The dicarboxylic acid combines in a 1 to 1 molecular ratio. It is to be noted that the piperazinium salts of the 3, 4, 6, and 8 carbon acids melt within about 2° of each other. Mixed melting points of various combinations of these salts (approximately 50–50) show depressions of about 6°. The *N*-phenylpiperazinium salts of the 3 carbon acid and Kel F 8114 melt within 3° of each other. A mixture of these two salts (approximately 50–50) shows a depression of about 30°. The *N*-phenylpiperazinium salts of the 4, 6, and 8 carbon acids melt close together. Mixtures of various combinations of these salts (approximately 50–50) show depressions of from 15 to 20°. The mixed melting points were determined in sealed tubes.

(1) C. B. Pollard and D. E. Adelson, *J. Am. Chem. Soc.*, **56**, 150 (1934).

(2) C. B. Pollard, D. E. Adelson, and J. P. Bain, *J. Am. Chem. Soc.*, **56**, 1759 (1934).

(3) C. B. Pollard and D. E. Adelson, *J. Am. Chem. Soc.*, **58**, 532 (1936).

(4) M. Prigot and C. B. Pollard, *J. Am. Chem. Soc.*, **70**, 2758 (1948).

(5) C. B. Pollard and N. S. Gidwani, *J. Org. Chem.*, **22**, 992 (1957).

(6) R. N. Haszeldine, *J. Chem. Soc.*, 2789 (1950).

TABLE I

PIPERAZINIUM SALTS OF PERHALO-ORGANIC ACIDS

Fluoro Acid	Formula	M.P. °C.	Data Concerning Piperazinium Salts							
			Calcd.				Found			
			C	H	F	Cl	C	H	F	Cl
Perfluoroacetic	CF_3COOH	229–231	30.6	3.85	36.3	...	30.08	3.79	36.64	...
Perfluoropropionic	CF_3CF_2COOH	241–242.5	29.0	2.92	45.9	...	29.54	3.11	45.58	...
Perfluorobutyric	$CF_3(CF_2)_2COOH$	240.8–241.8	28.0	2.35	51.8	...	28.25	2.52	51.64	...
Perfluorohexanoic	$CF_3(CF_2)_4COOH$	240.5–241.5	26.9	1.69	58.6	...	26.63	1.76	58.41	...
Perfluorooctanoic	$CF_3(CF_2)_6COOH$	240–241	26.3	1.54	62.36	...	26.48	1.41	62.19	...
Kel F 683	$Cl(CF_2\text{-}CFCl)_2CF_2COOH$	Above 250	23.64	1.49	...	26.16	23.85	1.65	...	26.42
Kel F 8114	$Cl(CF_2\text{-}CFCl)_3CF_2COOH$	Above 250	22.96	1.16	...	27.11	22.81	1.49	...	27.05
Perfluoroglutaric	$HOOC(CF_2)_3COOH$	269–270	33.15	3.71	34.96	...	33.24	3.62	34.68	...
Perfluoromethoxy-acetic[a]	CF_3OCF_2COOH	191–191.5	26.9	2.76	42.6	...	27.11	2.70	42.83	...

[a] The preparation and structure determination of this acid will be the subject of a forthcoming publication.

TABLE II

N-PHENYLPIPERAZINIUM SALTS OF PERHALO-ORGANIC ACIDS

Fluoro acid	Formula	M.P. °C.	Data Concerning N-Phenylpiperazinium Salts							
			Calcd.				Found			
			C	H	F	Cl	C	H	F	Cl
Perfluoroacetic	CF_3COOH	151–154	52.2	5.48	20.6	...	52.32	5.48	20.82	...
Perfluoropropionic	CF_3CF_2COOH	144–144.5	47.8	4.64	29.1	...	47.72	4.52	29.38	...
Perfluorobutyric	$CF_3(CF_2)_2COOH$	124–126	44.7	4.02	35.4	...	44.33	4.00	35.61	...
Perfluorohexanoic	$CF_3(CF_2)_4COOH$	122–124	40.3	3.18	44.0	...	40.05	3.40	43.75	...
Perfluorooctanoic	$CF_3(CF_2)_6COOH$	125.5–128	37.5	2.62	49.5	...	37.63	2.62	50.10	...
Kel F 683	$Cl(CF_2\text{-}CFCl)_2CF_2COOH$	133–134	36.6	2.88	...	20.2	36.76	3.00	...	20.1
Kel F 8114	$Cl(CF_2\text{-}CFCl)_3CF_2COOH$	141–142	33.7	2.36	...	22.1	33.55	2.71	...	21.88

The melting points and mixed melting points of the piperazinium and *N*-phenylpiperazinium salts, in conjunction with the physical constants of the acids, have been useful in these laboratories for the identification of perfluoro organic acids.

Various attempts to obtain specimens of the 5 and 7 perfluoro acids proved futile.

Data concerning the piperazinium and N-phenylpiperazinium salts of perfluoro acids prepared are shown in Tables I and II.

EXPERIMENTAL

Piperazinium salts. About 1 ml. of the acid and 10 ml. of propanol-2 were placed in a small beaker packed in ice. Anhydrous piperazine was slowly added with stirring until the mixture was basic to litmus paper. Another 10 ml. portion of propanol-2 was added with stirring and the slurry was filtered while cold. Ten milliliters of boiling 95% ethanol were added to the crude product; water was added dropwise to the boiling mixture until the solid dissolved. The solution was cooled in an ice bath until crystallization was complete. Three recrystallizations gave a constant melting product.

The piperazinium salts of Kel F 683, Kel F 8114 and perfluoroglutaric acids were recrystallized from boiling water.

The piperazinium salt of perfluorooctanoic acid was crystallized from boiling 1-butanol.

N-Phenylpiperazinium salts. About 4 ml. of the acid and 20 ml. of propanol-2 were placed in a small beaker packed in ice. *N*-Phenylpiperazine was slowly added with stirring until the mixture was basic to litmus paper. The mixture was heated until the solid dissolved. The crystals which formed on cooling were recrystallized three times to give a constant melting product.

The *N*-phenylpiperazinium salts of Kel F 683 and Kel F 8114 acids were recrystallized from hot absolute ethanol.

The melting points were determined in sealed tubes by means of a brass block preheated to within 5 degrees of the respective melting point.

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Instability of Certain Organophosphorus Compounds Containing Pentavalent Phosphorus[1]

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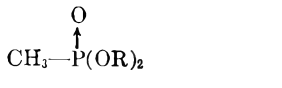
In connection with the preparation of a variety of potentially toxic organophosphorus compounds,

(1) This work was done on a subcontract with the University of Chicago in fulfillment of a contract with the Chemical Corps.

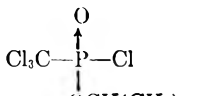
(2) Member of the Armed Forces assigned to the Army Chemical Corps.

several unstable structures have been encountered. The present report is concerned with the preparation and properties of certain of these compounds.

Of three derivatives (I–III) of methylphosphonic acid whose preparation has been attempted, only the bistetrahydrofurfuryl methylphosphonate, I, was sufficiently stable to permit isolation in a pure condition, and this compound suffered some polymerization during distillation. The analogous furfuryl ester (II) decomposed violently when



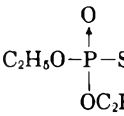
I. R = tetrahydrofurfuryl
[II. R = furfuryl]



III

distillation was attempted at 100°. In view of the activity of sarin (isopropyl methylphosphonofluoridate) as an anticholinesterase, the analogous isopropyl trichloromethylphosphonochloridate, III, was prepared, but it proved to be too unstable to permit satisfactory purification. Replacement of the chlorine on phosphorus by fluorine, using sodium fluoride in benzene,[3] was unsuccessful. In view of the fact that boiling water hydrolyzes only one chlorine[4] in trichloromethylphosphonic dichloride, it is of interest that hydrolysis of the ester acid chloride, III, yields the trichloromethylphosphonic acid.

Attempts to prepare two S-substituted derivatives (IV, V) of diethyl phosphorothioate, by reaction of the appropriate halide with diethyl

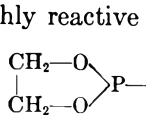


IV. R = CH_2—CN

V. R = CH_2—CH_2—N

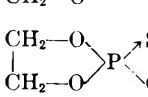
potassium phosphorothioate, yielded highly unstable materials. Although a compound distillable with decomposition was obtained in the attempted preparation of IV, its analysis was in poor agreement with that calculated, and it altered rapidly on standing at room temperature.

A simple derivative, VI, and a polyfunctional derivative, VII, of ethylene phosphite were prepared from ethylene phosphorochloridite. Although these compounds are stable to distillation and to storage in absence of moisture and air, they are highly reactive compounds as has been previously reported.[5] Ethyl ethylene phosphite (VI) reacts relatively slowly with dry air, and the product is a polymer, not ethyl ethylene phosphate. In contrast, reaction of VI with sulfur yields the ethyl ethylene phosphorothioate, VIII. The latter compound, obtained in poor yield by distillation, decomposes slowly at room temperature, rapidly at 160°. The trimethylene compound analogous to VII was also prepared, and was found to be less reactive toward water than is VII. Reaction of either VII or the trimethylene analog with sulfur yields unstable products which rapidly polymerize.



VI. R = C_2H_5

VII. R = CH_2—CH_2—$N(C_2H_5)_2$



VIII

It was noted that the phosphorus esters containing the five- or six-membered rings may be recognized by characteristic bands in the infrared, regardless of whether the phosphorus is tri- or pentavalent. For compounds containing the five-atom ring, $\overline{OCH_2CH_2OP}$, there occurs a very sharp, intense band at 10.82–10.84μ, while compounds containing the similar six-atom ring display absorption at 10.69–10.71μ. Such bands have been observed in no other phosphorus compounds.

EXPERIMENTAL[6]

Bistetrahydrofurfuryl methylphosphonate (I). A mixture of 18 g. (0.18 mole) of tetrahydrofurfuryl alcohol and 18 g. (0.18 mole) of triethylamine was added dropwise with stirring to a solution of 11 g. (0.083 mole) of methylphosphonic dichloride in 100 ml. of dry benzene. The reaction was exothermic, and the temperature was allowed to rise to reflux. The mixture was stirred for 30 min. after completion of addition, the amine salt was removed by filtration, and the filtrate was concentrated at reduced pressure. Distillation of the residue yielded 17.8 g. (45%) of the di-ester, b.p. 138°/0.5 mm., n_D^{25} 1.4700–1.4703. A sample redistilled for analysis left a residue of about one third its weight and had b.p. 150°/0.8 mm., n_D^{25} 1.4699.

Anal. Calcd. for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01; P, 11.72. Found: C, 50.02; H, 8.15; P, 11.59.

Isopropyl trichloromethylphosphonochloridate (III). To a solution of 2.0 g. (8.5 mmole) of sublimed trichloromethylphosphonic dichloride[7] in 20 ml. of anhydrous ether, stirred at 0°, there was added in one portion 0.85 g. (8.5 mmole) of triethylamine. To the slightly cloudy solution there was next added during about 15 min. a solution of 0.51 g. of dry isopropyl alcohol in 20 ml. of anhydrous ether. After addition was complete, stirring with cooling in an ice bath was continued for 30 min., then the amine salt was removed by suction filtration and washed with dry ether. Removal of solvent from the filtrate at reduced pressure left a colorless oily residue weighing 1.95 g. (98% yield). This material crystallized on cooling in an ice bath and remelted at room

(3) B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 695 (1948).

(4) A. Ya. Yakubovich and V. A. Ginsburg, *Doklady Akad. Nauk S.S.S.R.*, **82**, 273 (1952); *Chem. Abstr.*, **47**, 2685 (1953). This behavior has been verified during the present investigation.

(5) A. E. Arbuzov, V. M. Zoroastrova, and N. I. Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, 1948, 208; *Chem. Abstr.*, **42**, 4932 (1948).

(6) Analyses are by the Microanalytical Division, Department of Chemistry, University of California. Boiling points are uncorrected; unless otherwise specified, distillations were through a half-meter simple Podbielniak column of the type which has been described in detail (J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, pp. 237–243). Melting points were determined on a Fisher micro hot stage.

(7) K. C. Kennard and C. S. Hamilton, *Org. Syntheses*, **37**, 82 (1957).

temperature. The analytical sample was evaporatively distilled at 0.1 mm. pressure.

Anal. Calcd. for $C_4H_7O_2PCl_4$: Cl, 54.6. Found: Cl, 52.0.

Repetition of this preparation on a larger scale yielded similar results and gave material with an identical infrared spectrum. When such material stood 8 days in a closed container at room temperature it became dark red and more viscous, and an altered infrared spectrum was observed.

Hydrolysis of isopropyl trichloromethylphosphonochloridate was carried out by heating on a steam bath for 90 min. a 1.0-g. sample of the oily ester acid chloride with 20 ml. of water. The oil was insoluble in cold water but the mixture became homogeneous as soon as heated. Freeze-drying of the reaction mixture left a semisolid residue weighing 0.74 g. A solution of this residue in 20 ml. of dry ether was treated dropwise with *N*-methylaniline until precipitation was complete. The precipitate was collected by suction filtration, washed with dry ether, and dried. The colorless solid, weight 0.68 g., was recrystallized from absolute alcohol to yield colorless plates, m.p. 220–223° (dec.). The m.p. reported[8] for *N*-methylanilinium trichloromethylphosphonate is 224–225° (dec.).

Anal. Calcd. for $C_8H_{11}O_3NPCl_3$: equiv. wt., 153. Found: equiv. wt., 155.

N-(2-chloroethyl)pyrrolidine was prepared by a published method for preparing amino halides.[9] To a solution of 18 g. (0.16 mole) of *N*-(2-hydroxyethyl)pyrrolidine (b.p. 72–73°/10 mm., n_D^{25} 1.4716) in 75 ml. of benzene, there was added dropwise during 0.5 hr. a solution of 20 g. (0.17 mole) of thionyl chloride in 50 ml. of benzene. The reaction was cooled in ice during the addition and a subsequent 1-hr. period of stirring. The mixture was poured into ice and water containing 25 g. of sodium hydroxide, and the product extracted with ether. Distillation yielded 15.2 g. (72%) of product, b.p. 60–63°/23 mm.

The relatively unstable *N*-(2-chloroethyl)pyrrolidine was characterized by conversion to the *picrate* in anhydrous ether. After crystallization from ethanol, the m.p. was 107.3–107.8°.

Anal. Calcd. for $C_{12}H_{15}N_4O_7Cl$: C, 39.73; H, 4.17; N, 15.45. Found: C, 39.83; H, 4.28; N, 15.67.

Attempts to convert this halide to a phosphorothioate (V) by reaction with diethyl potassium phosphorothioate[10] yielded a resinous undistillable material.

Ethylene phosphorochloridite. Commercial ethylene glycol (150 g.) was added dropwise with stirring to 450 g. of phosphorus trichloride, as the reaction mixture was maintained at 0–5°. After addition was complete, the solution was stirred at room temperature for 1 hr. and at 80–90° for 2 hr. The mixture was then distilled through a Claisen head, and the product collected in the range 60–80°/45 mm. was fractionated through a half-meter Vigreux column with heated jacket and partial reflux head. After a small fore-run, there was collected 121.0 g. (39.5%) of product, b.p. 65–66°/42 mm., n_D^{25} 1.4897; lit.,[11,12] b.p. 66–68°/47 mm., n_D^{20} 1.4894; b.p. 71.3°/50 mm., n_D^{25} 1.4878.

There has been reported[12] a more elaborate method of preparation which gives a better yield.

Ethyl ethylene phosphite (VI). To a stirred solution of 63 g. (0.5 mole) of ethylene phosphorochloridite in 200 ml. of anhydrous ether, there was added during 1 hr. at 10° a solution of 23 g. (0.5 mole) of absolute ethanol and 51 g. (0.5 mole) of triethylamine in 50 ml. of anhydrous ether. After stirring had been continued for an additional 0.5 hr. at room temperature, the mixture was diluted with 200 ml. of ether and the precipitated amine salt removed by filtration. Distillation of the filtrate and washings through a Claisen head yielded 56 g. (83%) of phosphite, b.p. 54–55°/16 mm., n_D^{20} 1.4411; lit.[5,12] b.p. 50.5–51°/15 mm., n_D^{20} 1.4395; b.p. 60–61°/21 mm., n_D^{25} 1.4390.

Dry air was bubbled through a 10-g. sample of this phosphite for 70 hr. while it was heated on a steam bath. A Dry Ice–cooled condenser was necessary to prevent sweeping of the phosphite from the flask in the stream of air. Distillation of the resultant product yielded 5.6 g. of starting material, b.p. 54°/15 mm. n_D^{20} 1.4410, and a nonvolatile residue.

Ethyl ethylene phosphorothioate (VIII). Sulfur (2.1 g., 0.066 mole) was added in small portions with stirring to 10 g. (0.066 mole) of ethyl ethylene phosphite. Addition was at such a rate as to keep the temperature of the exothermic reaction at 35–40°. Stirring was continued for 1 hr. after completion of the addition, then a trace of sulfur was removed by filtration and the product distilled to yield 4.4 g. (36%) of VIII, b.p. 79°/0.5 mm., n_D^{25} 1.4857.

Anal. Calcd. for $C_4H_9O_3PS$: C, 28.57; H, 5.39. Found: C, 28.65; H, 5.23.

A sample which had stood overnight had n_D^{25} 1.4861; after heating for 15 min. at 160° the n_D^{25} was 1.5060, and the viscosity had increased markedly.

2-(Diethylamino)ethyl ethylene phosphite (VII). A solution of 50 g. (0.43 mole) of diethylaminoethanol and 50 g. (0.50 mole) of triethylamine was added dropwise with stirring to a solution of 50 g. (0.40 mole) of ethylene phosphorochloridite in 500 ml. of benzene. The temperature of the reaction mixture was maintained at 5–10° with an ice bath, and the addition required about 1 hr. After the mixture had warmed to room temperature the amine salt was removed by filtration, and the product obtained from the filtrate was distilled to yield 29.1 g. (36%) of phosphite VII, b.p. 95–97°/4 mm., n_D^{25} 1.4618–1.4620. A sample redistilled for analysis had b.p. 97°/4 mm., n_D^{25} 1.4620.

Anal. Calcd. for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; N, 6.76. Found: C, 46.57; H, 8.54; N, 6.75.

2-(Diethylamino)ethyl trimethylene phosphite was prepared by the same procedure described for VII, utilizing 45 g. (0.38 mole) of diethylaminoethanol, 38 g. (0.38 mole) of triethylamine and 46.8 g. (0.33 mole) of trimethylene phosphorochloridite (b.p. 67–68°/12 mm., prepared as described for ethylene phosphorochloridite; lit.[12] b.p. 77°/25 mm.). There was obtained a yield of 38.2 g. (52%), b.p. 107–110°/3.5–4.0 mm., n_D^{25} 1.4592–1.4609. The analytical sample had b.p. 110°/4.0 mm., n_D^{25} 1.4609.

Anal. Calcd. for $C_9H_{20}NO_3P$: C, 48.86; H, 9.11; N, 6.33. Found: C, 48.75; H, 8.96; N, 6.23.

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(8) I. S. Bengelsdorf and L. B. Barron, *J. Am. Chem. Soc.*, **77**, 2869 (1955).

(9) D. S. Breslow, R. S. Yost, H. G. Walker, and C. R. Hauser, *J. Am. Chem. Soc.*, 66, 1921 (1944).

(10) T. W. Mastin, G. R. Norman, and E. A. Weilmuenster, *J. Am. Chem. Soc.*, **67**, 1662 (1945).

(11) P. A. Rossiiskaya and M. I. Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, **1947**, 509; *Chem. Abstr.*, **42**, 2924 (1948).

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Synthesis of 1-Substituted Thymines

ROBERT C. SMITH AND STEPHEN B. BINKLEY

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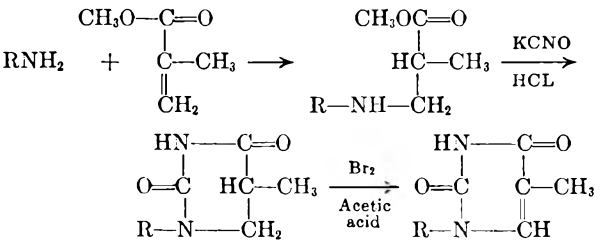
Gearien and Binkley[1] have recently reported a method for the synthesis of 1-substituted uracils in which ethyl acrylate reacted with a primary

(1) J. E. Gearien and S. B. Binkley, *J. Org. Chem.*, **23**, 491 (1958).

amine to form an *N*-substituted-β-alanine ester which, when treated with potassium cyanate and hydrochloric acid, yields a 1-substituted dihydrouracil. The 1-substituted dihydrouracil was brominated and dehydrobrominated to yield a 1-substituted uracil.

In an attempt to prepare 1-substituted thymines methyl methacrylate was substituted for the ethyl acrylate in the above synthesis. The illustrated series of reactions has been carried out.



R = benzyl, isopropyl, methyl, or furfuryl.

The 1-substituted dihydrothymines and 1-substituted thymines in which the substituent was either benzyl, isopropyl, or methyl were prepared and characterized. The 1-furfuryldihydrothymine was also prepared. Two of these compounds, 1-benzylthymine and 1-methylthymine, have previously been synthesized. Johnson and Derby[2] prepared 1-benzylthymine by the hydrolysis of 2-ethylmercapto-1-benzyl-5-methyl-4-oxypyrimidine. Johnson and Clapp[3] prepared 1-methylthymine by the hydrolysis of 2-ethylmercapto-1,5-dimethyl-4-oxypyrimidine. Shaw and Warrener[4] have prepared the same compound by treating *N*-ethoxycarbonyl-β-methoxy-α-methylacrylamide with methylamine.

The *N*-substituted-β-aminoisobutyric esters were prepared by refluxing the proper primary amine with methyl methacrylate in methanol. The compounds prepared in this manner were converted to the dihydrothymines by treatment with potassium cyanate and hydrochloric acid. When the resulting 1-substituted dihydrothymines were treated with bromine in refluxing glacial acetic acid, the 1-substituted thymines were isolated. This was in contrast to the similar bromination of 1-substituted dihydrouracils[1] in which the brominated uracil was isolated. Under the same conditions the 1-substituted dihydrothymines appear to add bromine and dehydrobrominate spontaneously yielding only the 1-substituted thymines. The treatment of 1-furfuryldihydrothymine with bromine resulted in the production of black tars. Several attempts have been made to dehydrogenate this compound with no success.

The compounds prepared were characterized by melting point comparisons with those compounds previously prepared, by elemental analysis, and in the case of the 1-substituted thymines by ultraviolet absorption spectrum.

EXPERIMENTAL[5]

Preparation of the methyl esters of N-substituted-β-aminoisobutyrates. A mixture of methyl methacrylate and a primary amine was refluxed in methanol for 48 hr. The alcohol was removed under reduced pressure and the product was distilled under vacuum.

Methyl N-benzyl-β-aminoisobutyrate was prepared from 54.7 g. (0.51 mole) of benzylamine and 50.0 g. (0.50 mole) of methyl methacrylate. The product (74.6 g., 72%) was a colorless liquid, b.p. 142–144° at 14 mm.

Anal. Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 6.63.

Methyl N-isopropyl-β-aminoisobutyrate. Isopropylamine (35.1 g., 0.60 mole) and 58.0 g. (0.58 mole) of methyl methacrylate gave 49.6 g. (54%) of a colorless liquid, b.p. 48° at 2 mm.

Anal. Calcd. for $C_8H_{17}O_2N$: N, 8.80. Found N, 8.72.

Methyl N-methyl-β-aminoisobutyrate. When 17.1 g. (0.55 mole) of methylamine and 58.0 g. (0.58 mole) of methyl methacrylate were heated in a Magne Dash Autoclave at 80° for 24 hr. 28.0 g. (37%) of methyl *N*-methyl-β-aminoisobutyrate were obtained. This colorless liquid boiled at 74° at 0.5 mm.

Anal. Calcd. for $C_6H_{13}O_2N$: N, 10.68. Found: N, 10.82.

Methyl N-furfuryl-β-aminoisobutyrate. Furfurylamine (38.8 g., 0.40 mole) and 39.0 g. (0.39 mole) of methyl methacrylate gave 48.7 g. (64%) of a colorless liquid, b.p. 92–94° at 1 mm.

Anal. Calcd. for $C_{10}H_{15}O_3N$: N, 8.10. Found: N, 7.18.

1-Substituted dihydrothymines. The methyl ester of *N*-substituted-β-aminoisobutyrate was dissolved in water with the aid of hydrochloric acid. This solution was added to potassium cyanate (10% excess) in water and was allowed to stand overnight. The heavy oil which formed was separated and heated at 120° (20 mm.) for 2 hours. Upon cooling the oil solidified and was recrystallized from isopropanol.

1-Benzyldihydrothymine. The methyl ester of *N*-benzyl-β-aminoisobutyric acid (72.1 g., 0.35 mole) and 30.0 g. (0.37 mole) of potassium cyanate gave 52.8 g. (70%) of 1-benzyldihydrothymine melting at 100–102°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: N, 12.84. Found: N, 12.72.

1-Isopropyldihydrothymine was prepared from 49.6 g. (0.31 mole) of methyl *N*-isopropyl-β-aminoisobutyric acid and 28.4 g. (0.35 mole) of potassium cyanate. The product weighed 37.3 g. (70%) and melted at 139–140°.

Anal. Calcd. for $C_8H_{14}O_2N_2$: N, 16.46. Found: N, 16.52.

1-Methyldihydrothymine was prepared from 18.2 g. (0.14 mole) of the methyl ester of N-methyl-β-aminoisobutyric acid and 12.0 g. (0.15 mole) of potassium cyanate. The product weighed 10.1 g. (51%) and melted at 131–133°.

Anal. Calcd. for $C_6H_{10}O_2N_2$: N, 19.71. Found. N, 19.67.

1-Furfuryldihydrothymine. The methyl ester of N-furfuryl-β-aminoisobutyric acid (48.7 g., 0.25 mole) and 21.0 g. (0.26 mole) of potassium cyanate gave 35.0 g. (69%) of 1-furfuryldihydrothymine melting at 98–100°.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.76; H, 5.70; N, 13.42.

1-Substituted thymines. A well stirred, refluxing solution of 3 to 5 g. of the 1-substituted dihydrothymine in 20 ml. of glacial acetic acid was heated to boiling. One equivalent of

(2) T. B. Johnson and J. H. Derby, *Am. Chem. J.*, **40**, 444 (1908).

(3) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 49 (1908).

(4) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 157 (1958).

(5) Analyses were conducted by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points and boiling points are uncorrected. The ultraviolet absorption spectra of the 1-substituted thymines were measured in methanol solution on a Beckmann Ratio Recording Spectrophotometer.

bromine in 10 ml. of acetic acid was added dropwise to the boiling solution. After refluxing for 2 hr., the mixture was cooled and sodium hydroxide added to precipitate the product which was then recrystallized from methanol.

1-Benzylthymine. 1-Benzyldihydrothymine (3.0 g., 0.0138 mole) when treated with one molecular equivalent of bromine gave 2.0 g. (67%) of 1-benzylthymine, which melted at 161–163° (lit.[2] 160°); λ_{max} 271 mμ, λ_{min} 236 mμ; ϵ = 10,500.

1-Isopropylthymine. 1-Isopropyldihydrothymine (3.0 g., 0.018 mole) when treated with one molecular equivalent of bromine gave a 75% yield of 1-isopropylthymine. After recrystallization from isopropanol, it melted at 213–216°.

Anal. Calcd. for $C_8H_{12}O_2N_2$: N, 16.66. Found: N, 16.71 λ_{max} 271 mμ, λ_{min} 236 mμ; ϵ = 9830.

1-Methylthymine. 1-Methyldihydrothymine (5.0 g., 0.035 mole) when treated with one molecular equivalent of bromine gave a 75% yield of 1-methylthymine. After recrystallization from methanol,it melted at 288°; (lit.[3,4] 280–282°) λ_{max} 272 mμ, λ_{min} 237 mμ; ϵ = 8000.

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Ring Derivatives of Phenothiazine. III. Esters of 2-Phenothiazinecarboxylic Acid

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The facile synthesis of 2-phenothiazinecarboxylic acid by the basic hydrolysis of the pyridine addition product of 2-chloroacetyl-10-acetylphenothiazine,[3] in contrast to its earlier preparation, which involved hypochlorite oxidation of 2-acetylphenothiazine,[4] and which gave low yields and complex products, has made this acid available for further studies.

Because of the great interest in 2-substituted phenothiazines, as a prototype for physiologically interesting esters[5] of this acid, and as intermediates for other derivatives, some simple alkyl esters of 2-phenothiazinecarboxylic acid have been prepared. These esters were prepared either by direct alkylation of the acid with an alkyl halide or sulfate, or by alcoholysis of the methyl ester. The latter method gave better yield and may be quite valuable in the synthesis of some larger alkyl esters, particularly when the alcohols are more available than the halides.

The need for relatively large amount of this acid led to studies on its preparation. The method of Burger[3] has been improved to give yields of 90–95%. The preparation of the acid by hydrolysis of 2-cyanoacetylphenothiazine[6] could not be improved beyond a 15% yield and was, therefore, not satisfactory.

These compounds have been submitted for physiological testing to the Sloan-Kettering Institute and the Upjohn Drug Co.; results will be published elsewhere.

EXPERIMENTAL[7]

2-Phenothiazinecarboxylic acid. A mixture of 40.2 g. (0.13*M*) of crude 2-chloroacetyl-10-acetylphenothiazine and 266 ml. of anhydrous pyridine was warmed at 90° for 20 min. The mixture was extracted with ether until the odor of pyridine was gone, leaving a gummy yellow solid. Hydrolysis of this solid with 400 ml. of 5% sodium hydroxide solution for 1 hr., treatment with Norit, filtration, and acidification with concentrated hydrochloric acid gave the acid as a yellow solid. Crystallization from acetone-ethanol mixture gave 30 g. (95%) of yellow crystals, melting at 276–278°.

Preparation of esters. (*a*) *Direct alkylation.* The esters were prepared by refluxing a mixture of the acid, one to two equivalents of the alkyl halide or sulfate, catalytic amounts of potassium iodide, and an equivalent of anhydrous potassium carbonate in acetone for 24 hr. After cooling, the reaction mixture was poured into water, filtered, dried, and recrystallized from ethanol-acetone mixtures. All of the esters are yellow solids. The results are given in Table I.

TABLE I

Esters of 2-Phenothiazinecarboxylic Acid

Alkyl Group	M.P., °C.	Percentage Yield, Method (a)	Percentage Yield, Method (b)	Analyses, Nitrogen, Calcd.	Analyses, Nitrogen, Found	Analyses, Sulfur, Calcd.	Analyses, Sulfur, Found
Methyl[4]	166–167	93		5.45	5.39	12.47	12.49
Ethyl[4]	151–152	97		5.17	5.10	11.83	11.89
n-Propyl	162–163	69	70	4.91	4.89	11.23	11.20
n-Butyl	161–162	76	Quan.	4.68	4.71	10.72	10.93
n-Amyl	148–150	56	75	4.47	4.57	10.20	10.20

(1) Present address, Department of Chemistry, Brown University, Providence, R. I.

(2) A portion of this work was taken from the master's thesis of Carlos Smith, Fisk University, May 1957.

(3) A. Burger and J. Clements, *J. Org. Chem.*, 19, 1113 (1954).

(4) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, 68, 2673 (1946).

(5) Unpublished studies of these laboratories.

(6) S. P. Massie, I. Cooke, and W. Hills, *J. Org. Chem.*, 21, 1006 (1956).

(7) All melting points are uncorrected. Analyses are by the Upjohn Laboratories, courtesy, Dr. R. F. Heinzelmann.

(*b*) *Alcoholysis.* Twenty to thirty ml. of the alcohol were treated with 0.1 g. of sodium. When reaction was completed, one gram of methyl 2-phenothiazinecarboxylate was added, and the mixture was refluxed 4–5 hr. The mixture was poured into water, filtered, dried, and recrystallized from ethanol-acetone mixtures.

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A New Technique in Preparing 2,4-Dinitrophenylhydrazones. Use of Diglyme as Solvent

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An encumberance long associated with the characterization of carbonyl compounds by their 2,4-dinitrophenylhydrazones is the difficulty of obtaining concentrated solutions of 2,4-dinitrophenylhydrazine. The low solubility of the reagent in useful solvents is usually overcome by working with boiling solvents or with highly acidic solutions, since the salts of the reagent are more soluble than the reagent itself. Thus, 2,4-dinitrophenylhydrazones are usually prepared by resorting to one of several techniques now in practice. These are, for example, adding to the carbonyl compound a solution of the reagent in concentrated sulfuric acid, water, and ethanol[1]: adding a solution of the reagent in ethanol containing hydrochloric acid[2]; adding a solution of the reagent in 85% phosphoric acid and ethanol[3]; boiling the carbonyl compound in a methanol solution of the reagent acidified with hydrochloric acid[4]; boiling the carbonyl compound, reagent, and hydrochloric acid in ethanol[5]; uniting the carbonyl compound, reagent and hydrochloric acid in a mixture of ethanol and dioxane[6]; and adding an alcoholic solution of the carbonyl compound to a saturated solution of the reagent in 2*M* hydrochloric acid.[7]

It has now been found that 2,4-dinitrophenylhydrazine is quite soluble in the dimethyl ether of diethylene glycol, for which solvent the name diglyme has been coined.[8] Solutions of the reagent made by warming 1 g. in 25 to 30 ml. of the solvent are stable at room temperature. The neutral solution is deep red in color. Acidification with hydrochloric acid turns the color to yellow. It is not necessary to acidify the reagent solution for storage, however. Solutions of the reagent in diglyme have been found to be admirable for the preparation of derivatives, using, as is customary, hydrochloric acid for catalysis.

Moderate success was also achieved in the use of acetic acid instead of hydrochloric acid for catalysis. The reason for using acetic acid was two-fold. The use of a weak acid for catalysis in solutions at room temperature or lower may be applicable to the preparation of derivatives of sensitive compounds. Also, in the preparation of derivatives of carbonyl compounds formed in the oxidation of glycols by lead tetraacetate the precipitation of the derivative may be complicated by the precipitation of lead chloride, unless the trouble is taken first to separate the carbonyl compounds from lead acetate. If acetic acid can be used for catalysis of 2,4-dinitrophenylhydrazone formation it may be possible to use crude oxidation mixtures in the preparation of derivatives. Results with lead tetraacetate oxidation solutions will be published elsewhere. As can be seen in Table I success was achieved in the four cases tried. However, the formation of the derivatives was slow. In the case of benzaldehyde the derivative crystallized nicely from solution 30 min. after adding the acetic acid. In the cases of methyl *p*-tolyl ketone and 7-ethyl-1-tetralone the derivatives crystallized out overnight. In each case, however, the amount of derivative obtained was much smaller than expected from the amount of compound used. The use of solutions of 2,4-dinitrophenylhydrazine in acetic acid alone or in aqueous acetic acid is to be avoided since acetylation of the reagent occurs when warming to dissolve. No acetylation occurred in a control diglyme experiment.

As might be expected, triglyme[8] and tetrahydrofuran can be used as solvents for 2,4-dinitrophenylhydrazine. Undoubtedly, other solvents may be found. Because tetrahydrofuran needs to be distilled prior to use and because of its volatility, we found diglyme to be preferred. It was found unnecessary to distill the diglyme before use.

(1) R. L. Shriner, R. C. Fuson and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p. 219.

(2) W. J. Hickinbottom, *Reactions of Organic Compounds*, 2nd ed., Longmans, Green and Co., Ltd., New York, N. Y., 1948, p. 161.

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

(4) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, 2nd ed., Interscience Publishers, New York, N. Y., 1957, p. 393.

(5) R. Adams and J. R. Johnson, *Laboratory Experiments in Organic Chemistry*, 4th ed., Macmillan Co., New York, N. Y. 1953, p. 257.

(6) I. N. Nazarov, L. A. Kazitsyna, and I. I. Zarekskaya, *J. Gen. Chem., USSR*, **27**, (89), 606 (1957).

(7) S. Veibel, *The Identification of Organic Compounds*, 1st English ed. (based on the 4th Danish ed.), G. E. C. Gad, publisher, Copenhagen, Denmark, 1954, p. 101.

(8) H. C. Brown, E. T. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

EXPERIMENTAL

The following procedure was used, in general, in preparing the derivatives given in Table I.

TABLE I

MELTING POINTS[a] AND LITERATURE VALUES

Compound	M.P.	Lit., °C.
methyl *n*-hexyl ketone[b]	58–59	58[k]
methyl isobutyl ketone[b]	92–93[h]	95[k]
methyl isopropyl ketone[b]	123–124	117[k], 119–120[m]
acetone[b]	125–126	126[k]
acetone[b,e]	124–126	126[k]
cyclohexanone[c]	160–161	161[k]
acetaldehyde[b]	165–166[i]	168[k]
formaldehyde[b]	165–166	166[k]
benzaldehyde[d]	238–240	237[k]
benzaldehyde[c,e]	239–240	237[k]
benzaldehyde[d,f]	239–240	237[k]
benzaldehyde[d,g]	239–240	237[k]
acetophenone[d]	247–248	250[k]
cinnamaldehyde[d]	255–256	255[k]
methyl *p*-tolyl ketone[d]	257–259[j]	260[k]
methyl *p*-tolyl ketone[c,e]	247–254	260[k]
7-ethyltetralone-1[d]	271–272	275[n]
7-ethyltetralone-1[c,e]	273–274	275[n]
p-hydroxybenzaldehyde[d]	284–284.5	280[k]

[a] Uncorrected. [b] Dilution with water needed to precipitate derivative. [c] Derivative crystallized out slowly. [d] Derivative precipitated immediately on adding acid. [e] Ten drops of acetic acid used instead of hydrochloric acid. [f] Triglyme solution of reagent. [g] Tetrahydrofuran solution of reagent. [h] Recrystallized from ethanol: m.p. before was 86–89°. [i] Recrystallized from ethanol; m.p. before was 153–154°. See ref. 4, p. 586. [j] Recrystallized from diglyme: m.p. before was 249–256°. [k] Ref. 1. [m] Ref. 4. [n] This was prepared in these laboratories by a conventional technique and recrystallized from ethyl acetate. Calcd. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.80. Found[9]: C, 61.21; H, 5.19; N, 15.51.

A solution of 4 g. of 2,4-dinitrophenylhydrazine was prepared by warming in 120 ml. of diglyme and allowed to stand at room temperature for several days. Five ml. of this solution, at room temperature, was added to approximately 0.1 g. of the carbonyl compound dissolved in 1 ml. of 95% ethanol. Where the carbonyl compound was insoluble in 95% ethanol it was dissolved in diglyme, as, for example, in the case of *p*-hydroxybenzaldehyde. Three drops of concentrate hydrochloric acid were then added, causing the immediate formation of the derivative. In some cases the derivative precipitated immediately, in others dilution with water was necessary, while in one the derivative crystallized out slowly. The derivative was filtered, washed with ethanol or aqueous ethanol and dried by suction. In only three cases was it necessary to recrystallize the derivative to obtain a satisfactory melting point. Thus, the new technique gave *excellent crudes* in most cases, within a few minutes work.

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Oxidation of Methyl 8-Nitrodehydroabietate. II[1]

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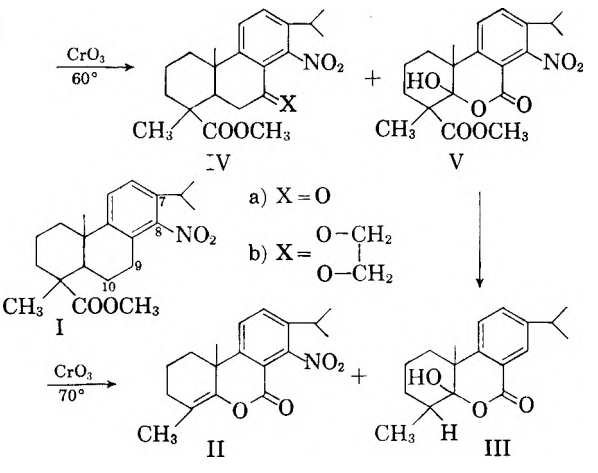
We wish to report the results of a study of the oxidation of methyl 8-nitrodehydroabietate I with chromium trioxide at 60°. The oxidation of I with this trioxide at 70° has been shown to involve the destruction of the hydrophenanthrene system, and the products of the oxidation have been formulated as the ketol lactone III and the enol lactone II arising from III by dehydration.[1] It has now been found possible to isolate compounds IVa and V from oxidations at 60° as intermediates in the formation of the ketol lactone III.

The neutral fraction of the oxidation mixture in the present work consists of methyl 9-oxo-8-nitrodehydroabietate IVa and is characterized by way of its 2,4-dinitrophenylhydrazone and ethylene ketal derivatives. The ultraviolet spectrum of IVa

FIGURE I



is consistent with this formulation, since the conjugation of the carbonyl function at C-9 with the phenyl ring causes a shift in the positions of the absorption maxima of methyl 8-nitrodehydroabietate I as well as a large increase in the intensity of absorption (see Table I). Formation of the ethylene ketal IVb blocks this conjugation and its spectrum is very similar to that of I, although a small bathochromic shift is noticed in this case owing to the presence of the polar ketal group. The infrared spectrum (Table I) of the ketone IVa also shows the presence of the conjugated ketonic system by an absorption band at 5.91μ.

(1) Paper I: H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **77**, 6707 (1955).

(2) Felton Chemical Co., Inc., 599 Johnson Ave., Brooklyn 37, N. Y.

TABLE I

SPECTRAL DATA

Compound	Ultraviolet $\lambda_{max}^{95\%\ EtOH}$	Ultraviolet mμ (log ε)	Carbonyl stretch (μ)
I	264(2.88)	272(2.81)	5.81
IVa	245(3.93)	300(3.33)	5.80, 5.91
IVb	269(2.77)	277(2.79)	5.80

The acidic fraction of the oxidation mixture consists of a monobasic acid, according to analytical data, containing one less carbon atom than the starting material I. The infrared spectrum of this compound V is remarkable in that the hydroxyl region shows resolution into two peaks at 2.94μ and 3.05μ. Since compounds of the ketol lactone type, *e.g.*, III, have similar spectra,[1,3] this acid is formulated as V. In order to further establish this structure, V was refluxed with acetic acid containing Cr^{3+} ion. Under these nonoxidizing conditions solvolysis of the methyl ester and decarboxylation occur with formation of the known compound III.

The isolation of IVa and V from I provides further insight into the processes which lead to the destruction of the diterpenic acid ring system during vigorous oxidation. The first point to be attacked is the benzyl carbon at C-9. Further oxidation of the 9-oxo compound thus formed gives rise to the ketol lactone V which in turn is shown to lead to the ketol lactone III on further heating in acetic acid.

EXPERIMENTAL[4]

Methyl 8-nitrodehydroabietate (I). Methyl 8-nitrodehydroabietate was made by the method of Campbell and Morgana.[5] The infrared spectrum showed absorptions at 5.81μ and 6.56μ. The ultraviolet spectrum showed: $\lambda_{max}^{95\%\ EtOH}$ 264 mμ(log ε 2.88), 272 mμ(log ε 2.81).

Oxidation of methyl 8-nitrodehydroabietate. Methyl 8-nitrodehydroabietate (1.0 g., 2.8 mmole) was dissolved in 50 ml. of glacial acetic acid contained in a three-neck flask immersed in a bath held at 60°. During stirring a solution of chromic acid (1.12 g., 10.8 mmole) in the minimum amount of water necessary to achieve solution and 20 ml. of glacial acetic acid was added over the course of 2 hr. Stirring was continued for an additional 6 hr. The acetic acid was removed at aspirator pressure and the residue was taken up in ether and washed with water (discard) until the washings were colorless (removal of Cr^{3+}). The ether was then washed with a 1% sodium carbonate solution (to *p*H 10). This alkaline extract is discussed further under *Acidic fraction*.

(a) *Neutral fraction* [*Methyl 9-oxo-8-nitrodehydroabietate* (IVa)]. The ether solution was dried over anhydrous potassium carbonate and the solvent evaporated to give 0.63 g. (1.7 mmole) of a yellow solid, yield 63%. Recrystallization from methanol gave yellow plates, m.p. 195–196.5°, [α] +153.5° (C = 0.945).

Anal. Calcd. for $C_{21}H_{27}NO_6$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.39; H, 7.38; N, 3.51.

The infrared spectrum showed absorption at 5.80μ, 5.91μ and 6.49μ. The ultraviolet spectrum showed: $\lambda_{max}^{95\%\ EtOH}$ 245 mμ(log ε 3.93), 300 mμ(log ε 3.33).

The *2,4-dinitrophenylhydrazone* derivative was obtained as red needles, m.p. 193–194.5°, after recrystallization from methanol.

Anal. Calcd. for $C_{27}H_{31}N_5O_8$: C, 58.58; H, 5.64; N, 12.65. Found: C, 58.51; H, 5.41; N, 12.38.

(b) *Acidic fraction* [*Methyl 9-oxo-10-oxa-11-hydroxy-8-nitrodehydroabietate* (V)]. The alkaline extract from above was filtered and heated. While boiling, enough 1% hydrochloric acid was added to just cause turbidity. The resulting suspension was cooled, filtered by suction, and dried. A light brown solid was obtained, yield (0.195 g., 0.48 mmole) 18%.

Recrystallization from methanol gave light tan prisms, m.p. 183.25–184.5°, [α] −201° (C = 1.00).

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.44; H, 6.17; N, 3.85, 3.44.

Saponification equivalent, Calcd. 391. Found 379.

The infrared spectrum had absorption at 2.94μ, 3.05μ, 5.81μ, 5.89μ, and 6.50μ. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ EtOH}$ 294 mμ(log ε 3.79).

Methyl 9-ethylene ketal-8-nitrodehydroabietate (IVb). Methyl 9-oxo-8-nitrodehydroabietate (IVa) (0.95 g., 2.5 mmole) was refluxed for 24 hr. with a solution of *p*-toluenesulfonic acid monohydrate (200 mg.) in a mixture of 40 ml. of benzene and 20 ml. of ethylene glycol. The apparatus was arranged for the continuous removal of water from its azeotrope with benzene. The *p*-toluenesulfonic acid was neutralized with methanolic potassium hydroxide and the reaction mixture was poured into 100 ml. of benzene. The benzene was washed with six portions of water and dried over anhydrous potassium carbonate. Removal of the benzene at the water pump gave oily crystals. By recrystallization from methanol 0.37 g. (0.89 mmole, 36%) of white plates were obtained, m.p. 203.5–204.5°. Recrystallization from hexane gave white plates, m.p. 204.5–206°; [α] 142° (C = 0.55).

Anal. Calcd. for $C_{23}H_{31}NO_6$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.39; H, 7.28; N, 3.19.

The infrared spectrum showed absorption at 5.80μ, 6.54μ, and 9.24μ. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ EtOH}$ 269 mμ(log ε 2.77), 277 mμ(log ε 2.79).

Hydrolysis of methyl 9-ethylene ketal-8-nitrodehydroabietate. Methyl 9-ethylene ketal-8-nitrodehydroabietate (IVb) (24 mg., 0.06 mmole) was dissolved in a mixture of 5 ml. of glacial acetic acid and 1 ml. of water. The solution was heated on the steam bath for 0.5 hr. and while still hot, water was added dropwise until turbidity persisted. The reaction mixture was cooled, and filtered by suction. The filter cake was washed with water, dried, and recrystallized from methanol to give yellow plates, m.p. 191.5–193°. The yield (15 mg., 0.035 mmole) was 60%. The infrared spectrum of this material is identical with that of authentic methyl 9-oxo-8-nitrodehydroabietate (IVa).

Solvolysis of methyl 9-oxo-10-oxa-11-hydroxy-8-nitrodehydroabietate (V). Methyl 9-oxo-10-oxa-11-hydroxy-8-nitrodehydroabietate (V) (0.24 g., 0.61 mmole) was dissolved in 25 ml. of glacial acetic acid. Chromium oxide (0.24 g., 1.58 mmole) was added and the reaction mixture was refluxed for 17 hr.

The acetic acid was removed at aspirator pressure and the residue heated to 150° for 5 min. while still under vacuum. The solid was taken up in ether and the ether solution was washed with 5% aqueous sodium hydroxide until alkaline to litmus. The alkaline extract was boiled for 5 min., cooled, and then acidified with 5% hydrochloric acid.

The precipitate formed was filtered by suction and dried. A white powder was obtained, yield (0.11 g., 0.34 mmole)

(3) E. S. Hansen and H. H. Zeiss, *J. Am. Chem. Soc.*, **77**, 1643 (1955).

(4) All melting points are corrected. All infrared spectra were taken in chloroform, ultraviolet spectra in 95% ethanol and rotations (D line) in chloroform. Microanalyses were performed by the Schwartzkopf Microanalytical Laboratories, Woodside 77, New York, N. Y.

(5) W. Campbell and M. Morgana, *J. Am. Chem. Soc.*, **63**, 1838 (1941).

52%. Recrystallization from 95% ethanol gave white prisms, m.p. 230–231° (lit.[3] 231–232°). The infrared spectrum showed absorption at 2.79μ, 2.99μ, 5.78μ, 6.42μ and was identical with that of an authentic sample of 1,12-dimethyl-7-isopropyl-9-oxo-10-oxa-11-hydroxy-8-nitro-1,2,3,4,9,10,-11,12-octahydrophenanthrene (III).[6] The ultraviolet spectrum showed: $\lambda_{max}^{95\%\ EtOH}$ 293 mμ(log ϵ 3.19).[6]

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(6) M. Tsutsui, Ph.D. Thesis, Yale University, 1955.

Photochemical Oxidation of 5-Nitro-2-furfuryl Iodide

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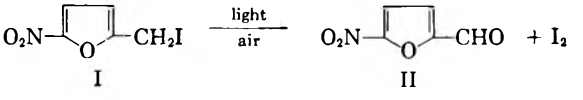
The oxidation of certain substituted bromomethanes to aldehydes by means of dimethyl sulfoxide was recently described by Kornblum and associates.[1] We wish to report a formally similar reaction, the photochemical air oxidation of 5-nitro-2-furfuryl iodide, I, to 5-nitro-2-furfural, II, and iodine.



I II

The synthesis of I was desirable in connection with this laboratory's continuing interest in chemotherapeutic nitrofurans.[2] It was readily effected by the reaction of 5-nitro-2-furfuryl nitrate with sodium iodide in acetone.

Chloroform solutions of I were stable for at least 2 weeks in the dark but liberated iodine when exposed to light. This was accompanied by the appearance of a new peak at 5.89μ in the infrared spectrum, corresponding to the carbonyl absorption of II. Treatment of the crude iodine-free product with semicarbazide hydrochloride gave the semicarbazone of II, although in unsatisfactory yield. As an estimate of the time necessary for completion of the reaction and a more quantitative estimate of the yield was desired, the reaction rate was followed by sodium thiosulfate titration and by infrared analysis of the reaction mixture. The results showed the reaction to be essentially complete in 70 hr., and the maximum yield of II to be 54%. By chromatography on alumina a 34% yield of II was isolated and identified by its infrared spectrum and conversion to 5-nitro-2-furfural phenylhydrazone in 90% yield.

EXPERIMENTAL[3,4]

5-Nitro-2-furfuryl nitrate. To 720 ml. of acetic anhydride was added, with stirring, 189 g. (2.1 moles) of concentrated nitric acid followed by 108 g. (1.1 mole) of furfuryl alcohol. The temperature was held at 20–25° by means of an ice bath. The total time of addition was 12–15 min. The mixture was heated to 40° for 1 hr. and then cooled to 25°. One l. of water and 300 g. of trisodium phosphate were added and the temperature was raised to 60° for 1 hr., cooled to 10–15° and the solid which separated was collected. The yield was 88 g. (42%) m.p. 34–36°. Recrystallization from isopropyl alcohol raised the m.p. to 36–36.5°.

Anal. Calcd. for $C_5H_4N_2O_6$: C, 31.92; H, 2.14; N, 14.89. Found: C, 32.05; H, 2.34; N, 14.75.

5-Nitro-2-furfuryl iodide. A solution of 179 g. (0.95 mole) of 5-nitro-2-furfuryl nitrate in 250 ml. of acetone was added to a saturated solution of 150 g. (1.00 mole) of sodium iodide in acetone. After standing in the cold for 6 hr. the sodium nitrate was removed by filtration and the acetone was evaporated from the filtrate at 30° by means of a rotary evaporator. The residue was diluted with 100 ml. of isopropyl alcohol and chilled. The orange crystals were collected, washed with a little isopropyl alcohol and dried. The yield was 184 g. (76%) m.p. 58–59°.

Anal. Calcd. for $C_5H_4INO_3$: C, 23.74; H, 1.59; N, 5.54; I, 50.17. Found: C, 23.91; H, 1.53; N, 5.64; I, 50.4.

Rate determinations. Two 1-l. 1% chloroform solutions of 5-nitro-2-furfuryl iodide were allowed to stand 70 hr. in 2-l. Erlenmeyer flasks continually exposed to laboratory light. Periodically 10-ml. aliquots were removed and titrated with 0.1*N* sodium thiosulfate to the disappearance of the pink color. Infrared spectra,[5] were determined in 0.5-mm. matched sodium chloride cells with chloroform in the solvent cell. A standard curve of analytically pure 5-nitro-2-furfural was prepared and was shown to obey Beer's Law over the concentration range studied.

Isolation and characterization of 5-nitro-2-furfural. After 90–100% of the iodine had been liberated, the two solutions were combined and shaken with 200 ml. of 10% sodium thiosulfate solution to remove the iodine. The chloroform layer was separated, dried, and the chloroform removed at 30–40° by a rotary vacuum evaporator. The residue was 10 g. of dark, golden liquid. Several small-scale experiments indicated that purification could be effected by chromatography and the remaining product, 7.21 g., in about 50 ml. of benzene was added to a column containing 500 g. of acid-washed alumina. Development and elution with benzene yielded 1.54 g. of slightly impure 5-nitro-2-furfuryl iodide, m.p. 49–52, in the 350 ml. of eluent. The next 2 l. of benzene yielded 2.46 g. of 5-nitro-2-furfural. The infrared spectrum of this sample was identical with the spectrum of authentic 5-nitro-2-furfural. The corrected yield, based on unrecovered 5-nitro-2-furfuryl iodide, was 34%. To provide a solid derivative, the product was dissolved in ethanol and treated with an aqueous solution containing 2.5 g. of phenylhydrazine hydrochloride. The red precipitate was collected, washed with ethanol and water, and dried at 60°. The yield was 3.5 g. (90%) m.p. 190–192°. λ_{max}^{EtOH} 465 mμ (log ϵ 4.32).

(1) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, 79, 6562 (1957).

(2) For a recent paper in this series, see J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, 78, 5349 (1956).

(3) All melting points were taken on a calibrated Fisher-Johns apparatus.

(4) Microanalyses were carried out by Mr. Gordon Ginther and the ultraviolet spectra were determined by Mr. Curtis Eaton and Mrs. Catherine Gravesen.

(5) A Perkin-Elmer Model 21 instrument employing sodium chloride optics was used.

Authentic 5-nitro-2-furfural phenylhydrazone melts at 190–192°. $\lambda_{max}^{60\% EtOH}$ 467 mμ (log ε 4.31).[6,7]

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(6) Unpublished results obtained in these laboratories.

(7) J. A. Buzard, M. Paul, and V. Ells, *J. Assoc. Offic. Agr. Chemists*, 39, 512 (1956).

A Convenient Synthesis of 4(5)-Amino-5(4)-imidazolecarboxamide Hydrochloride[1]

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4(5)-Amino-5(4)-imidazolecarboxamide was first isolated by Stetten and Fox[2] from a culture of *E. coli* inhibited by sulfanilamide. It has since been shown to be the precursor of purines in the *de novo* synthesis of nucleic acids (in these biosynthetic processes it occurs as the ribotide).[3] It has also been shown that exogenous 4(5)-amino-5(4)-imidazolecarboxamide greatly increases the incorporation of guanine into the nucleic acids of certain tumors in mice and significantly increases its incorporation in normal body tissues.[4] It appears to be an *in vitro* inhibitor of guanase.[5,6]

None of the several synthetic methods which have been developed by various investigators[7] is convenient for the preparation of large quantities of this biologically important compound. An examination of these routes to 4(5)-amino-5(4)-imidazolecarboxamide led to the conclusion that the procedure of Shaw and Woolley[7a] could be most readily adapted to a large scale preparation of the compound. The conversion of ethyl cyanoacetate in three steps to phenylazomalonamamidine hydrochloride is quite good and can be carried out on large amounts of material. The reductive formylation of phenylazomalonamamidine hydrochloride can also be performed on a large scale, but the isolation of the resulting formylaminomalonamamidine and dry fusion of this material to give 4(5)-amino-5(4)-imidazolecarboxamide is not adaptable to large quantities. In addition, the fusion yields a green specimen of the imidazole which is difficult to free from its pigmented impurities.

We have found that phenylazomalonamamidine hydrochloride can be reduced in formic acid solution either catalytically or with zinc dust and, after removal of the palladium-on-charcoal catalyst or the excess zinc dust, cyclized to 4(5)-formylamino-5(4)-imidazolecarboxamide by simply refluxing the now colorless solution.[8] The removal of the excess formic acid gave a white solid which was triturated with ethanol to remove the by-product formanilide and, if the zinc reduction was used, the 4-formylamino-5-imidazolecarboxamide was then recrystallized from water to rid it of zinc salts. When the catalytic reduction was employed simple trituration gave material which was about 98% pure.

The 4(5)-formylamino-5(4)-imidazolecarboxamide was easily converted to 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride by refluxing it in dilute hydrochloride acid. The white material obtained was usually sufficiently pure to use without further purification. Up to 100 g. of both compounds has been prepared in one reaction sequence using the zinc reduction, but better yields were obtained from the runs using catalytic reduction, the average yield of 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride being 70%.

Pure 4(5)-amino-5(4)-imidazolecarboxamide was readily prepared from a water solution of its hydrochloride by treatment with Dowex-1.

EXPERIMENTAL

4(5)-Formylamino-5(4)-imidazolecarboxamide and 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride. Method A (zinc reduction). Phenylazomalonamamidine hydrochloride (25.0 g.) was added in portions to a stirred suspension of zinc dust (50 g.) in 98% formic acid (225 ml.) at 25°. The excess zinc dust was removed by filtration; the filtrate was refluxed for 8 hr. and then taken to dryness *in vacuo*. The solid residue was dissolved in hot water (700 ml.) and the resulting solution allowed to stand overnight in a refrigerator. The 4(5)-formylamino-5(4)-imidazolecarboxamide which crystallized from the solution was removed by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 4.45 g. (28%); $\lambda_{max}^{pH\ 7}$ 269 mμ (ε 12,900) [lit.,[9] $\lambda_{max}^{pH\ 6}$ 268 mμ (ε 10,900)].

Anal. Calcd. for $C_5H_6O_2N_6$: C, 38.97; H, 3.94; N, 36.37. Found: C, 39.26; H, 4.20; N, 36.29.

The filtrate from the isolation of the 4(5)-formylamino-5(4)-imidazolecarboxamide was saturated with hydrogen sulfide. The precipitated zinc sulfide was removed by filtration and the excess hydrogen sulfide by concentration of the solution *in vacuo*. The solution was then acidified with dilute hydrochloric acid, refluxed for 15 min., and evapo-

(1) This work was supported by funds from National Institutes of Health, Contract No. SA 43-ph-876 and from the Union Carbide Chemicals Co.

(2) M. R. Stetten and C. L. Fox, Jr., *J. Biol. Chem.*, 161, 333 (1945).

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(7a) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 181, 89 (1949). (b) A. Windaus and W. Langenbeck, *Ber.*, 56, 683 (1923). (c) A. H. Cook, I. Heilbron, and E. Smith, *J. Chem. Soc.*, 1440 (1949). (d) C. S. Miller, S. Gurin, and D. W. Wilson, *Science*, 112, 654 (1950).

(8) The ultraviolet spectrum of the solution before reflux showed that it contained an appreciable quantity of 4(5)-formylamino-5(4)-imidazolecarboxamide indicating that some cyclization had occurred during the reduction procedure.

(9) E. Shaw, *J. Biol. Chem.*, 185, 439 (1950).

rated to dryness *in vacuo*. The residue was recrystallized from water-alcohol-ether to give 4.55 g. (27%) of pure 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride: m.p., 254° (lit.,[7a] 255–256°); $\lambda_{max}^{pH\ 7}$ 277 mμ (ε12,300).

4(5)-Amino-5(4)-imidazolecarboxamide hydrochloride. Method B (catalytic reduction). To 3 g. of 30% palladium-on-charcoal catalyst[10] wetted with 6 ml. of water and 10 ml. of methyl cellosolve in a 500-ml. pressure bottle was added phenylazomalonamamidine hydrochloride (30.0 g.) suspended in 270 ml. of 98% formic acid.[11] Reduction in a Parr shaker required 3–4 hr. The catalyst was removed by filtration and the formic acid by evaporation *in vacuo*. The resulting white solid was triturated with absolute ethanol (50 ml.) to remove the by-product formanilide and traces of hypoxanthine. The residue, practically pure 4(5)-formylamino-5(4)-imidazolecarboxamide, was suspended in 1*N* hydrochloric acid (150 ml.), and the mixture was refluxed for 15 min.

This solution was evaporated to dryness *in vacuo* and the residual white solid dried *in vacuo* over phosphorus pentoxide: yield, 14.4 g. (71%); m.p., 256°; $\lambda_{max}^{pH\ 13}$ 277 mμ (ε 12,500). Three other runs gave an average yield of 70%.

An aqueous solution of 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride (500 mg.) was converted to the free base by treatment with Dowex 1(carbonate form); yield, 218 mg. (56%); m.p. 170–171° (lit.[12] 169.8–171.4°).

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(11) When 98% formic acid was added to the dry catalyst, a violent reaction ensued. It was necessary with some batches of phenylazomalonamamidine to pretreat the solution with a portion of catalyst which was then replaced with fresh catalyst before reduction. In all cases this pretreatment increased the rate of reduction.

(12) W. Shive, W. W. Ackermann, M. Gordon, M. E. Getzendaner, and R. E. Eakin, *J. Am. Chem. Soc.*, **69**, 725 (1947).

(13) Affiliated with the Sloan-Kettering Institute.

Preparation of Hydroperoxide by the Autoxidation of 4-Vinylcyclohexene

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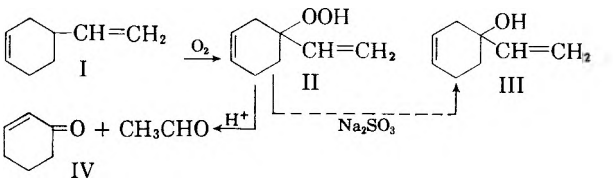
In 1911, Lebedew and Skawronskaja[1] prepared 4-vinylcyclohexene (I) by dimerizing butadiene and observed that it readily took up air. This observation is in agreement with our present knowledge concerning the autoxidation of olefins which indicates that the ease with which olefins react with molecular oxygen, forming hydroperoxide initially, depends upon the presence of reactive allylic hydrogen.[2] 4-Vinylcyclohexene has three positions alpha to a double bond where oxidation may be expected. The rate of its uncatalyzed oxidation and the isolation of hydroperoxide and alcohol fractions from the oxidation product is reported in this paper.

(1) C. B. Lebedew and H. A. Skawronskaja, *Zhur. Russ. Fiz-Khim. Obshchestva*, **43**, 1126 (1911).

(2) A. V. Tobolsky and R. B. Mesrobian, *Organic Peroxides*, Interscience Publishers Ltd., London, 1954, pp. 4–7.

The identification of II in the hydroperoxide isolated indicates the high reactivity of ring hydrogen activated by a vinyl group. Structure II



was demonstrated by acid decomposition of the hydroperoxide to 2-cyclohexenone (IV) and acetaldehyde. If the hydroperoxy function were located elsewhere on the ring, fission of the vinyl group would not be anticipated. The formation of 2-cyclohexenone is expected since it has been reported[3] that the rearrangement of 3-cyclohexenone, the first predicted product, to the conjugated ketone occurs readily under acid conditions. No evidence for the existence of other hydroperoxides was obtained.

Oxidations conducted at 90° give rise to the alcohol III which distills before the hydroperoxide and has an infrared spectra indistinguishable from it. The relative yields of alcohol and hydroperoxide obtained at different reaction times and temperatures indicate that the alcohol arises by thermal decomposition of the hydroperoxide. The same alcohol, as demonstrated by its spectra, may be prepared by reduction of the hydroperoxide with sodium sulfite, a reagent which is known to selectively reduce the hydroperoxide group to the hydroxyl group.[4] Hydrogenation of III required two moles of hydrogen but the products formed were not identified. The lack of any distinguishing differences between the spectra of II and III confirms the statement of Philpotts and Thain,[5] who studied the spectra of a series of alcohols and their corresponding hydroperoxides, that at higher molecular weights it is difficult to distinguish between an alcohol and its hydroperoxide.

The rate at which 4-vinylcyclohexene reacts with oxygen was determined at 70° and 90°. The oxidation begins immediately and the rate increases until it becomes constant and maximum at 20% reacted. The maximum rate is 1.6 times faster than that of cyclohexene under the same conditions. The rapidity of this oxidation can best be seen by comparing it to the frequently studied oxidation of cumene which has a comparable rate only when catalyzed by cobalt naphthenate. The formation of hydroperoxide was followed, as is commonly done, by iodometric analysis of the reaction solution. Only an approximate picture of the relationship between hydroperoxide formation and oxygen consumption was obtained in this way

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(4) E. H. Farmer and A. Sundralingham, *J. Chem. Soc.*, 121 (1942).

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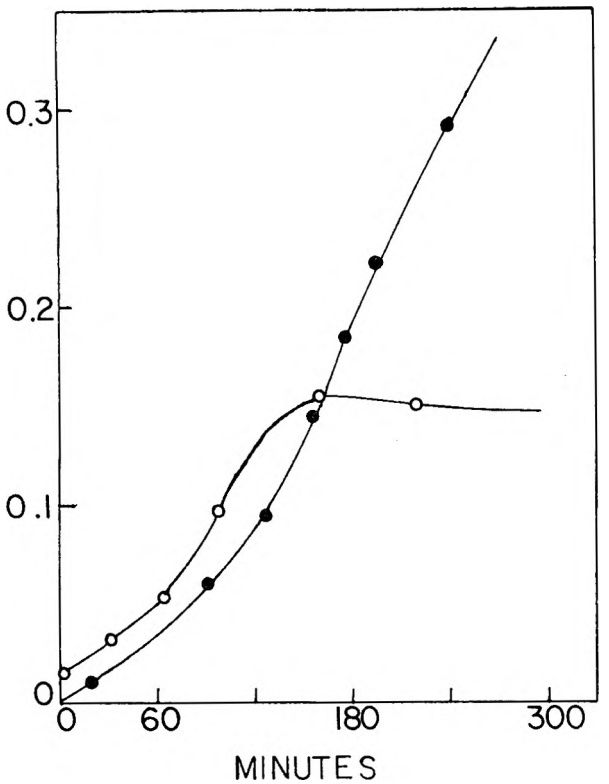

Fig. 1. Oxidation of 4-vinylcyclohexene at 90°. Closed circles, moles of oxygen reacted per mole of olefin charged; open circles, fraction of reaction mixture titrating as vinylcyclohexene hydroperoxide

(Fig. 1) since evaluation of the analytical procedure indicated it to be unreliable, probably giving low results. It is certain, however, that most of the oxygen consumed appears as hydroperoxide in the early stages of the reaction. The attainment of a steady state concentration of hydroperoxide corresponds with the attainment of a constant oxidation rate.

EXPERIMENTAL

Oxidation of 4-vinylcyclohexene. The apparatus consisted of a reaction flask fitted with a condenser, gas inlet, and an aniline point thermometer covering the appropriate temperature range. The flask was heated with a Glas-Col mantle and the temperature controlled to ±0.2° with a Thermocap relay. Stirring at over 1000 r.p.m. was provided by a Teflon covered magnetic stirring bar. Oxygen was fed into the system through a precision wet type pressure governor, a wet test meter, and a tower filled with Drierite. The exit gas passed from the outlet condenser through a Dry Ice trap, a drying tower, a carbon dioxide absorption bulb filled with Ascarite, another drying tower, a wet test meter, and an exit capillary.

A carefully cleaned 100-ml. flask was filled with 43.28 g. (0.4 mole) of redistilled Phillips "99 mole %" 4-vinylcyclohexene, n_D^{20} 1.4630. The olefin was quickly heated to 70°, rapid stirring initiated, and the oxygen admitted. Adjustment of the pressure governor and exit capillary gave an exit gas of from 8 to 9 ml./min. The oxygen absorbed was determined at frequent intervals from the difference in the inlet and exit wet test meter readings. The reaction becomes exothermic, and provisions must be made to cool the outside of the flask with air to allow the Thermocap to operate. The production of heat was not investigated but since it appeared to be somewhat greater than anticipated from work with other olefins, there is some possibility that polymerization or hydroperoxide decomposition is involved.

A plot of the oxygen consumed against time indicates that the rate gradually increases and becomes constant at approximately 600 min. at 70° and from 160 to 180 min. at 90°. The maximum rates for these temperatures in moles of oxygen absorbed/mole initial olefin, sec. are 1.4×10^{-5} and 3.4×10^{-6}, respectively.

Oxidation of cyclohexene and cumene. In the same manner, 32.85 g. (0.4 mole) of redistilled cyclohexene, n_D^{20} 1.4451, was oxidized at 70°. A constant rate of 8.7×10^{-6} was attained in approximately 450 min. The oxidation of pure cumene, n_D^{20} 1.4910, was attempted at 90° but no reaction was observed in 435 min. Negligible reaction occurred with cumene containing 2% cumene hydroperoxide as initiator in 420 min. but in the presence of 1% by weight of Nuodex cobalt naphthenate, cumene showed a maximum rate of 3.7×10^{-5} after an induction period of 120 min.

Rate of formation of hydroperoxide. The formation of hydroperoxide was followed by duplicating rate runs and removing samples for analysis at intervals. At 90°, a constant concentration of hydroperoxide was reached in 160 min. The peroxide values obtained depended on the method of analysis, the highest steady state concentration being 22% by method C and 15% by method A (see last section—values reported in this paper were obtained by A, unless otherwise indicated). The separation of a light yellow oil on the walls of the flask became perceptible at approximately the time in which the maximum hydroperoxide concentration was reached but these phenomena are not associated since the concentrations of hydroperoxide in the oil and the solution were nearly the same.

Isolation of products. (a) The reaction product from the oxidation of 108.2 g. (1.0 mole) of 4-vinylcyclohexene for 245 min. at 90° was poured off from 22.6 g. of insoluble oil and simply distilled under reduced pressure. After removal of the 4-vinylcyclohexene, 8.2 g. of distillate (46% hydroperoxide) was collected between 55 and 78° below 1 mm. Redistillation through a 1 ft. semimicro Vigreux gave 2.5 g. of alcohol at 46°/1 mm., titrating for 3.5% hydroperoxide, and 2 g. of hydroperoxide, titrating for 60% hydroperoxide, at 50–55°/0.5 mm.

(b) The oxidation product obtained by oxidizing 1189 g. (11 moles) of 4-vinylcyclohexene for 190 min. at 90° was removed from an insoluble oil coating the reaction flask, and the unreacted 4-vinylcyclohexene distilled off at 30 mm. through a 2 ft. unpacked column. After adding 0.5 g. of 2,6-di-*tert*-butyl-*p*-cresol, 255 g. of residue was transferred to a 500 ml. flask and the following fractions collected at 0.5 mm.: (1) 25–41°, 10.8 g., 2.3% hydroperoxide; (2) 41–52°, 8.9 g., 6.6% hydroperoxide; (3) 53–67°, 31 g., 23% hydroperoxide; (4) 67°, 26 g., 46% hydroperoxide (76.8% by method C); (5) 67–70°, 14.3 g., 51.9% hydroperoxide. The distillation was discontinued at this point because of decomposition evidenced by a slight rise in pressure, in spite of continuous pumping, and a sharp rise in pot temperature. The pot residue analyzed for 38% hydroperoxide. All the distillates had identical infrared spectra.

(c) Oxidation of 216.4 g. (2.0 moles) of 4-vinylcyclohexene at 90° for 22.4 hr. gave an increase in weight of 40.6 g. and resulted in the formation of approximately equal volumes of immiscible layers. Distillation gave 4 g. of water, 84.3 g. of 4-vinylcyclohexene, 38.5 g. of alcohol (6% hydroperoxide), 114.6 g. of red pot oil containing 3.9×10^{-4} mole active oxygen/g., and 14.3 g. of gray residue. A brown powder could be obtained from the red oil by taking it up in ethanol and reprecipitating with ether. The powder dissolved on warming with alkali and could be reprecipitated with acid. It could not be purified by recrystallization and became gummy on further treatment.

(d) At 50°, 432.7 g. (4.0 moles) of 4-vinylcyclohexene was oxidized for 48 hr. with an off gas of 18 ml./hr. to give an

oxidate analyzing for 9.4% hydroperoxide. Distillation gave a forerun of 383 g. of 4-vinylcyclohexene, 23 g. of hydroperoxide (68.5%) at 64–66°/0.5 mm., 20.3 g. of pot residue and 3 g. of trap residue. The hydroperoxide was fractionated in a 1-ft. semimicro Vigreux column to give 9 ml. of distillate boiling at a constant 55°/0.5 mm. with n_D^{25} 1.4951 and D_4^{20} 1.0164 and analyzing for 81% hydroperoxide. M_D is 40.9 (calculated M_D 39.2).

Reduction with sodium sulfite. To 50 ml. of a stirred 25% solution of sodium sulfite, cooled in an ice bath, was added dropwise 14.1 g. (0.1 mole) of hydroperoxide of 76.8% purity (method C). After 1 hr. the reaction was allowed to reach room temperature and stirred for 1.5 hr. more. The product was extracted with ether and dried over Drierite. After removing the ether, 10 g. of distillate was collected at 46–49°/0.5 mm. It analyzed for 5.25% hydroperoxide (method C). Its infrared spectra were superimposable on that of the starting hydroperoxide, both spectra being obtained with a Baird IR model 4-55 using a 0.03-mm. cell. Both spectra showed a band at 5.8μ indicating an estimated carbonyl impurity of less than 5%.

Acid decomposition. A solution of 14.1 g. (0.1 mole) of hydroperoxide (76.8%—method C) in 80 ml. of glacial acetic acid containing 0.16 ml. of 70% perchloric acid was allowed to stand overnight at room temperature. A slurry of 26 g. of sodium bicarbonate in 150 ml. of water was added dropwise, and the gas evolved passed through a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The precipitate formed was identified as acetaldehyde 2,4-dinitrophenylhydrazone by a mixed melting point determination. The decomposition mixture was extracted with ether and the ether washed with sodium bicarbonate and water and dried. Distillation through a Vigreux column gave 5.1 g. of ketone at 64–70°/4 mm., n_D^{20} 1.4818 and a pot residue of 5.0 g. of black tar.

The infrared spectra of the distillate showed the expected bands at 6.0μ and 6.1μ as well as a band at 5.8μ probably due to the unconjugated 3-cyclohexenone. Absorption due to hydroxyl, vinyl unsaturation, or aldehyde carbonyl (C—H stretching) was absent. The ultraviolet spectra showed the reported[3] max. 225 mμ for 2-cyclohexenone. The semicarbazone melted at 161–162° (reported m.p. 161°, 163°) after one recrystallization from water. The 2,4-dinitrophenylhydrazone after several recrystallizations from alcohol, yielded cerise crystals melting at 180–181° (rapid heating). An authentic sample of 2-cyclohexenone, prepared by oxidizing cyclohexene,[6] yielded an orange derivative melting at the reported[3] 160–161°. Its melting point was not depressed by admixture with the decomposition product derivative. Both 2,4-dinitrophenylhydrazones showed maxima in the ultraviolet at 377 mμ (ϵ = 21,000), 285 mμ and 250 mμ and a minimum at 310 mμ.

Fractionation of the ketone, from a similar experiment, through a spinning band column gave a fraction at 41°/1 mm. n_D^{25} 1.4950, which had a carbonyl equivalent weight of 99 (calculated for cyclohexenone 96) by hydroxylamine titration.[7]

Hydrogenation. Fifteen g. of alcohol, containing 6.34 m. eq. of hydroperoxide impurity, was hydrogenated at 60 lb. pressure using 170 ml. of ethanol as solvent and 0.5 g. of rhodium on alumina as catalyst. The absorption of hydrogen ceased after 0.13 mole was consumed. With 0.2 g. of platinum oxide, a total of 0.256 mole of hydrogen was used. Addition of fresh catalyst did not result in any further reduction. Compensating for the reduction of the hydroperoxide impurity, the hydrogen consumed was 0.242 mole; calculated for vinylcyclohexenol 0.240 mole.

Fractionation of the reduction product gave the following fractions after removal of the solvent: (1) 2.3 g. 100–107.5°/50 mm., n_D^{25} 1.4522; (2) 4.4 g., 107.5–111.5°/50 mm., n_D^{25} 1.4500; (3) 3.8 g., 111.5–119.5°/50 mm., n_D^{25} 1.4600.

Analysis of hydroperoxide. Approximately 0.5 g. samples of oxidate were analyzed by refluxing in isopropyl alcohol containing 1 ml. of saturated potassium iodide and titrating the iodine released with sodium thiosulfate (A). The arsenious oxide procedure gave equivalent results.[7] Other iodometric methods were checked using approximately 0.1 g. samples of distilled hydroperoxide. The variations in conditions and the percentage vinylcyclohexene hydroperoxide found for the identical liquid are: (A) 49.1%; (B) 0.5 g. powdered potassium iodide in 100 ml. isopropyl alcohol, 10 ml. acetic acid, 10 ml. acetic anhydride, reflux 30 min., 46.1%; (C) 0.5 g. powdered potassium iodide in 25 ml. acetic acid, 60° for 30 min., 76.8%; (D) as in C, dark for 120 min., 64%; (E) as in C with 1 ml. saturated potassium iodide, 51.9%. Elemental analysis of this sample assuming the remaining component to be vinylcyclohexenol gives agreement with method C. Calcd. for 76.82% $C_8H_{12}O_2$ and 23.18% $C_3H_{12}O$: C, 70.20; H, 8.93. Found: C, 70.09; H, 8.87.

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Potential Purine Antagonists. XVIII. Preparation of Some 6-Alkylthiopurines and 4-Alkylthiopyrazolo[3,4-*d*]pyrimidines[1]

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Since 6-methylthiopurine has been shown to inhibit R C carcinoma in mice,[2] a number of additional 6-alkylthiopurines have been synthesized in our Laboratory. Since antitumor activity has recently been found with various derivatives of pyrazolo[3,4-*d*]pyrimidine,[3] it seemed of interest to prepare analogous isomeric 4-alkylthiopyrazolo-[3,4-*d*]pyrimidines to see if these derivatives would possess antitumor activity.

Skinner, Shive, *et al.*[4,5] have previously reported the preparation of several 6-alkylthiopurines by alkylation of 6-purinethiol with the appropriate alkyl halide.

Recent preparation of 1-methyl-4-methylthiopyrazolo[3,4-*d*]pyrimidine[6] from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine[6] and methanethiol in a

(1) Supported in part by research grant CY-4008 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(3) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, Jr., Cancer Research, 17, 579 (1957).

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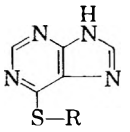
TABLE I

6-ALKYLTHIOPURINES



R	Meth. of Synth.	Recorded M.P.	M.P.	Yield, %	pH 1 λ_{max}, Mμ	pH 1 ε	pH 11 λ_{max}, Mμ	pH 11 ε	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	A	185[a]	203–204	57	225	10,800	226	10,100	46.6	4.4	31.1	46.7	4.3	31.0
					298	16,200	292	15,300						
n-C_3H_7	A	163–165[a]	184–185	61	225	9,700	224	10,400	49.4	5.2	28.8	49.6	5.6	28.9
					300	15,700	294	16,500						
iso-C_3H_7	A		243–244	43	225	9,200	227	10,900	49.4	5.2	28.8	49.6	5.2	29.1
					300	15,500	295	14,700						
$CH_2CH:CH_2$	C		173–174	74	221	10,200	226	12,300	50.0	4.2	29.1	50.0	4.2	28.9
					296	15,900	294	16,300						
n-C_4H_9	A	126–127[a]	150–151	69	225	9,400	228	11,400	51.9	5.7	26.9	52.2	5.7	26.9
					300	15,600	294	16,200						
sec-C_4H_9	C		197–198	61	225	8,700	229	9,400	51.9	5.7	26.9	52.2	5.8	27.1
					300	14,600	295	13,500						
iso-C_4H_9	C		202–203	61	226	10,000	228	12,500	51.9	5.7	26.9	51.8	5.9	27.2
					300	17,300	294	17,100						
n-C_5H_{11}	B	78–79[a]	107–108	58	226	9,300	228	11,300	54.0	6.3	25.2	54.2	6.2	24.9
					300	15,100	294	16,000						
iso-C_5H_{11}	C		124–125	63	226	9,300	228	11,300	54.0	6.3	25.2	54.2	6.0	25.4
					300	15,100	294	16,000						
n-C_6H_{13}	B	77[b]	95–96	43	226	9,400	228	12,000	55.9	6.8	23.7	55.6	7.2	23.9
					300	15,300	294	16,500						
n-C_7H_{15}	B	79–81[b]	109–110	51	226	9,500	228	13,000	57.6	7.2	22.4	57.6	7.0	22.2
					300	16,300	294	15,500						
n-C_8H_{17}	B	78–80[b]	97–98	49	226	9,600	228	14,000	59.1	7.6	21.5	59.0	7.4	21.4
					300	16,300	294	16,000						
n-C_9H_{19}	B		95–96	44	226	9,700	228	14,000	60.6	8.3	20.3	60.4	8.3	20.1
					300	16,300	294	15,500						
n-$C_{12}H_{25}$	B		92–93	47	226	9,600	228	13,000	63.9	9.4	17.5	63.7	9.4	17.4
					300	16,000	294	14,000						

[a] Ref. (4). [b] Ref. (5).

basic solution suggested that 6-alkylthiopurines might be more conveniently prepared from 6-chloropurine. This general reaction proceeded smoothly, and most of the compounds described in Table I were prepared from the corresponding alkanethiols and 6-chloropurine. The melting points for the alkylthiopurines prepared from 6-chloropurine are in general somewhat higher than those recorded for the same compounds previously prepared[7] by alkylation of 6-purinethiol. In this regard 6-ethylthiopurine was prepared by the method of Skinner *et al.*[4] and was found to melt at 203–204° and gave no depression in mixed melting point when mixed with the same compound prepared from 6-chloropurine and ethanethiol.

The 4-alkylthiopyrazolo[3,4-*d*]pyrimidines listed in Table II were prepared similarly from 4-chloropyrazolo[3,4-*d*]pyrimidine[8] and the corresponding alkanethiols. It is interesting to note that the 4-alkylthiopyrazolo(3,4-*d*]pyrimidines melt consistently lower than the alkylthiopurines of similar structure.

EXPERIMENTAL[9]

Preparation of the 6-alkylthiopurines listed in Table I. Method (A). Ten to 15 g. of the appropriate alkylthiol was added to 70 ml. of 4% potassium hydroxide. To this vigorously stirred solution was added 6 g. of 6-chloropurine,[10] and the solution was heated for 30 min. on the steam bath. At the end of this time the *p*H of the solution was adjusted to 7 with dilute hydrochloric acid and the solution chilled. The crude product was filtered and recrystallized twice from ethylacetate.

Method (B). To 70 ml. of 4% potassium hydroxide was added 8 g. of the appropriate alkylthiol and 30 ml. of dioxane. This mixture was vigorously stirred and heated at 75° for 30 min. At the end of this period 6 g. of 6-chloropurine[10] was added to the solution and the mixture was stirred and heated at 75° for an additional hour. The *p*H of the solution was adjusted to 7 with dilute hydrochloric acid, and stirring was continued for 30 min. The solution was cooled

(7) Private communication with Dr. C. G. Skinner has revealed that the melting points previously recorded (see refs. 4 and 5) are in error due to their determination on a defective melting point apparatus; see *J. Org. Chem.*, **23**, 2046 (1958).

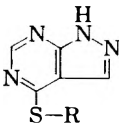
(8) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(9) All melting points were taken on the Fisher-Johns melting point apparatus and are uncorrected.

(10) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954). Purchased from Francis Earle Laboratories, Inc., Peekskill, N. Y.

TABLE II

4-ALKYLTHIOPYRAZOLO[3,4-*d*]PYRIMIDINES



R	Meth. of Synth.	M.P.	Yield, %	*p*H 1 λ_{max}, Mμ	*p*H 1 ε	*p*H 11 λ_{max}, Mμ	*p*H 11 ε	Calcd. N	Found N
C_2H_5	A	163	58	300	14,400	287	14,400	31.1	31.2
n-C_3H_7	A	107	55	300	14,500	287	15,500	28.8	28.8
iso-C_3H_7	A	116	50	300	13,900	287	14,500	28.8	28.8
n-C_4H_9	A	97–98	61	300	13,500	288	14,500	26.9	26.8
n-C_5H_{11}	B	86–87	54	301	12,400	289	10,400	25.2	24.9
n-C_6H_{13}	B	82	47	300	16,000	289	13,200	23.7	23.4
n-C_7H_{15}	B	68–69	49	301	14,000	287	14,000	22.4	22.2
n-C_8H_{17}	B	64	45	301	10,000	287	14,800	21.5	21.5

overnight and the crude product filtered, washed with ligroin, and recrystallized from an ethylacetate-heptane mixture.

Method (C). To 6 g. of 6-purinethiol,[11] dissolved in 100 ml. of 5% potassium hydroxide, was added 7 g. of the appropriate alkyl iodide. The mixture was refluxed and stirred until only one phase was present. The *p*H of the solution was adjusted to 7 with dilute hydrochloric acid and the solution cooled. The crude product was filtered, washed with ligroin, and thoroughly dried. The dried product was placed in the thimble of a soxhlet extractor and extracted continuously with benzene from 4 to 10 hr. The benzene extract was cooled and filtered and the product recrystallized from an ethylacetate-heptane mixture.

Preparation of the 4-alkylthiopyrazolo[3,4-d]pyrimidines listed in table II. Method (A). This method is essentially that of method (*A*) used for the preparation of the 6-alkylthiopurines. The only change in procedure was that 4-chloropyrazolo [3,4-*d*]pyrimidine[8] was employed instead of 6-chloropurine. The crude product was recrystallized from an ethylacetate-heptane mixture.

Method (B). This method is similar to that of method (*B*) above using 4-chloropyrazolo[3,4-*d*]pyrimidine[8] instead of 6-chloropurine. 4-Octylthiopyrazolo[3,4-*d*]pyrimidine was recrystallized from *n*-heptane rather than a mixture of ethylacetate and *n*-heptane.

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(11) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

Use of Acetone Dimethyl Acetal in Preparation of Methyl Esters

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When an ester is prepared by the reaction of an alcohol with an acid, the reaction is usually driven to completion by removing the water as an azeotrope with an inert solvent. In the preparation of methyl esters the use of an inert solvent which forms an azeotrope with water is unattractive because of the low water content of azeotropes which boil below methanol. In the preparation of dimethyl oxalate, Bowden[1] used 0.65 mole of concentrated sulfuric acid per mole of oxalic acid. The large amount of sulfuric acid apparently acted as a catalyst and also as a drying agent for the reaction. Clinton and Laskowski[2] reported that "the use of either methylene dichloride or ethylene dichloride as a solvent removes the necessity for continuous drying and gives very high yields of methyl esters." However, in their procedure for each mole of organic acid present there was used three moles of methanol and 300 ml. of solvent.

We have found that by using acetone dimethyl acetal, methyl esters can be prepared conveniently in nearly quantitative yields. The primary function of the acetal appears to be that of a water scavenger and the preparation can be represented by the following two reactions:

$$RCOOH + CH_3OH \xrightarrow{H^+} RCOOCH_3 + H_2O$$

$$H_2O + (CH_3)_2C(OCH_3)_2 \longrightarrow 2CH_3OH + CH_3\overset{\overset{O}{\|}}{C}CH_3$$

For each mole of water formed during the esterification reaction, two moles of methanol are introduced into the reaction solution by the hydrolysis of the acetone dimethyl acetal. As a result the process is self-accelerating. When methanol is present in the initial reaction mixture in excess of 20 mole % of the carboxylic acid groups present, the reaction rate is high throughout the preparation. In the absence of methanol, acetone dimethyl acetal reacts very slowly, if at all, with a carboxylic acid at temperatures up to 75°. (The acetone dimethyl acetal will crack to isopropenyl methyl ether and methanol in the presence of a

(1) E. Bowden in *Org. Syntheses*, Coll. Vol. II, 414 (1943).
(2) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, 70, 3135 (1948).

strong acid esterification catalyst as the temperature is raised above 65 to 75°.)

When acid hydrates such as oxalic acid dihydrate are to be esterified, no methanol is needed to initiate the reaction as the acetone dimethyl acetal is readily hydrolyzed by the water of hydration. To insure complete conversion of the acid, the amount of acetone dimethyl acetal used should be in slight mole excess (up to 10%) of the total water present and/or expected. The advantages of this method for preparing methyl esters are: (1) there is no need for a water azeotrope trap, (2) a high reaction rate is maintained during the entire esterification reaction, (3) acid hydrates can be readily esterified, and (4) the acid is completely converted to its methyl ester.

EXPERIMENTAL

Effect of acetone dimethyl acetal on the reaction rate during esterification. In Fig. 1 the results of four experiments on the

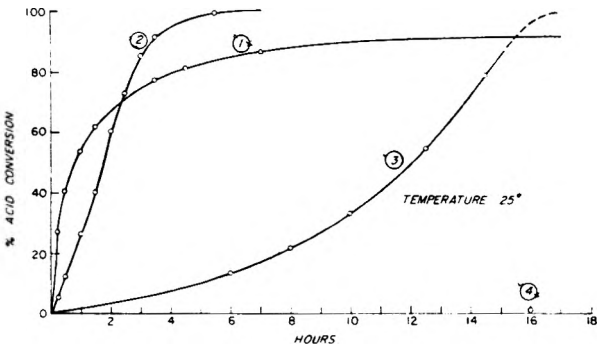

Fig. 1. Rate of esterification of propionic acid.

Moles of	1	2	3	4
Propionic acid	0.25	0.25	0.25	0.25
Methanol	0.75	0.25	0.075	0.00
Acetone dimethyl ketal	0.00	0.25	0.25	0.25
Hydrogen chloride	0.006	0.006	0.006	0.006

esterification of propionic acid are plotted. The quantity of each reactant used is as given plus sufficient anhydrous dioxane to make the total volume in each experiment 100 ml. The unreacted propionic acid was determined periodically by titrating an aliquot with standard ethanolic sodium hydroxide solution.

In experiment 1 the initial reaction rate was high but soon decreased and finally reached equilibrium where 94% of the propionic acid was converted. In experiment 2, two thirds of the methanol was present as a part of the acetone dimethyl acetal. The initial rate of this reaction was lower than in experiment 1; however, a high rate was maintained through almost all of the reaction period. In the early hours of experiment 3 the rate was low because the concentration of methanol was low. As the esterification proceeded, the concentration of the methanol increased as a result of the hydrolysis of the acetone dimethyl acetal and this effected a corresponding increase in the reaction rate. At 20 hr. all of the propionic acid in experiment 3 was converted and although no checks were made between 14 and 20 hr., the course of the reaction was probably as indicated. After 16 hr. there was no detectable conversion of the propionic acid in experiment 4. At 50 hr., 5% of the propionic acid was converted and from that point the reaction rate increased and all of the acid was converted. This experiment was repeated several times and each time there was essentially no reaction until 35 to 50 hr. and then there was a rapid conversion of the propionic acid. No special effort was made to exclude all atmospheric moisture or to use acetone dimethyl acetal that was absolutely free of methanol. Trace amounts of methanol and/or water would act as initiators for the reaction.

Esterification of dehydrated castor oil acids. A mixture of 200 ml. of dehydrated castor oils (1 ml. = 30.4 ml. $N/10$ NaOH), 0.60 mole of acetone dimethyl acetal, 0.3 mole of methanol and 0.012 mole of HCl was allowed to stand at room temperature. When checked 39 hr. later, more than 99% of the acids were esterified.

Preparation of dimethyl adipate. Four moles (585 g.) of adipic acid was added to a solution of 5 g. of *p*-toluenesulfonic acid dissolved in 5 moles (200 ml.) of methanol. This mixture was stirred in a 2 l. flask and maintained at 40° to 60°. As the reaction progressed, acetone dimethyl acetal was added in increments. By the end of 0.5 hr., 200 ml. had been added, by the end of 1 hr., 600 ml. total had been added (at this point all adipic acid was in solution), and by the end of 1.5 hr., a total of 1 l. (8 moles) of the acetone dimethyl acetal had been added. At the end of 2 hr. only 10% of the acid remained unreacted. After 4 hr. the reaction was 99% complete. One half of the crude solution was then distilled at a rate such that by the end of 3 hr. all of the acetone and methanol had been removed. This left a 98.8% yield of crude, straw colored dimethyl adipate, n_D^{25} 1.4275. On further distillation a 94% yield of pure dimethyl adipate (n_D^{25} 1.4263; b_{10}, 109°C.; lit.[3] n_D^{20} 1.4281; b_{20}, 122°C.) was recovered.

A similar experiment in which all of the reactants were mixed at one time and left overnight at room temperature (with stirring) resulted in 100% conversion of the adipic acid.

Preparation of dimethyl oxalate. One mole of oxalic acid dihydrate, 2 g. of *p*-toluenesulfonic acid and 2 moles of acetone dimethyl acetal were combined with stirring. Heat was applied so that a temperature of 50–55° was maintained. After 1.25 hr. another mole of acetone dimethyl acetal was added. After an elapsed reaction time of 2 hr. the final mole of acetone dimethyl acetal (4 mole total) was added. The reaction was 98% complete after 5 hr. at which time the methanol and acetone were distilled until only 175 ml. of the product–methanol solution remained. By cooling, filtering out the white crystalline product, and reworking the mother liquor, 107 g. of dimethyl oxalate (91% theory), m.p. 51–53° (lit.[1] m.p. 52.5–53.5°), was recovered.

Acknowledgment. The authors wish to thank Mr. Bernis Self for his aid in these experiments.

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(3) A. I. Vogel, *J. Chem. Soc.*, 333–341 (1934).

Heterocyclic Vinyl Ethers XIV. Photochemical Dimerization of 2-Nitrobenzo-1,4-dithiadiene and Reactions of Benzo-1,4-dithiadiene with Mercuric Salts[1]

William E. Parham,[2] Paul L. Stright, and William R. Hasek

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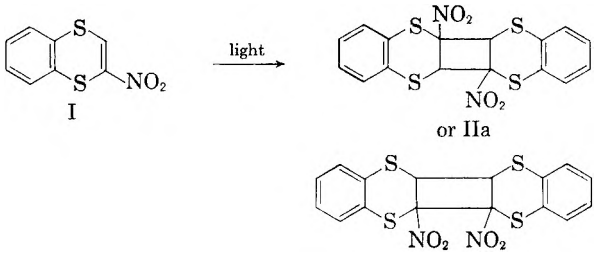
When 2-nitrobenzo-1,4-dithiadiene (m.p. 105–107°), which is red in color, is exposed to light, it is

converted into a yellow solid (69% yield) which melts at 170.5–172°. This solid has been shown to be a dimer of I by elementary analysis and molecular weight determinations.



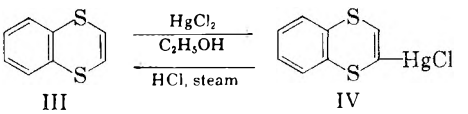
Oxidation of the dimer with potassium permanganate gave potassium benzene-*o*-disulfonate, characterized by its conversion into benzene-*o*-disulfonyl chloride, establishing that the nitro function remained attached to the more aliphatic carbon atoms during the dimerization.

Comparison of the infrared spectrum of I with that of the dimer showed that an increase in frequencies of the characteristic $-NO_2$ absorption accompanied dimerization (from 1515 to 1553 cm.$^{-1}$, and from 1320 to 1332 cm.$^{-1}$, respectively). These results suggested that the nitro group became less conjugated as a consequence of the dimerization,[3] since it has been previously observed that unconjugated nitro groups absorb at higher frequencies than do α,β-unsaturated nitro groups (compare nitrobenzene, 1535 and 1350 cm.$^{-1}$ with 1-nitropropane, 1553 and 1385 cm.$^{-1}$). The ultraviolet absorption spectra of I and that of the dimer also suggested that a decrease in conjugation of the nitro function accompanied dimerization. Thus, the monomer (I) showed two absorption maxima (235 mμ and 285 mμ), whereas the dimer showed only one at 239 mμ.

These data are consistent with the formulation of the dimer of I as the cyclobutane derivative IIa or IIb. Photochemical dimerizations of this type are well documented,[4] and cyclobutane structures have been established in several cases.[5] Structure IIa seems probable in view of the product reported for the photochemical dimerization of β-nitrosytrene.[5b]

Thiophene[6] and thianaphthene[7] are readily mercurated by reaction with mercuric chloride in ethanol or with mercuric acetate in ethanol and acetic acid. We have now examined the reaction of benzo-1,4-dithiadiene (III) with these reagents, employing conditions which give high yield of mercury derivatives with the thiophene analogs.

When benzo-1,4-dithiadiene (III) was treated with one equivalent of mercuric chloride in ethanol, there was obtained a 79% yield of a monomercurated derivative (m.p. 127–130°) which is thought to be 2-chloromercuribenzo-1,4-dithiadiene (IV).



Although the position of the attached chloromercury derivative in IV was not established, it was assigned the two position by analogy with other electrophilic substitutions reported for benzo-1,4-dithiadiene.[8] That the product IV still retained the benzo-1,4-dithiadiene system intact was shown by recovery of III in 90% yield when IV was treated with hydrochloric acid and steam. The identity of recovered III was established by comparison of its ultraviolet spectrum with that of authentic III, and by conversion of the recovered product into 2-nitrobenzo-1,4-dithiadiene (I) by nitration.

The reaction of I with mercuric acetate in ethanol or in 50% aqueous acetic acid was more complex, no pure products were obtained. When I was treated with mercuric acetate in ethanol at room temperature, there was obtained an amorphous product which partially decomposed on attempted recrystallization from ethanol with the formation of free mercury. Elemental analysis of the high melting insoluble products, obtained using a variety of conditions, suggested that the expected products were not present in significant amounts.

EXPERIMENTAL

Photodimerization of 2-nitrobenzo-1,4-dithiadiene. 2-Nitrobenzo-1,4-dithiadiene (0.40 g., 1.89 m.moles, m.p. 105–107°) was exposed to sunlight for 15 days, during which time the color changed from red to light brown. The resulting brown solid was extracted with several portions of benzene, and the insoluble residue was discarded. The combined benzene extract was evaporated, and the resulting light tan solid was triturated with ethanol (two 1-ml. portions) to remove any unchanged starting material. The remaining tan product (0.358 g., 88%, m.p. 168–170° dec.) was recrystallized from ethanol giving 0.274 g. (69%) of pale yellow needles melting at 170.5–172°.

Anal. Calcd. for $C_{16}H_{10}O_4S_4N_4$: C, 45.48; H, 2.39; N, 6.63. Found: C, 45.44; H, 2.52; N, 6.48.

(1) This work was supported by the Office of Ordnance Research, U. S. Army, Contract No. DA-11-022-Ord-2616.

(2) Presented in part at the 15th National Organic Symposium of the American Chemical Society, Rochester, N. Y., June 1957.

(3) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341, 1955. See also L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., 1954, p. 250.

(4) *Cf.* A. Mustafa, *Chem. Rev.*, **51**, 1 (1952).

(5) *Cf.* (a) dimer of stilbene, J. D. Fulton and J. D. Dunitz, *Nature*, **160**, 161 (1947), (b) dimer of β-nitrostyrene, D. B. Miller and H. Shechter, paper 137 presented before the Organic Division of the American Chemical Society, San Francisco, April 13–18, 1958.

(6) J. Volhard, *Ann.*, **267**, 172 (1892); W. Steinkopf and A. Killingstad, *Ann.*, **532**, 288 (1937).

(7) F. Challenger and S. A. Miller, *J. Chem. Soc.*, **59**, 893 (1937).

(8) W. E. Parham, T. M. Roder, and W. R. Hasek, *J. Am. Chem. Soc.*, **76**, 4957 (1954).

The ultraviolet absorption spectrum of this product, determined in ethanol solution, showed 239 mμ max. (ε 25,300). The infrared spectrum showed characteristic[3] NO_2 absorption at 1332 and 1553 cm.$^{-1}$ These values compare with 235 mμ max. (ε 14,700), 285 mμ max. (ε 8030), and NO_2 absorption at 1320 and 1515 cm.$^{-1}$, for the monomer I.

The molecular weight of the dimer was determined by the freezing point depression method using benzene and nitrobenzene as the solvent. The product was relatively insoluble in benzene.

Calcd. M.W. 422. Found (average of three determinations each): in benzene, 448; in nitrobenzene, 406.

Oxidation of dimer with potassium permanganate. The oxidation of the dimer (129 mg.), with subsequent conversion of the resulting potassium benzene disulfonate to benzene-*o*-disulfonyl chloride, was carried out by a procedure previously described using 2-nitrobenzo-1,4-dithiadiene.[8] The yield of pure benzene-*o*-disulfonyl chloride (m.p. and mixture m.p. 145–146°) was 52 mg. (31%).

Chlomercuration of Benzo-1,4-dithiadiene. Mercuric chloride (1.80 g., 0.0076 mole) was added to a solution of benzo-1,4-dithiadiene[8] (1.10 g., 0.0066 mole) in 95% ethanol, and the resulting solution was heated at the reflux temperature for 1 hr. Water (35 ml.) was added to the cool reaction mixture, and the resulting pale yellow solid (m.p. 125–130° with previous softening at 100°) was recrystallized from ethanol-water. The light yellow needles that resulted (2.10 g., 79% yield) melted at 127–130°.

Anal. Calcd. for $C_6H_5S_2ClHg$: C, 23.94; H, 1.26. Found: 24.23; H, 1.74.

Hydrolysis of ε-chloromercuribenzo-1,4-dithiadiene. A mixture containing IV (0.919 g., 0.00229 mole), concentrated hydrochloric acid (5 ml.), and water (20 ml.) was distilled with steam. The yellow oil in the distillate was recovered by ether extraction, and was shown to be benzo-1,4-dithiadiene (0.341 g., 90% yield, n_D^{25} 1.6706) by comparison of its ultraviolet spectrum with authentic III,[8] and by its conversion into 2-nitrobenzo-1,4-dithiadiene (m.p. and mixture m.p. 105–107°).

Reaction of benzo-1,4-dithiadiene with mercuric acetate. (*A*) A solution of benzo-1,4-dithiadiene (1.00 g., 0.006 mole), mercuric acetate (4.80 g., 0.0151 mole), glacial acetic acid (5 drops), ethanol (30 ml.), and water (10 ml.) was heated at the reflux temperature for 5 hr. It was noted that considerable free mercury formed in the reaction. The mixture of yellow amorphous solid and free mercury (3.35 g.) was collected by filtration; the high melting (>300°) yellow solid was insoluble in all common solvents employed, and no method was found to remove all of the free mercury.

(*B*) A mixture identical to that described in A was heated for 30 min. No free mercury was noted, and there was obtained 1.78 g. of yellow solid. This material was insoluble in all solvents tested, and it did not melt at 300°; however, the material changed from orange to pink to brown during the attempted melting.

Anal. Found: C, 13.61; H, 1.15.

(*C*) A solution of III (1.00 g., 0.0060 mole), mercuric acetate (2.10 g., 0.0066 mole), glacial acetic acid (5 drops), ethanol (50 ml.), and water (15 ml.) was allowed to stand for 4 days at room temperature. The fine pale yellow solid (1.01 g.) was isolated by centrifugation. This material underwent a series of color changes, orange to pink to brown, when heated, and melted at 212–214°.

Anal. Found: C, 16.72; H, 1.57.

Attempts to purify this material by recrystallization from ethanol were unsuccessful because of its partial decomposition into free mercury.

(*D*) A mixture containing III (2.00 g., 0.0120 mole), mercuric acetate (4.03 g., 0.0126 mole), and 50% aqueous acetic acid (30 ml.) was stirred for 5 hr. at 45–50°. The resulting gummy solid which precipitated was soluble in acetic acid; however, when it was reprecipitated by the addition of water, the resulting product was insoluble in all solvents tried. A sample of this material was triturated with chloroform, benzene, and finally twice with hot glacial acetic acid. The light brown solid showed no change when heated to 300°.

Anal. Calcd. for $C_{12}H_{10}O_4S_2Hg_2$: C, 21.08; H, 1.47. Found: C, 21.90; H, 0.90.

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Synthesis of Cycloheptatriene

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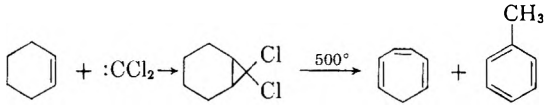
Several methods involving ring expansions are available for the synthesis of 1,3,5-cycloheptatriene (II). In the classical route,[1] the intermediate cycloheptanone is obtained by ring expansion of cyclohexanone. A more convenient preparation of cycloheptatriene is the irradiation by ultraviolet light of a solution of diazomethane in benzene.[2] In a third synthesis,[3] the solvolysis of the methanesulfonate of bicyclo[3.2.0]hept-2-en-6-ol was found to give a 50% yield of cycloheptatriene. More recently, II has been obtained by the thermal isomerization of bicyclo[2.2.1]heptadiene.[4]

A new two-step route to cycloheptatriene has now been discovered. It involves the preparation of 7,7-dichlorobicyclo[4.1.0]heptane (I), which can be obtained in 59% yield from dichlorocarbene and cyclohexene,[5] and its pyrolysis to a mixture of cycloheptatriene and toluene. At 500°, a 57% yield of a mixture of toluene (65%) and cycloheptatriene (35%) is obtained. The resulting solutions may be utilized to prepare derivatives of II, including tropylium bromide and Diels-Alder adducts.



I II

The effect of varying the temperature and residence time in the pyrolysis of I has not been ex-

(1) (a) R. Willstatter, *Ann.*, **317**, 204 (1901); (b) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

(2) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **72**, 2305 (1950); **73**, 828 (1951); **75**, 297 (1953); W. von E. Doering and L. H. Knox, U.S. Patent **2,647,081** (1953).

(3) (a) H. L. Dryden, Jr., *J. Am. Chem. Soc.*, **76**, 2841 (1954); (b) H. L. Dryden, Jr., and B. E. Burgert, *J. Am. Chem. Soc.*, **77**, 5633 (1955).

(4) (a) J. S. Chirtel and W. M. Halper, U.S. Patent **2,754,337** (1956); (b) Shell Chemical Corp., 50 West 50th Street, New York 20, N. Y., Technical Information Bulletin, *Laboratory Preparation of Cycloheptatriene from Bicycloheptadiene*, June 1956; (c) W. G. Woods, *J. Org. Chem.*, **23**, 110 (1958).

(5) W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

amined. Since it has been shown[4c] that cycloheptatriene can be almost quantitatively converted to toluene at 478°, a study of these variables might lead to improved yield of cycloheptatriene from I.

Related ring expansions resulting from reactions of dichlorocarbene have been reported and references to these are given by Skell and Sandler.[6]

It has been found that dichlorocarbene can be conveniently generated in anhydrous systems by reaction of chloroform with commercially available sodium methoxide in place of potassium *t*-butoxide. The reaction is carried out at 60–70° by adding solid sodium methoxide portionwise to a mixture of chloroform and carbene acceptor, or chloroform may be added dropwise to a slurry of sodium methoxide and the acceptor. With less available olefins, nonreactive diluents such as benzene may be used to provide fluid reaction mixtures. Although the stoichiometry of the reaction has not been examined in detail, titration of several reaction mixtures gave values consistent with the reaction of two moles of base with one mole of chloroform.

EXPERIMENTAL

7,7-Dichlorobicyclo[4.1.0]heptane from cyclohexene, chloroform, and sodium methoxide. In a dry flask connected to an auxiliary flask by large-bore rubber tubing and equipped with a stirrer, thermometer, and reflux condenser fitted with a calcium chloride drying tube, there was placed 400 ml. of purified cyclohexene and 40 ml. (0.5 mole) of reagent grade chloroform. The solution was heated to 65–70° and commercial sodium methoxide[7] was added portionwise from the auxiliary flask. The reaction was exothermic and the temperature was maintained between the above limits by intermittent cooling. A total of 54 g. (1 mole) of base was added over 2 hr. The mixture was then stirred at 65–70° for an additional 30 min. and finally was poured on ice water. The organic phase was separated, washed three times with water, and dried over anhydrous magnesium sulfate. Titration of all of the aqueous layers indicated only 0.012 mole of base remaining at the end of the reaction. Distillation of the organic phase gave 31 g. (38%) of 7,7-dichlorobicyclo-[*4.1.0*]heptane, b.p. 84–88° (18 mm.). The infrared spectrum was in agreement with that reported.[5]

Cycloheptatriene.[8] A pyrolysis tube 1¾ in. in diameter, containing a 5-in. section packed with glass tubing, was heated to an internal temperature of 490°. Over a period of 2.5 hr., 75 g. (0.455 mole) of 7,7-dichlorobicyclo[4.1.0]heptane was dropped into the tube. During this time the internal temperature was maintained between 490–520°, and a slow stream of nitrogen was also passed through the tube. Distillation of the pyrolysis product through a small ring-packed still at atmospheric pressure gave 24 g. of liquid, boiling over the range 107–110°, n_D^{25} 1.4970–1.5030. This corresponds to 57% of theory for C_7H_8. The mixture contained no halogen and reacted with 2% potassium permanganate and with bromine in carbon tetrachloride. A comparison of the infrared spectrum of the mixture with those of toluene and cycloheptatriene showed the mixture to consist of approximately 65% toluene and 35% cycloheptatriene. Quantitative hydrogenation[9] in 95% ethanol with PtO_2 catalyst gave values of 0.0217 and 0.0212 gram of hydrogen per gram of mixture. On the basis of the unsaturation being due to cycloheptatriene, the average hydrogenation value indicates the mixture to contain 33% cycloheptatriene.

A Diels-Alder adduct was prepared by mixing 1 g. of maleic anhydride and 2.9 g. of the cycloheptatriene-toluene mixture in 10 ml. of xylene. After refluxing for 12 hr. the toluene and xylene were removed under vacuum. The white residue melted at 94–98°, and after crystallization from chloroform melted at 99–101°, wt. 0.92 g. (48%). A further crystallization from hexane raised the melting point to 102–104°, reported m.p. 102–104°.[1b]

The mixture was further characterized by conversion to tropylium bromide.[10] Eleven grams of the C_7H_8 mixture (assumed to contain 30% cycloheptatriene) diluted with 30 ml. of carbon tetrachloride was cooled in an ice bath and a solution of 6.45 g. of bromine in 30 ml. of carbon tetrachloride was then added slowly. The solvents were removed under vacuum and the solid residue heated at 70° (1–4 mm.) for 9 hr. The residue was washed with ether and acetone to give 0.8 g. (13%) of tropylium bromide, m.p. 198–200° (dec.), reported m.p. 198–200° (dec.).[10]

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A Synthesis for *p*-Dimethylaminobenzoylformamides and Some of Their Reactions

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Staudinger and Stockmann[2] have shown that oxalyl chloride reacts readily with dimethylaniline to yield *p*-dimethylaminobenzoylformyl chloride (I). These authors showed also that treatment of this acid chloride, without isolation, with aniline gave the corresponding anilide.

We have found that treatment of the acid chloride (I) with aliphatic or cycloaliphatic secondary amines leads to the corresponding *p*-dimethylaminobenzoylformamides (II) in good over-all yield.

The secondary amines used were dimethylamine, diethylamine and *N*-methylpiperazine. The over-all yield for the two steps varied from 45% to 70%. The reactions may be carried out conveniently by adding one mole of oxalyl chloride to two moles of dimethylaniline in ether at ice bath temperatures followed by an excess of the amine. The amides are separated by filtration and purified by recrystallization.

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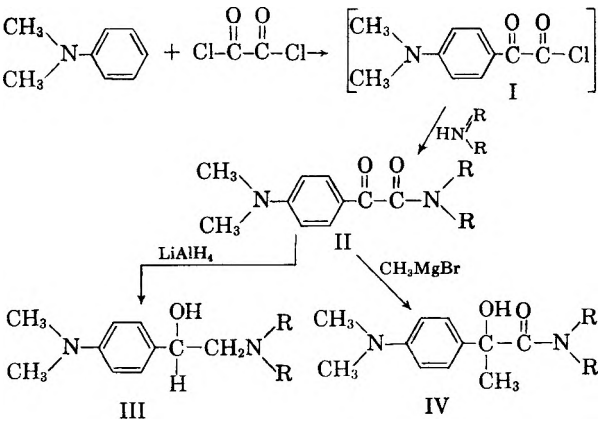
(2) H. Staudinger and H. Stockmann, *Chem. Ber.*, **42**, 3485 (1909).



Treatment of the amides II with lithium aluminum hydride gave the corresponding amino alcohols III in very good yield. These were isolated either in the form of the free base if a solid, or as the *dihydrochlorides*. Treatment of one of the amides, namely *N,N*-dimethyl-*p*-dimethylaminobenzoylformamide (II, R = CH_3), with an excess of methylmagnesium bromide in a benzene-ether solution gave *p*-dimethylamino-*N,N*-dimethylatrolactamide (IV) in 79% yield.

EXPERIMENTAL[3,4]

N,N-Dimethyl-p-dimethylaminobenzoylformamide. To a stirred solution of 38.1 g. (0.3 mole) of oxalyl chloride in 250 ml. of anhydrous ether cooled in an ice bath was added dropwise over the course of about 30 min., a solution of 72.7 g. (0.6 mole) of *N,N*-dimethylaniline in 250 ml. of anhydrous ether. The dark brown solution containing much solid was allowed to stand overnight in a refrigerator at 0–5°. To the reaction mixture (again cooled in an ice bath) was added 100 ml. of dimethylamine over the course of about 15 min. Stirring was continued at ice bath temperature for 0.5 hr. and at room temperature for 1.5 hr.

To the mixture was added *cautiously* a slurry of 50.4 g. of sodium bicarbonate in 100 ml. of water. The mixture was stirred well and filtered. The green solid was dissolved in chloroform and the chloroform solution washed with water. Evaporation of the chloroform gave a solid which after recrystallization from benzene–petroleum ether (b.p. 85–100°) with charcoal decolorization consisted of light yellow platelets melting at 136–137°; weight 44.6 g. (68%).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.26; H, 7.08: N, 13.01.

N,N-Diethyl-p-dimethylaminobenzoylformamide. The substitution of 70 ml. of diethylamine in the above procedure gave 33.4 g. (45%) of yellow slender prisms melting at 102–103° after recrystallization from a benzene-cyclohexane mixture (2:5).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 68.07; H, 8.16; N, 10.95.

1-Methyl-4-p-dimethylaminobenzoylformylpiperazine. The procedure described above for *N,N*-dimethyl-*p*-dimethylaminobenzoylformamide was employed using 125 ml. of *N*-methylpiperazine. There was obtained 57.5 g. (70%) of material melting at 117–117.5° and consisting of light yellow needles after recrystallization from a petroleum ether–benzene mixture (5:1).

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.18; H, 7.36; N, 14.99.

N,N-Dimethyl-β-hydroxy-p-dimethylaminophenethylamine dihydrochloride. To a mixture of 1.9 g. (0.05 mole) of lithium aluminum hydride in 75 ml. of anhydrous ether was added dropwise a solution of 5.5 g. (0.025 mole) of *N,N*-dimethyl-*p*-dimethylaminobenzoylformamide in 110 ml. of dry tetrahydrofuran. The reaction mixture was heated under reflux for 9 hr. and decomposed by the successive addition of 2 ml. of water, 2 ml. of a 10% sodium hydroxide solution, and 2.5 ml. of water. The reaction mixture was filtered and the solid washed well with ether. The ethereal filtrate was dried over anhydrous magnesium sulfate and the ether and tetrahydrofuran removed by distillation. The oily residue was redissolved in anhydrous ether and the *dihydrochloride* precipitated with gaseous hydrogen chloride. There was obtained 6.29 g. (90%) of colorless material melting at 124.5–125°. Recrystallization from ethanol gave material possessing the same melting point.

Anal. Calcd. for $C_{12}H_{20}N_2O.2HCl$: C, 51.25; H, 7.89; Cl, 25.21; N, 9.96. Found: C, 51.60; H, 8.19; Cl, 24.94; N, 10.07.

N,N-Diethyl-β-hydroxy-p-dimethylaminophenethylamine dihydrochloride was prepared in a similar manner from 6.2 g. (0.025 mole) of *N,N*-diethyl-*p*-dimethylaminobenzoylformide. There was obtained 6.5 g. (85%) of colorless prisms melting at 117.5–118° after recrystallization from anhydrous ethanol.

Anal. Calcd. for $C_{14}H_{24}N_2O.2HCl$: C, 54.36; H, 8.47; N, 9.06; Cl, 22.93. Found: C, 54.14; H, 8.17; N, 8.80; Cl, 22.83.

1-Methyl-4-(β-hydroxy-p-dimethylaminophenethyl)piperazine. The procedure described above for *N,N*-dimethyl-β-hydroxy-*p*-dimethylaminophenethylamine dihydrochloride was employed using 6.88 g. (0.025 mole) of 1-methyl-4-*p*-dimethylaminobenzoylformylpiperazine dissolved in 35 ml. of tetrahydrofuran. After hydrolysis of the reaction mixture and removal of the inorganic salts by filtration, a white solid began to precipitate in the organic mother liquors. This was removed by filtration. Additional material was obtained by stirring the inorganic salts with several portions of benzene and removing the benzene by distillation. The total yield of material was 4.05 g. (62%) melting at 126–126.5°. Recrystallization from petroleum ether (b.p. 85–100°) raised the melting point to 127–127.5°. No additional material could be obtained from the ether tetrahydrofuran mother liquors.

Anal. Calcd. for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.96. Found: C, 68.61; H, 9.81; N, 16.23.

p-Dimethylamino-N,N-dimethylatrolactamide. Sixty ml. of an ethereal methyl magnesium bromide solution (Arapahoe Chemical Co.) containing 0.15 mole of CH_3MgBr was added slowly to a stirred solution of 15 g. (0.0682 mole) of *N,N*-dimethyl-*p*-dimethylaminobenzoylformamide in 600 ml. of anhydrous benzene. After addition was started, the mixture was cooled in an ice bath. When addition was complete the ice bath was removed and the mixture stirred at room temperature for 1.5 hr. The mixture was decomposed by the addition of a 20% ammonium chloride solution. Solid separated in the mixture upon standing. This was removed by filtration and the filtrate transferred to a separatory funnel and the ether-benzene layer separated. Concentration and cooling of this solution gave additional solid material. The product after recrystallization from isopropyl alcohol melted at 144–146°; weight 12.68 g. (79%).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.21; H, 8.28; N, 12.14.

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(3) All melting points and boiling points are uncorrected for stem exposure.

(4) We wish to thank Mr. William Struck and Dr. James Johnson and their co-workers of the physical and analytical chemistry department of these laboratories for microanalytical and spectral data. Our thanks are due especially to Mr. Albert Lallinger for technical assistance.

cis-2,6-*p*-Dioxanedimethanol

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During a study of derivatives of *p*-dioxane, *cis*-2,6-*p*-dioxanedimethanol (I) and some of its derivatives have been prepared. Structures and configurations of these compounds were proved by relating them to 2,6-derivatives of *p*-dioxane whose configurations were proved by Summerbell and Stephens.[1]

Allyl ether was converted to 2,6-bis(iodomethyl)-*p*-dioxane (II) and the cis form was isolated by fractional crystallization.[1,2] Under mild conditions *cis*-II is converted by silver acetate to *cis*-2-acetoxymethyl-6-iodomethyl-*p*-dioxane (III) and under more severe conditions to *cis*-2,6-bis-(acetoxymethyl)-*p*-dioxane (IV), paralleling the observations of Summerbell and Stephens[3] on the corresponding 2,5-isomers. As would be expected III can also be converted to IV. Transesterification by the procedure of Summerbell and Stephens[3] gave *cis*-2,6-*p*-dioxanedimethanol (I) from IV.

The configurations of I, III, and IV were shown to be *cis* by oxidizing them to *cis*-2-6-*p*-dioxanedicarboxylic acid (V) with nitric acid.[1] Mixed melting points of the oxidation products with authentic V showed no depression.

EXPERIMENTAL

All melting points are uncorrected. No effort was made to investigate the conditions required for obtaining optimum yields, since the amounts obtained the first time were sufficient for the purposes for which the compounds were prepared.

cis-2-Acetoxymethyl-6-iodomethyl-p-dioxane (III). A solution of 200 g. of *cis*-2,6-bis(iodomethyl)-*p*-dioxane (m.p. 93–95°) in 300 ml. of benzene was refluxed with 210 g. of freshly prepared silver acetate for 43 hr. The mixture was filtered and the filtrate was concentrated by distilling the solvent. Addition of ethanol precipitated some II which was filtered off. An equal volume of methanol was added to the filtrate, and chilling gave 57 g. of solid, m.p. 40–42°. Fractional crystallization first from water and then from a mixture of petroleum ether and ethyl ether yielded III, m.p. 43.5–44.5°.

Anal. Calcd. for $C_8H_{13}IO_4$: C, 32.01; H, 4.37; I, 42.30. Found: C, 32.12, 31.89; H, 4.55, 4.50; I, 42.31, 42.18.

Some starting material (II) and a mixture of m.p. 38° were obtained by further work up of the solutions. Only 16 g. of purified III was obtained, but quantitative recovery was not attempted. However, infrared examination of the impure fractions and recovery of starting material indicated about 50% conversion and 70% yield. Oxidation of III with nitric acid gave V, m.p. and mixed m.p. with authentic V, 179–180°.

cis-2,6-bis(Acetoxymethyl)-p-dioxane (IV). Using a suspending medium of higher boiling point and a greater excess of silver acetate than in the preparation of III, a xylene-toluene solution of 107 g. of II was refluxed for 24 hr. with 330 g. of silver acetate. The silver salts were removed and the filtrate was freed of solvent by distillation, leaving 88 g. of residue. This was distilled at the full vacuum of the pump (about 0.5 mm.) giving 72 g. of distillate in the boiling range 115–117° and a small liquid residue. The distillate contained 33.1% iodine, and on standing in the refrigerator it partially crystallized. The crystals were filtered off, purified, and further separated into two components identified as III and a small amount of II. The oily liquid filtrate, 41 g., completely solidified at 0° and melted from about 10° to 27°. It was believed to be a mixture of II, III, and IV.

This 41 g. of liquid was again treated with excess silver acetate (93 g.), this time in 750 ml. of glacial acetic acid, and the mixture was heated and stirred for 48 hr. just below reflux temperature. The mixture was cooled and filtered, and 32 g. of silver iodide was recovered by treating the filter cake with dilute nitric acid to remove the excess silver acetate. After distilling the acetic acid from the filtrate, the product was rapidly distilled and the fraction boiling around 120° (0.5 mm.) was collected. The distillate gave a negative test for iodine, solidified in the refrigerator, and did not remelt at room temperature. Recrystallization from benzene-petroleum ether and ethyl ether–petroleum ether mixtures gave 21 g. of pure IV, m.p. 44–45°.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.81, 51.71; H, 7.02, 6.90.

The infrared spectrum showed strong acetate bands and negligible hydroxyl content. Oxidation with nitric acid[1] gave V, m.p. 178–179°; mixed m.p. with authentic V was the same.

cis-2,6-p-Dioxanedimethanol (I). Transesterification was conducted according to Summerbell and Stephens,[3] refluxing 15 g. of IV in 100 ml. of 3.5% methanolic hydrogen chloride for 1 hr. The solvent was removed *in vacuo* and small amounts of a mixture of benzene and isopropyl alcohol were added and distilled off until the vapors no longer gave an acid reaction with moist indicator paper. The residue was rapidly distilled, boiling at 115° (about 0.5 mm.), yield 8 g. Seed crystals were prepared in a small sample and they caused the distillate to solidify to colorless, very hygroscopic crystals. The material was recrystallized from a mixture of benzene, isopropyl alcohol, and a little petroleum ether, taking care to exclude moisture. The analytical and melting point samples were carefully dried *in vacuo* over phosphorus pentoxide and sealed off under dry air. The *cis*-2,6-*p*-dioxanedimethanol thus obtained melted at 57–58°.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.65; H, 8.16; mol. wt., 148. Found: C, 48.55, 48.49; H, 8.38, 8.28; mol. wt., 143. The carbon content and molecular weight values indicate a water content of 0.5%. In the mass spectrometer the highest mass number found was 148.

Nitric acid oxidation of I gave a solid which was recrystallized from water and then from a mixture of benzene-dioxane-petroleum ether. The crystals from water are apparently a hydrate, melting and resolidifying after some boiling at about 110°, then remelting at 180°. The carefully dried analytical sample melted at 180° (lit.[1] for *cis*-2,6-*p*-dioxanedicarboxylic acid, m.p. 177–178°, 179°).

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.58; neut. equiv., 88.1. Found: C, 40.86, 41.02; H, 4.48, 4.68; neut. equiv. 86.6, 87.9.

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Rearrangement Resulting from Intramolecular Diazo Coupling and Cleavage

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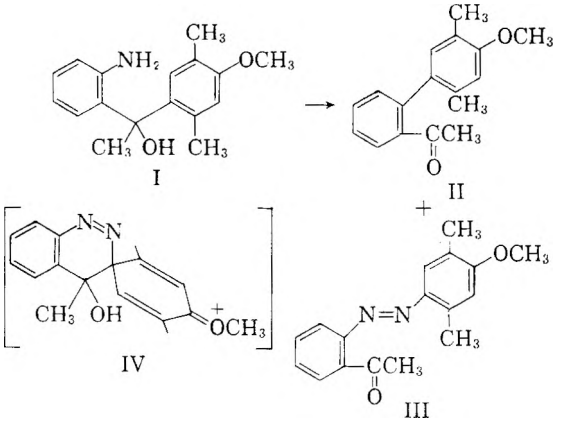
During an investigation of the 1,3-rearrangement which accompanies the deamination of certain *o*-aminophenylcarbinols[1] we prepared the amino alcohol I and treated it with nitrous acid. In addition to phenolic material and the expected rearrangement product II, an 18% yield of the azo ketone III was isolated. The structure of III was proved by comparison with the compound obtained from methylation of the coupling product of 2,5-dimethylphenol and diazotized *o*-aminoacetophenone.

This novel result may be rationalized in terms of cleavage of the intramolecular coupling product IV. The process may be similar to the cleavage reaction which occurs when various para substituted phenol or aniline derivatives are treated with diazonium salts[2] or halogen.[3,4] The cleavage of IV would be expected to lead to an azobenzene with the *syn* structure, but the aqueous acid present in the reaction mixture was apparently sufficient to cause isomerization to the more stable *anti* isomer.[5]



EXPERIMENTAL

1-o-Aminophenyl-1-(4-methoxy-2,5-dimethylphenyl)ethanol (I). A solution of 8.0 g. (0.032 mole) of 2-amino-2′,5′-dimethyl-4′-methoxybenzophenone[6] in 100 ml. of benzene was added dropwise to a solution of methylmagnesium iodide, prepared from 11 g. (0.45 mole) of magnesium and 65 g. (0.46 mole) of methyl iodide in 300 ml. of ether. After 20 hr. at reflux the mixture was hydrolyzed with aqueous ammonium chloride, the organic layer was dried over calcium sulfate, and the solvent was evaporated. The residue crystallized from 70% petroleum ether–30% benzene. Recrystallization from the same solvents yielded 4.0 g. (47%) of colorless crystals, m.p. 121–122°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.16. Found: C, 75.24; H, 7.65; N, 5.22.

Diazotization of the amino alcohol I. The amino alcohol (5.4 g., 0.020 mole) was dissolved in a mixture of 200 ml. of water, 50 ml. of ethanol, and 4.0 g. of concentrated sulfuric acid. A solution of 2.5 g. (0.036 mole) of sodium nitrite in 20 ml. of water was added dropwise at 5°. Added standing for 1 hr. at 5° the solution was allowed to stand at room temperature until the evolution of nitrogen ceased. The precipitated oil was taken up in ether and the ether solution was extracted with dilute alkali to furnish 1.2 g. of acidic oily material, presumably a phenol. The neutral material was adsorbed on a column of ordinary alumina. Elution with 20–30% benzene in petroleum ether (30–60°) furnished 0.80 g. of a light oil (ν_{film} 1670 cm.$^{-1}$) which crystallized from 95% ethanol as a colorless solid (0.63 g., 13%), m.p. 77–78°. The ketone was assigned the structure *o*-(2,5-dimethyl-4-methoxyphenyl)acetophenone (II) on the basis of the spectrum, the formation of a carbonyl derivative, and the analogy to other examples of this rearrangement.[1,7]

Anal. Calcd. for $C_{17}H_{18}O_2$; C, 80.33; H, 7.08. Found: C, 80.55; H, 7.28.

The *2,4-dinitrophenylhydrazone* melted at 201.5–202.5°.

Anal. Calcd. for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.07; N, 12.90. Found: C, 63.62; H, 5.11; N, 12.83.

Elution with 50% benzene–petroleum ether afforded a red oil which crystallized from 80% aqueous ethanol to yield 1.0 g. (18%) of orange-red needles, m.p. 92–93°, ν_{CHCl_3} 1680 cm.$^{-1}$ The compound was identical with the azo ketone III prepared as described in the following paragraphs.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.18; H, 6.28; N, 9.97.

Repetition of the experiment in which the diazotization was carried out in aqueous dioxane and the period of standing at 5° was shortened to 15 min., led to essentially the same result (21% acidic material, 13% ketone II, 14% azo ketone III).

o-Aminoacetophenone. Thirty-five g. (0.21 mole) of *o*-nitroacetophenone[8] was suspended in a mixture of 200 ml. of water and 50 ml. of ethanol, and a solution of 100 g. of sodium dithionate in 100 ml. of water was added in three portions. After 1 hr. at 60° the reaction mixture was steam-distilled, and the yellow oil was distilled under reduced pressure to yield 15 g. (52%) of the amino ketone, b.p. 96–98°/4 mm. (reported,[9] 124°/10 mm.).

2-Acetyl-2′,5′-dimethyl-4′-hydroxyazobenzene. *o*-Aminoacetophenone (16 g., 0.12 mole) was diazotized in dilute aqueous acid and coupled with 15 g. (0.12 mole) of 2,5-dimethylphenol in the usual manner. After recrystallization from 95% ethanol there was obtained 20 g. (61%) of a red solid, m.p. 183–185°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97. Found: C, 71.57; H, 6.14.

2-Acetyl-2′,5′-dimethyl-4′-methoxyazobenzene (III). The azo phenol (20 g., 0.074 mole) was converted to its sodium salt with an equivalent of sodium ethoxide in ethanol, and the solution was treated with 20 g. (0.14 mole) of methyl iodide at reflux for 3 hr. After treatment of the crude product with alkali to remove unreacted phenol, the residue was crystallized from ethanol to yield 12 g. (60%) of orange-red

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needles, m.p. 92–93°, undepressed by the compound obtained from the diazotization of amino alcohol I. The infrared spectra of the two samples were identical.

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Observations on *N*-Methylacetonitrilium and *N*-Phenylbenzonitrilium Hexachloroantimonates[1]

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In recent years syntheses and some reactions of the *N*-substituted nitrilium salts, R—C≡N⁺—R′, X⁻ (X⁻ = a complex anion of the type BF_4^-, $SbCl_6^-$, *etc.*), have been reported by Klages[2] and Meerwein[3] and their co-workers.

As a result of these investigations, the status of the unsubstituted nitrilium salts has been considerably clarified.[2] Further, a reliable knowledge of the structure and chemistry of the stable *N*-alkylnitrilium salts may be expected to improve our understanding of reactions which may involve nitrilium cations as reactive intermediates (*e.g.*, the Beckmann rearrangement of oximes and derivatives, various alkylations of nitriles,[4] and reactions of the imidoyl chlorides, Ar—CCl=N—R, and sulfonate esters, Ar—C(OSO₂R′)=NR).

In this connection we wish to record the preparation of the simplest member of the alkylated series, *N*-methylacetonitrilium hexachloroantimonate (I), its spectroscopic characterization, and a comparison with the previously known *N*-phenylbenzonitrilium hexachloroantimonate (II), together with some new chemical observations on these materials.

Treatment of the acetonitrile–antimony pentachloride complex with excess methyl chloride produced 49% of I in five weeks at room temperature.

$$CH_3—C{\equiv}N \rightarrow SbCl_5 + CH_3Cl \longrightarrow [CH_3—C{\equiv}N^+—CH_3 \longleftrightarrow CH_3—C^+{=}N—CH_3] + SbCl_6^-$$

I

$$I + C_6H_5NH_2 \longrightarrow CH_3—C(NHCH_3){=}N—C_6H_5$$

$$C_6H_5—CCl{=}N—C_6H_5 + SbCl_5 \longrightarrow$$

III

$$[C_6H_5—C{\equiv}N^+—C_6H_5 \longleftrightarrow C_6H_5—C^+{=}N—C_6H_5] + SbCl_6^-$$

II

$$II \xrightarrow{C_6H_5NH_2} C_6H_5—C(NHC_6H_5){=}N—C_6H_5$$

$$\downarrow C_6H_5OH$$

$$C_6H_5—C(OC_6H_5){=}N—C_6H_5$$

The nitrilium salt was characterized chemically by conversion to the known *N*-methyl-*N*′-phenylacetamidine on treatment with aniline. *N*-Phenylbenzonitrilium hexachloroantimonate (II), was prepared according to Meerwein[3] by the action of antimony pentachloride on *N*-phenylbenzimidoyl chloride (III). Compound II also reacted with aniline to give *N*,*N*′-diphenylbenzamidine as well as with phenol which produced phenyl *N*-phenylbenzimidate.

The reaction producing I from acetonitrile–antimony pentachloride and methyl chloride fails when conducted in the presence of excess acetonitrile, in which case the mixture blackens in a few days and a tarry product results. In addition, partial destruction of the pure nitrilium salt (I), was observed when attempts were made to cast films for infrared measurements from acetonitrile solution. In each case the product was distinguished by intense infrared absorption in the 1650 cm.$^{-1}$ region, and various weaker bands at lower frequencies. These observations suggest polymerization involving intermediates such as

$$CH_3—N{=}C(CH_3)—N{=}C^+—CH_3$$

IV

which is considered to arise by electrophilic attack on the nitrogen of the nitrile by the unsaturated carbon of the nitrilium cation.[5]

N-Alkylnitrilium salts have also been prepared[3] by direct alkylation of the nitrile with trialkyl oxonium salts or with decomposing aryldiazonium ions. Those prepared by Meerwein, including (II), were characterized by hydrolysis to *N*-alkylamides.[3] These facts taken with the above conversions to amidines and imidoesters amply confirm the main structural features of the indicated formulas. Furthermore, measurement of the electrical conductivity of *N*-methylbenzonitrilium hexachloroantimonate in liquid sulfur dioxide[2] clearly established the material as a strong electrolyte.

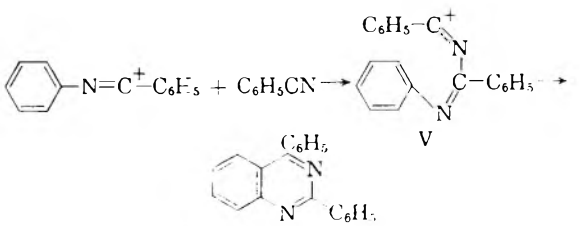
(1) Ethylidynemethylammonium chloroantimonate (V) and benzylidynephenylammonium chloroantimonate (V).

(2) F. Klages and W. Grill, *Ann.*, **594**, 21 (1955).

(3) H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Ber.*, **89**, 209 (1956); H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig. *Ber.*, **89**, 224 (1956).

(4) E. E. Magat, U. S. Patent 2,628,216; *Chem. Abstr.*, **47**, 5129 (1953); *J. Am. Chem. Soc.*, **73**, 1028 (1951); and references cited by Meerwein.[3]

(5) The quinazoline synthesis reported by Meerwein[3] appears analogous, *e.g.*,



Indeed, when the *N*-aryl group is substituted in both *ortho* positions, the adducts analogous to V were isolated as stable salts. In this case there is no evidence for incorporation of more than one nitrile molecule.

Our observations on the infrared spectrum of I support and refine the structure given for that material. The observed fundamental vibrational frequencies for the *N*-methylacetonitrilium ion were assigned[6] by analogy with those of the infrared and Raman spectra of the isoelectronic molecule dimethylacetylene[7,8] and are shown in Table I.

TABLE I

FUNDAMENTAL VIBRATIONAL FREQUENCIES AND ASSIGNMENTS FOR THE *N*-METHYLACETONITRILIUM ION

Frequency ($Cm.^{-1}$)	Assignment	Description	Species
2919 vs	ν_1	CH stretch	A_1
2416 vs	ν_2	$C{\equiv}N^+$ stretch	A_1
1343 vs	ν_3	CH_3 deform.	A_1
702 m	ν_4	C—C stretch	A_1
(inactive)	ν_5	CH_3 torsion	A_2
2988 vs	ν_6	CH stretch	A_1
1383 m	ν_7	CH_3 deform.	A_1
1122 w	ν_8	N^+—C stretch	A_1
2988 vs	ν_9	CH stretch	E
1421 m	ν_{10}	CH_3 deform.	E
1090 s	ν_{11}	CH_3 rock	E
[~380]	ν_{12}	$C{\equiv}N^+$—C	E
2955 s	ν_{13}	CH stretch	E
1400 m	ν_{14}	CH_3 deform.	E
1020 vs	ν_{15}	CH_3 rock	E
[~150]	ν_{16}	C—$C{\equiv}N^+$ bend	E

[ ] Estimated from observed combination bands. vs = very strong, s = strong, m = medium, w = weak, vw = very weak.

Thirteen of the 15 expected infrared-active fundamentals were observed directly, and the two skeletal bending frequencies, which are beyond the range of the spectrometer, were estimated from observed combination bands. A comparison of the vibrational frequencies of dimethylacetylene and I shows only one significant difference; that is, in the —C≡C— stretching frequency of 2310 $cm.^{-1}$ in dimethylacetylene. which is to be compared with the —C≡N^+— stretching frequency of 2416 $cm.^{-1}$ in the *N*-methylacetonitrilium ion. This difference can be shown[6] to be due to an increase in the triple bond stretching force constant upon replacing ≡C— by ≡N^+—.

Although the close similarity of the spectrum of I with the combined infrared and Raman spectra of dimethylacetylene cannot be taken as proof that their structures are analogous, it does provide strong support for this assumption. Furthermore, the absence of any observed splitting of the E-species bands is consistant with a linear C—C≡N^+—C chain.

In the infrared spectrum of II the —C≡N^+— stretching frequency drops to approximately 2300 $cm.^{-1}$

(6) For a normal coordinate treatment of the *N*-methylacetonitrilium ion see G. C. Turrell and J. E. Gordon, *J. Chem. Phys.*, in press.

(7) B. L. Crawford, Jr., *J. Chem. Phys.*, **7**, 555 (1939).

(8) I. M. Mills and H. W. Thompson, *Proc. Roy. Soc. (London)*, **226A**, 306 (1954).

EXPERIMENTAL[9]

Materials. Acetonitrile (Eastman Spectro Grade) and methylene chloride were distilled from phosphorus pentoxide. Fisher Reagent antimony pentachloride was used without purification. *N*-Phenylbenzimidoyl chloride was prepared according to Wallach and Hoffman[10] and was distilled through a 2-ft. Podbielniak column, b.p. 151.5–152.5° (2 mm.), m.p. 40.5–42°.

Infrared measurements. Infrared spectra of the nitrilium salts I and II were observed from 400 $cm.^{-1}$ to 4000 $cm.^{-1}$ using potassium bromide, sodium chloride and calcium fluoride prisms. The sodium chloride region was investigated with a Perkin-Elmer model 137 "Infracord." A double-beam, ratio-recording infrared spectrometer of the type described by Hornig, Hyde, and Adcock[11] was used to cover the calcium fluoride and potassium bromide regions. The spectra were observed at room temperature from samples prepared in the form of Nujol and perfluorokerosene mulls pressed between sodium chloride plates.

N-Methylacetonitrilium hexachloroantimonate (I). Excess acetonitrile and 2.35 g. (0.00785 mole) of antimony pentachloride were placed in a Pyrex ampoule and the excess nitrile was evaporated at reduced pressure leaving the pale yellow crystalline complex. Methyl chloride was passed over Drierite and condensed in the ampoule at Dry Ice temperature to a volume of 3 ml.; the sealed ampoule was stored at room temperature with frequent shaking for 5 weeks during which time the powdery complex dissolved and large transparent prisms of the nitrilium salt were deposited. The latter were decanted and washed with 6 portions of methylene chloride giving 1.5 g., 49%, of the nitrilium salt, m.p. 178–181° dec.

Anal. Calcd. for $C_3H_6Cl_6NSb$: C, 9.22; H, 1.55; Cl, 54.47; N, 3.59. Found: C, 9.14; H, 1.80; Cl, 54.28,[12] 54.31,[12] 50.8,[13] N, 3.24.

Reaction of N-methylacetonitrilium hexachloroantimonate with aniline. Treatment of 1.88 g. (0.0048 mole) of the nitrilium salt with 0.45 g. (0.0048 mole) of aniline in 15 ml. of dry benzene at room temperature for 12 hr. gave a tarry mixture which was poured into 50 ml. of cold 3*N* sodium hydroxide; the aqueous phase and suspended solid were extracted thoroughly with benzene, and the combined dried (potassium carbonate) benzene solutions were evaporated to 0.51 g. of oil and crystals. The latter was chromatographed on 15 g. of Merck alumina, 280 ml. of benzene-hexane, 2:1, eluting 0.235 g., 33% of *N*-phenyl-*N'*-methylacetamidine, m.p. 70–71.5°, after an initial oily fraction weighing 0.88 g. The analytical sample was recrystallized four times from hexane (82% recovery) and sublimed at 0.1 mm. and 60°, m.p. 71–72.5° (reported[14] 72°).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.90. Found: C, 72.82; H, 8.11; N, 19.08.

N-Phenylbenzonitrilium hexachloroantimonate, (II). After the procedure of Meerwein *et al.*[3] antimony pentachloride and *N*-phenylbenzimidoyl chloride were mixed in methylene

(9) Unless otherwise stated, all manipulations were carried out in a dry box maintained with phosphorus pentoxide. Melting points are uncorrected; those above 150°, or for moisture sensitive compounds, were determined in evacuated capillaries. Microanalyses were performed by the Microchemical Laboratory, Massachusetts Institute of Technology, and the Mikroanalytisches Laboratorium im Max Planck Institüt für Kohlenforschung (Mülheim).

(10) O. Wallach and M. Hoffmann, *Ann.*, **184**, 79, (1877).

(11) D. F. Hornig, G. E. Hyde, and W. A. Adcock, *J. Optical Soc. Am.*, **40**, 497 (1950).

(12) By sodium peroxide fusion followed by chloride determination.[2]

(13) By the Carius method; the contaminated silver chloride obtained was dissolved in potassium iodide and determined by difference.

(14) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1514 (1948).

chloride and the precipitate was washed with five portions of fresh solvent and dried on the vacuum line to give 95% of the nitrilium salt as a pale yellow powder, m.p. 230–233° to a scarlet melt (reported[3,2] 231–234°, 236–237°).

Reaction of N-phenylbenzonitrilium hexachloroantimonate with aniline. A solution of 0.58 g. (0.0062 mole) of aniline in 25 ml. of dry benzene was treated with 2.93 g. (0.0057 mole of II and the mixture was worked up as described for the reaction of I, giving 1.53 g. of yellow solid. Chromatography of a 0.63 g. aliquot on 13 g. of Merck alumina gave 0.38 g. of *N,N'*-diphenylbenzamidine, m.p. 145.7–147° (reported[14] 146.5–147°), eluted by 320 ml. of methylene chloride-hexane, 1:1. The yield is thus 59%. The analytical sample was crystallized three times from isopropanol (recovery, 89%) and sublimed at one micron and 135°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.77; H, 5.95; N, 10.41.

The *picrate* was prepared in benzene, m.p. 218–219° (reported[14] 221°).

Reaction of N-phenylbenzonitrilium hexachloroantimonate with phenol. A mixture of 4.36 g. (0.00847 mole) of the nitrilium salt and 1.0 g. (0.0106 mole) of phenol in 25 ml. of dry benzene was kept overnight at room temperature, refluxed for 15 min. and finally treated with cold, aqueous alkali to *p*H 10. Working up as in the preceding section provided 2.18 g. of yellow solid. A 0.60-g. aliquot chromatographed on 18 g. of Merck alumina gave 0.325 g. of phenyl *N*-phenylbenzimidoate, m.p. 104–105°, eluted by 50 ml. of benzene-hexane, 3:1, yield, 51%. The analytical sample was crystallized twice from hexane and sublimed at one micron and 92°, m.p. 104.5–106° (reported[14] 104.5–105°).

Anal. Calcd. for $C_{19}H_{15}NO$: N, 5.13. Found: N, 5.14.

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Nitrosation of Acylated 1,2-Diaminoethenes[1]

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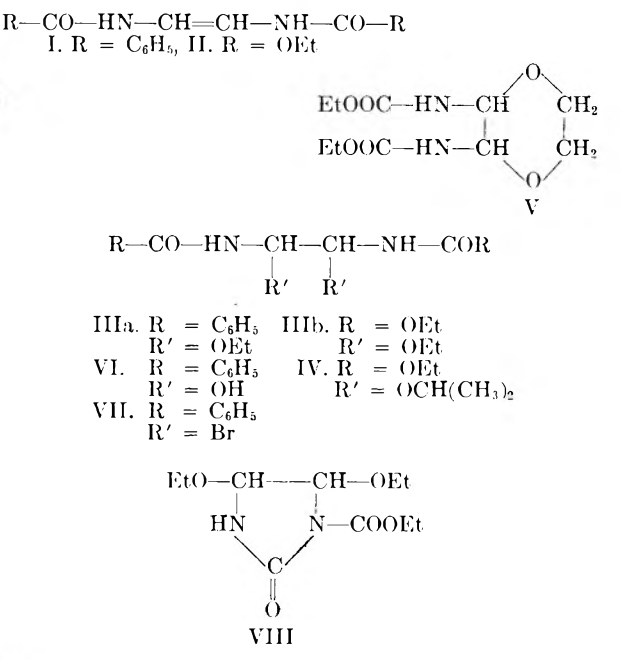
Acylated 1,2-diaminoethanes have been reported in the literature to react normally with nitrous acid to the expected bis-*N*-nitroso derivatives.[2] As reported in this paper the reaction of acylated 1,2-diaminoethenes takes an entirely different course.

Starting materials for this investigation were 1,2-di(benzoylamino)ethene[3] (I) and 1,2-di(carbethoxyamino)ethene (II). The latter compound could not be obtained *via* the Curtius degradation of fumaric acid as reported in the literature.[4] An isomer, probably the *cis*-II, however, was easily obtained by the Bamberger cleavage of imidazole with ethyl chloroformate and alkali. The identity of the *cis*-II was confirmed by catalytic hydrogenation to the known 1,2-di(carbethoxyamino)ethane. Both I and II reacted in alcoholic solution with ethyl or isoamyl nitrite in the presence of hydrochloric acid with immediate development of an intense blue-green color which soon disappeared whereupon colorless crystals deposited. These crystals turned out to be the corresponding 1,2-diethoxy-1,2-di(carbethoxyamino)ethanes (IIIa, resp. IIIb). Replacement of ethanol by isopropylalcohol in this reaction led from II to the corresponding isopropoxy compound IV while ethylene glycol yielded the dioxane derivative V. In an aqueous system the glycol VI was obtained from I with sodium nitrite and hydrochloric acid. Compounds IIIa and VI have previously been obtained from I *via* the dibromide VII.[3] In the case of IIIa we obtained apparently a stereoisomer, m.p. 240–241°, whereas Ruggli reports two isomers, m.p. 190–191°, and m.p. 219° *via* his route. The glycol VI was obtained as a mixture of two stereoisomers, m.p. 162–164°, and m.p. 180–182°, while Ruggli isolated in this case only the lower melting isomer. It is obvious the glycol and its ethers can occur both as meso- and racemic forms. When the nitrosation of II with isoamyl nitrite and alcoholic hydrogen chloride was carried out for a prolonged period, the originally formed crystals of IIIb went again into solution. A new compound could then be isolated which derived from IIIb by the loss of one molecule of alcohol. Presumably, ring closure to 1-carbethoxy-4,5-diethoxyimidazolidinone-2 (VIII) occurred.



(1) This article is based on work performed under Project 116 B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corp., New York, N. Y.

(2) H. Holter and H. Bretschneider, *Monatsh.*, **53/54**, 963 (1929); C. M. Samour and J. P. Mason, *J. Am. Chem. Soc.*, **76**, 441 (1954); T. Lieser and G. Beck, *Chem. Ber.*, **84**, 137 (1950); H. Lettre and U. Brose, *Naturwissenschaften*, **36**, 57 (1949).

(3) P. Ruggli, R. Ratti, and E. Henzi, *Helv. Chim. Acta*, **12**, 332 (1929).

(4) R. Radenhausen, *J. prakt. Chem.*, [2] **52**, 453 (1895).

The observed abnormal course of the nitrosation of acylated 1,2-diaminoethenes with formation of highly reactive addition products to the double bond which on subsequent alcoholysis or hydrolysis yield the corresponding alkoxy derivatives or glycols is apparently caused by the two electron-releasing groups symmetrically positioned to the thereby activated double bond. Similar reactions have already been observed by Ruggli *et al.* in the case of I[3] and with 3,4-diphenylimidazolinone-2.[5] The well-known oxidation of uric acid to uric acid glycol may also belong to this kind of reaction.[6]

EXPERIMENTAL[7]

Starting materials. The *1,2-di(benzoylamino)ethene* (I) was obtained according to Ruggli[3] in a 77% yield, m.p. 212–213°, while *1,2-di(carbethoxyamino)ethene* (II) was prepared similarly from imidazole (5 g.) and ethyl chloroformate (50 g.) at 0°. The crude product of 14.4 g. (96.5%) was recrystallized from ligroin or aqueous alcohol to yield colorless crystals, m.p. 139–141°.

Anal. Calcd. for $C_8H_{14}N_2O_4$: C, 47.51; H, 6.97; N, 13.85. Found: C, 47.48; H, 6.90; N, 13.89.

II is soluble in concd. hydrochloric acid but after several minutes at room temperature the color of the solution changes to a greenish black due to decomposition.

To 2 g. of II in 60 ml. of absolute alcohol 20 mg. of $PdCl_2$ was added and the mixture hydrogenated at room temperature. The calculated amount of hydrogen was consumed in 44 min. The Pd was filtered off and after evaporation of the alcohol *in vacuo* 1.7 g. (85%) of 1,2-di(carbethoxyamino) ethane, m.p. 114°, was obtained. The mixed melting point with an authentic sample prepared from ethylenediamine and ethyl chloroformate[8] showed no depression.

1,2-Diethoxy-1,2-di(benzoylamino)ethane (IIIa). To a suspension of I (2 g.) in 50 ml. of absolute alcohol isoamyl nitrite (1.8 g.) was added and dry hydrogen chloride bubbled through the reaction mixture at 0°. A blue green coloration developed immediately and within 2 hr. all material went into solution. Water was added to the now colorless, ice-cooled reaction mixture whereupon 1.3 g. (49%) of crude IIIa, m.p. 169–173°, separated. After one recrystallization from ethanol the melting point rose to 240–242°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.78; N, 7.85. Found: C, 67.27; H, 6.78; N, 7.89.

1,2-Diethoxy-1,2-di(carbethoxyamino)ethane (IIIb) was obtained analogously from II (3 g.) and isoamyl nitrite (3.5 g.). Also in this case an immediate deep blue coloration was observed which changed soon to dark green, whereupon crystallization of IIIb started. After 20 min. 1.6 g. (37%) of colorless needles, m.p. 148°, were obtained. After one recrystallization from water IIIb melted at 151–152°.

Anal. Calcd. for $C_{12}H_{24}N_2O_6$: C, 49.30; H, 8.27; N, 9.58. Found: C, 49.18; H, 8.29; N, 9.69.

With an excess of ethyl nitrite instead of isoamyl nitrite the reaction yielded IIIb in a 69% yield. With isopropyl alcohol and isoamyl nitrite II yielded 57% of *1,2-diisopropoxy-1,2-di(carbethoxyamino)ethane* (IV), colorless needles from aqueous isopropyl alcohol, m.p. 159–161°.

Anal. Calcd. for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.74. Found: C, 52.81; H, 8.49; N, 8.74.

The reaction of II (1 g.) with isoamyl nitrite (1 g.) and hydrogen chloride in ethylene glycol (30 ml.) yielded analogously *2,3-di(carbethoxyamino)-1,4-dioxane* (V) (1.1 g., 85%), colorless needles after recrystallization from ethanol, m.p. 190–191°.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: C, 45.79; H, 6.91; N, 10.67. Found: C, 45.80; H, 6.75; N, 10.76.

1,2-dihydroxy-1,2-di(benzoylamino)ethane (VI). A solution (1.1 g.) of sodium nitrite in 10 ml. of water was added dropwise at 0° to a suspension of I (2 g.) in 100 ml. of concd. HCl. Each drop caused immediately a blue coloration which faded quickly to yellow. After stirring for 1 hr., 1 g. of unchanged starting material was filtered off. Addition of water to the filtrate yielded a crystalline precipitation of VI (0.8 g., 70%), m.p. 168–177°. Repeated recrystallization from alcohol separated this material into approximately equal amounts of a more soluble fraction, m.p. 162–164° and into a soluble fraction, m.p. 180–182°. The lower melting product was identical with the product obtained by Ruggli.[3] The higher melting isomer gave the following analytical data:

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.55; H, 4.98; N, 9.53.

When the higher melting isomer was sublimed in a vacuum benzamide, m.p. 132–133°, was obtained besides polyglyoxal. An attempted hydrolysis of VI with 40% aqueous KOH yielded benzoic acid as the only isolable product.

1-Carbethoxy-4,5-diethoxyimidazolidinone-2 (VIII). When the reaction of II (3 g.) and isoamyl nitrite (3.5 g.) in absolute ethanol with hydrogen chloride was carried on for 2 hr., the originally formed crystals went again into solution. To remove the excess of hydrochloric acid, potassium carbonate was added and then the solvent removed *in vacuo*. The residue was extracted with boiling ethanol from which 1.1 g. (30%) of VIII crystallized on cooling. M.p. 200–202°.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: C, 48.78; H, 7.36; N, 11.37. Found: C, 49.02. H, 7.43; N, 11.03.

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(5) H. Biltz, Ann., **368**, 156, 262 (1909).

(6) H. Biltz and H. Schauder, *J. prakt. Chem.* [2], **106**, 169 (1923).

(7) Melting points are uncorrected (Fisher-Johns); analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(8) E. Fischer and H. Koch, *Ann.*, **232**, 228 (1885).

Benzo-1,2,3-triazines

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Recent work has demonstrated that amino-chlorobenzo-1,2,4-triazines possess remarkable pharmacological properties.[2] It seemed, therefore, of interest to investigate some representatives of the benzo-1,2,3-triazine series.

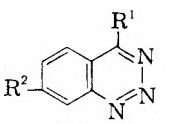
Benzo-1,2,3-triazines substituted in the 4-position are generally obtained by the diazotization of *o*-aminobenzoic acid derivatives. The desired 4-aminobenzo-1,2,3-triazine (I) and 4-hydrazino-benzo-1,2,3-triazine (II), however, were not accessible by this route, since *o*-aminobenzamidine and *o*-aminobenzamidrazone could not be prepared from *o*-aminobenzonitrile. The reluctance of *o*-

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) F. J. Wolf, K. Pfister, R. M. Wilson, Jr., and C. A. Robinson, *J. Am. Chem. Soc.*, **76**, 3551 (1954); F. J. Wolf, R. M. Wilson, Jr., K. Pfister, and M. Tishler, *J. Am. Chem. Soc.*, **76**, 4611 (1954).

aminobenzonitrile to addition at the C≡N bond has already been observed by Pinner.[3] Compounds I and II could be obtained from the easily accessible 4-thiomethylbenzo-1,2,3-triazine[4] (III) by reaction with ammonia resp. hydrazine at room temperature, while 7-chloro-4-mercaptobenzo-1,2,3-triazine (IV) reacted with hydrazine to 7-chloro-4-hydrazinobenzo-1,2,3-triazine (V). The 4-hydroxylamino-7-chlorobenzo-1,2,3-triazine (VIII) and the 4-hydroxylamino-7-methoxybenzo-1,2,3-triazine (X) were prepared by diazotization of the corresponding substituted *o*-aminobenzamidoximes. By-products in this reaction were the 7-chloro-4-hydroxybenzo-1,2,3-triazine (IX) and the 7-methoxy-4-hydroxybenzo-1,2,3-triazine (XI).

The attempted reduction of VIII with sodium borohydride in methanol led to 2-amino-4-chlorobenzonitrile (XII) in a quantitative yield. This result was somewhat surprising since reduction of 4-hydroxybenzo-1,2,3-triazine with zinc dust and ammonium hydroxide yielded indazolone.[5] It was then found that the conversion of VIII to XII is achieved by mild alkalies as sodium carbonate or sodium bicarbonate alone. The reduction of VIII to XII is, therefore, an intramolecular process, presumably preceded by ring cleavage of VIII to the *o*-diazonium hydroxide of the benzamidoxime. A somewhat similar cleavage of condensed pyrimidine derivatives was recently reported by Taylor.[6]



	R^1	R^2
I	NH_2	H
II	$NH{\cdot}NH_2$	H
III	SCH_3	H
IV	SH	Cl
V	$NH{\cdot}NH_2$	Cl
VIII	NHOH	Cl
IX	OH	Cl
X	NHOH	OCH_3
XI	OH	OCH_3

Several of the above described benzotriazines were tested pharmacologically, but none of them showed any outstanding action, X being the best with an adrenergic blocking action similar to apresoline, but only 1/30 as active.[7]

EXPERIMENTAL[8]

4-Aminobenzo-1,2,3-triazine (I). Anhydrous ammonia was bubbled for 6 hr. into the alcoholic solution of III (1.9 g.) with ice-cooling. After 4 days at room temperature 930 mg., m.p. 278–279° (dec.) crystallized from the alcoholic solution. The crude material (60%) was recrystallized from alcohol or glacial acetic acid, melting at 284–285°.

Anal. Calcd. for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.41; H, 3.96; N, 38.00.

The hydrochloride was prepared by dissolving I in a mixture of 2*N* hydrochloric acid–methanol and evaporation *in vacuo*, m.p. 160–163° (dec.).

4-Hydrazinobenzo-1,2,3-triazine (II). To III (2 g.) in 30 ml. of alcohol 0.6 g. of hydrazine hydrate was added. An immediate evolution of methylmercaptan was observed. After standing overnight 1 g. (55%) was obtained which was recrystallized from ethanol, melting at 191–192° (dec.).

Anal. Calcd. for $C_7H_7N_5$: N, 43.45. Found: N, 43.79.

7-Chloro-4-mercaptobenzo-1,2,3-triazine (IV). To a solution of 2-amino-4-chlorobenzonitrile[9] (4.5 g.) in 25 ml. of pyridine triethylamine (3 g.) was added and H_2S passed into the reaction mixture for 4 hr. at room temperature. The mixture was then poured into 200 ml. of water whereupon a dark oil separated which became solid on shaking. The crude 2-amino-4-chlorobenzothioamide thus obtained was recrystallized from water to yield 4.3 g. (78%), m.p. 150–151°.

Anal. Calcd. for $C\text{-}H_7ClSN_2$: N, 15.00; S, 17.17. Found: N, 14.87; S, 17.08.

To dilute HCl cooled to 0° 2 g. of 2-amino-4-chlorobenzothioamide was added followed by the dropwise addition of $NaNO_2$ (0.8 g.) in water. The colorless crystals changed gradually to a yellow amorphous material. Crystallization of the crude material from alcohol yielded 1.4 g. (67%) of IV, melting at 215–217° (dec.).

Anal. Calcd. for $C_7H_4ClSN_3$: C, 42.53; H, 1.53; N, 21.26. Found: C, 43.08; H, 1.52; N, 21.29.

4-Hydrazino-7-chlorobenzo-1,2,3-triazine (V). Hydrazine hydrate (0.4 g.) was added to IV (1 g.) in alcohol. An immediate evolution of H_2S was observed. After refluxing for 3 hr. the precipitated colorless needles were collected on a filter. The product was recrystallized from dioxane to yield 0.8 g. (80%), m.p. 195–198° (dec.).

Anal. Calcd. for $C_7H_6ClN_5$: N, 35.80: Found: N, 35.66.

2-Amino-4-chlorobenzamidoxime (VII). To 2-amino-4-chlorobenzonitrile (8 g.) in 150 ml. of absolute alcohol hydroxylamine hydrochloride (3.7 g.) and sodium (2.4 g.) was added and the mixture refluxed for 20 hr., diluted with water, and extracted with ether. Evaporation of the dried solvent yielded 8.5 g. (86%), melting at 127–128° after recrystallization from alcohol–water.

Anal. Calcd. for $C_7H_8ClN_3O$: C, 45.29; H, 4.34; N, 22.63. Found: C, 45.31 H, 4.26; N, 22.62.

4-Hydroxylamino-7-chlorobenzo-1,2,3-triazine, hydrate (VIII). To the ice-cooled solution of 10.5 g. of the preceding product in dilute hydrochloric acid, sodium nitrite (3.9 g.) in water was added dropwise. Every drop caused precipitation of the bright yellow benzo-1,2,3-triazine derivative. After filtering off and washing with water VIII was recrystallized from aqueous alcohol whereby 7.6 g. (70%) of bright yellow needles of VIII, m.p. 205–206° (dec.) was obtained in form of the hydrate.

Anal. Calcd. for $C_7H_5ClN_4O{\cdot}H_2O$: C, 39.12; H, 3.28; N, 26.17; Cl, 16.51. Found: C, 39.57; H, 3.55; N, 26.12; Cl, 16.44.

A small amount of crystals precipitating from the mother liquors were identified as *7-chloro-4-hydroxybenzo-1,2,3-triazine* (IX) by mixed melting point with an authentic sample prepared as follows:

2-Amino-4-chlorobenzamide[10] was prepared in a quantitative yield by heating 2-amino-4-chlorobenzonitrile with 85% sulfuric acid for 90 min. on a steam bath, m.p. 185–186° (lit. 181°). To 2-amino-4-chlorobenzamide (2.4 g.) in dilute hydrochloric acid, sodium nitrite (1 g.) in water was added.

(3) A. Pinner, *Die Iminoäther*, Berlin, 1892, p. 192.

(4) A. Reissert and F. Grube, *Ber.*, **42**, 3717 (1907).

(5) G. Heller, *J. prakt. Chem.* [2] **111**, 7 (1925).

(6) E. C. Taylor, R. J. Knopf, and J. R. Barton, Abstracts of 133rd Meeting of The American Chemical Society, San Francisco, April 1958, p. 2M.

(7) We are very much indebted to the E. R. Squibb Division of Olin Mathieson Chemical Corporation for the testing of these compounds in their laboratories.

(8) Melting points were determined with the Fisher-Johns apparatus; analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(9) R. L. McKee, M. K. McKee, and R. W. Bost, *J. Am. Chem. Soc.*, **69**, 940 (1947).

(10) L. B. Hunn, *J. Am. Chem. Soc.*, **45**, 1027 (1923).

After standing overnight in an icebox 2.2 g. (86%) of colorless needles separated from the reaction mixture which after recrystallization from alcohol melted at 219–220° (dec.).

Anal. Calcd. for $C_7H_7ClN_2O$: C, 46.24; H, 2.22; N, 23.13. Found: C, 46.22; H, 2.38; H, 23.16.

4-Hydroxylamino-7-methoxybenzo-1,2,3-triazine (X). The 2-amino-4-methoxybenzamidoxime (VI) was prepared from 2-amino-4-methoxybenzonitrile[11] in a manner quite analogous to that described above for the amidoxime (VII). The crude VI (2 g.) was dissolved without further purification in 2*N* hydrochloric acid and sodium nitrite (0.7 g.) dissolved in water was added dropwise with ice-cooling. The benzotriazine (X) which separated (1.1 g., 62.5%) was recrystallized from glacial acetic acid and dried for analysis over potassium hydroxide at 100°; m.p. 215–216 (dec.).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.15. Found: C, 49.75; H, 4.00; N, 29.23.

When the mother liquor of the diazotization of VI was kept overnight in an ice-box 0.2 g. (12.5%) of *4-hydroxy-7-methoxybenzo-1,2,3-triazine* (XI) crystallized. XI was recrystallized from water, colorless needles, m.p. 220–221° (dec.).

Anal. Calcd. for $C_8H_7N_3O_2$: N, 23.72. Found: N, 24.19.

Reduction of VIII with sodium boronhydride. A solution of $NaBH_4$ (2 g.) in methanol was added to a finely divided suspension of VIII (2 g.) in 300 ml. of methanol and refluxed for 4 hr. Addition of water precipitated 0.7 g. of 2-amino-4-chloro-benzonitrile (XII), m.p. 160–161°. XII was identified by a mixed melting point with an authentic sample.[9]

When VIII was dissolved in 2*N* NaOH, 2*N* Na_2CO_3, or dilute $NaHCO_3$ the solution became turbid after a few minutes and the nitrile XII precipitated in an almost quantitative yield.

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(11) A. H. Cook, I. B. Heilbron, K. J. Reed, and M. N. Strachan, *J. Chem. Soc.* 861 (1945).

Morphine-*N*-Methyl-C^{14}

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Several years ago Rapoport *et al.*[1] reported the synthesis of morphine-*N*-methyl-C^{14} from codeine-*N*-methyl-C^{14} in a 22% yield. In order to increase the availability of labeled morphine for pharmacological studies, methods of preparation were investigated which would give a good yield of product in a one step synthesis from normorphine.

A consideration of the instability of morphine toward high temperatures, strong acids, and strong alkalies, of the ease with which the molecule is *O*-methylated, and of the susceptibility of the isolated carbon-carbon bond toward catalytic hydrogenation,[2] eliminated selection of many of the classical methods for *N*-methylation. Since Tarpey *et al.*[3] have shown in the case of 4-phenyl-4-carbethoxypiperidine that formaldehyde-C^{14}-formate reductive methylation occurs exclusively with incorporation of the *N*-methyl-C^{14} group into the molecule, this method was adapted to the synthesis of morphine-*N*-methyl-C^{14}.

The results of paper chromatography and infrared studies indicated that morphine is largely destroyed when refluxed for 4 hr. with half an equivalent of 37–38% formalin solution and two equivalents of formic acid. The infrared spectrum of the crude resinous reaction product obtained from refluxing normorphine with a 20% excess each of formalin and formic acid showed the presence of a significant quantity of morphine. Application of the findings of Wagner and co-workers[4] on the factors influencing the Wallach reaction greatly facilitated the final selection of reaction conditions. High temperatures for extended periods enhance decomposition of the product so the procedure employed entailed gentle reflux in absolute ethanol for a short period.

N-Methylation of normorphine proceeded smoothly in the case of nonlabeled material, but difficulty was encountered in the direct application of the procedure to commercially available paraformaldehyde-C^{14} because of varying amounts of impurities. To avoid the assay for percentage formaldehyde-C^{14} freed under the reaction conditions, the syntheses were carried out in two stages; first the reaction was executed in the usual manner assuming complete depolymerization, and second the crude product was recycled using a small quantity of unlabeled paraformaldehyde in order to convert all of the original starting material to morphine.

In the early stages of development of the reaction conditions, the crude product was always found to contain 3–5% normorphine. This impurity could be removed neither by recrystallization from a wide variety of solvents or solvent mixtures nor by precipitation of the bases from aqueous solution at any *p*H. Chromatography on neutral or basic alumina using a number of different solvents and solvent mixtures failed to effect the desired separation. Application of a solvent system which produced significantly different R_f values for morphine and normorphine on paper strips to a powdered cellulose column proved acceptable for the separation of the two alkaloids. Since losses on the cellulose column were greater than those in the recycling procedure, the latter method was adopted for the synthesis of the labeled material. The cellulose chromatography procedure is somewhat tedious in application to larger amounts of material but is reported here as a technique satisfactory for

(1) H. Rapoport, C. H. Lovell, and B. M. Tolbert, *J. Am. Chem. Soc.*, **73**, 5900 (1951).

(2) L. F. Small and R. E. Lutz, *Chemistry of the Opium Alkaloids*, U. S. Treasury Department, Public Health Service Supplement No. 103, Washington, 1932, pp. 138–170.

(3) W. Tarpey, H. Hauptman, B. M. Tolbert, and H. Rapoport, *J. Am. Chem. Soc.*, **72**, 5126 (1950).

(4) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949); W. L. Borkowski and E. C. Wagner, *J. Org. Chem.*, **17**, 1128 (1952).

the separation of milligram quantities of normorphine and morphine.

EXPERIMENTAL[5]

Preparation of morphine-N-methyl-C^{14}. Normorphine,[6] (195 mg. 0.72 mmole), m.p. 275–277° (dec.), 8.5 cc. of absolute ethanol, 25.4 mg. (0.85 mmole, *ca.* 1.2 mc./mmole) of paraformaldehyde-C^{14}, and 0.85 cc. (16 mmoles) of 87–90% formic acid were heated under gentle reflux for 90 min. The alcohol and excess formic acid were removed at reduced pressure under nitrogen with a final heating period of 5 min. at 110°. The residue was dissolved in 3.5 cc. of 0.25*N* hydrochloric acid and the crude product precipitated by addition of *N* sodium hydroxide to *p*H 9. After 2 hr. at 0°, the crystals were removed by centrifugation, washed with 1.0 cc. of ice-cold water in two portions and dried *in vacuo*. The crude product weighed 167 mg. (76% from normorphine, 64% from paraformaldehyde-C^{14}), contained 2–5% normorphine (*vide infra* paper chromatography) and was radiochemically pure (*vide infra* autoradiography).

Purification of morphine-N-Methyl-C^{14}. Crude morphine-*N*-methyl-C^{14}, 331 mg. (1.2 mmoles) in 10.0 cc. of absolute ethanol was treated as above with 20.0 mg. (0.67 mmole) of unlabeled paraformaldehyde and 1.0 cc. (19 mmoles) of 87–90% formic acid. After precipitation from water, the pale yellow crystals weighed 300 mg., contained no normorphine and were radiochemically pure. The product dissolved in 3.0 cc. of absolute methanol was applied to a column (400 × 9 mm.) containing 5.0 g. of neutral alumina.[7] Elution was effected with 80 cc. of absolute methanol. After removal of the solvent in the absence of light at reduced pressure under nitrogen, the residue was dissolved in acid and precipitated as previously. The fine white crystals weighed 255 mg. (59% from normorphine, 50% from paraformaldehyde-C^{14}); m.p. 251–253° (dec.) [Kempf[8] reported a m.p. 253–254 (dec.), cor.], specific activity 0.6 mc/mmole. The picrate was recrystallized from absolute ethanol, m.p. 161–163° (dec.). [lit. 163–165° (dec.), corr.[9]]. The mixture melting point with an authentic sample showed no depression.

Chromatography. Paper chromatography on Whatman #1 paper strips was carried out at 25.0 ± 0.5° using the organic layer separated at 20.0 ± 1.0° from a combination of benzene, methyl alcohol, isoamyl alcohol, water, pyridine mixed in the volume ratios of 9:6:3:2:1. This solvent system resulted in R_f values of 0.64 ± 0.02 for morphine and 0.40 ± 0.03 for normorphine. The color of the spots was developed by spraying with Schwartz Laboratories Diazo Blue B, 50 mg. dissolved in 15 cc. of 0.25*N* *p*H 9 borate buffer. A yellow coloration appeared for normorphine and orange for morphine. In 0.1 mg. samples, 1% normorphine was readily detectable. A butanol–acetic acid–water system (1-butanol saturated at 25° with 4% aqueous acetic acid) was also used.

Column chromatography was carried out on a powdered cellulose column (300 × 20 mm.) employing the above five-solvent system used for the paper strips. In a typical run, a 60-mg. sample containing 3–5% normorphine was applied to a prewashed column in 5 cc. of solvent. After a forerun of 40 cc., uncontaminated morphine appeared in the next four 5-cc. eluates (80% yield) followed by pure normorphine. Twice this load was successfully applied to a 600 × 20 mm. column.

Autoradiography. Paper chromatograms of crude and of pure morphine-*N*-methyl-C^{14} (*ca.* 0.1 mg.) using both the five solvent system and the butanol–acetic acid–water system were exposed to Kodak No-Screen Medical x-ray film for 24-hr. periods. The film was developed in open trays with D-19 developer for 5 min. at 25° and fixed with F-10 fixer. In all instances, only one spot appeared on the film. The R_f value corresponded exactly to that of an authentic sample of morphine.

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(5) All melting points are uncorrected.

(6) Kindly supplied by Dr. Carl Pfister, Merck and Co., Inc., Rahway, N. J.

(7) T. Reichstein and C. W. Shoppee, *Discuss. Faraday Soc.*, **7**, 305 (1949).

(8) R. Kempf, *J. prakt. Chem.*, [2] **78**, 201 (1908).

(9) C. W. Maplethorpe and N. Evers, *Pharm. J.*, **115**, 137 (1925).

Pyridine-1-oxides. IV. Nicotine-1-oxide, Nicotine-1′-oxide, and Nicotine-1,1′-dioxide[1,2]

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Although nicotine (I) is an important alkaloid available commercially in large quantities, its *N*-oxides have not been thoroughly characterized. We report in this paper the preparation and characterization of nicotine-1′-oxide (II), nicotine-1-oxide (III), and nicotine-1,1′-dioxide (IV).

Nicotine-1′-oxide (II) was first prepared in poor yield by Pinner[4–6] by direct oxidation of nicotine with dilute hydrogen peroxide, but it was referred to as Pinner's "oxynicotine" in the absence of knowledge of its structure. Its correct structure was later advanced,[7] other methods for its preparation have been reported[8,9] and a number of reactions of II have been discussed, including its reduction to nicotine.[9–12] We have now

(1) For the previous paper in this series, see E. C. Taylor, A. J. Crovetti, and N. E. Boyer, *J. Am. Chem. Soc.*, **79**, 3549 (1957).

(2) This work was supported in part by grants from the National Science Foundation and from the Smith, Kline and French Foundation.

(3) Present address: Research Department, Hooker Chemical Corporation, Niagara Falls, N. Y.

(4) A. Pinner and R. Wolffenstein, *Ber.*, **24**, 61 (1891).

(5) A. Pinner, *Ber.*, **28**, 456 (1895).

(6) A. Pinner, *Arch. Pharm.*, **231**, 378 (1893).

(7) M. Auerbach and R. Wolffenstein, *Ber.*, **34**, 2411 (1901).

(8) G. Ciamician and P. Silber, *Ber.*, **48**, 181 (1915).

(9) C. H. Rayburn, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **63**, 115 (1941).

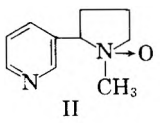
(10) M. Polonovski and M. Polonovski, *Compt. rend.*, **184**, 1333 (1927).

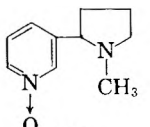
(11) M. Polonovski and M. Polonovski, *Bull. soc. chim. France*, (4) **41**, 1190 (1927).

(12) It is relevant to point out that Pinner's "nicotone", which can be prepared from II by distillation, has been shown to be 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine [C. H. Rayburn, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **72**, 1721 (1950)]. "Pseudooxynicotine" has been shown to be 3-pyridyl-3-methylaminopropyl ketone [P. G. Haines and A. Eisner, *J. Am. Chem. Soc.*, **72**, 1719 (1950)].

found that the direct oxidation of nicotine with 10% hydrogen peroxide gives almost quantitative yields of nicotine-1′-oxide (II), characterized as its dipicrate.

Very little information is available in the literature concerning nicotine-1,1′-dioxide (IV). A nicotine dioxide was mentioned by Badgett *et al.*, but neither its source nor its nature was disclosed.[13] A nicotine dioxide was claimed by Weil[14] by the irradiation of nicotine in the presence of oxygen, but no structure was advanced for the product or for an intermediate $C_{10}H_{12}N_2$ postulated in the same reaction. Frankenburg[15] has reported the isolation of a yellow oil, $C_{10}H_{14}N_2O_2$, apparently identical with Weil's product, from fermented tobacco, but the product again was neither characterized nor was a structure assigned. Several years later, Weil patented a process for the oxidation of nicotine by irradiation in the presence of oxygen and methylene blue[16]; the product was claimed to be a dimeric compound $(C_{10}H_{14}N_2O_2)_2$ for which no structure was suggested. We have now found that nicotine-1,1′-dioxide (IV) may be readily prepared by the reaction of nicotine with 30% hydrogen peroxide or with perlauric acid. The latter procedure is particularly convenient, since the only contaminant is lauric acid which is readily removed from the reaction mixture by filtration.


II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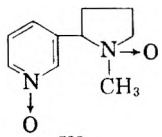
IV

The literature contains no mention of nicotine-1-oxide (III).* This compound has now been prepared by the reduction of the dioxide (IV) with sulfur dioxide.

Since these nicotine oxides are liquids which cannot be distilled without decomposition, they were characterized as their picrates. Details of their preparation and characterization are given below.

EXPERIMENTAL[17]

Nicotine-1′-oxide (II). A mixture of 204 g. of 10% aqueous hydrogen peroxide and 32.4 g. of nicotine was allowed to stand at room temperature for 2 days, and then concentrated in a rotating film evaporator in the presence of platinum foil. The residual pale, straw-colored oil was dissolved in absolute ethanol, the solution treated with charcoal and filtered, and the filtrate concentrated again in the same manner. The resulting oil was treated with an excess of picric acid in ethanol to give 124 g. (98%) of the dipicrate of II; m.p. 168–169° dec.[18] The product was recrystallized from 65% aqueous ethanol for analysis.

Anal. Calcd. for $C_{10}H_{14}N_2O.2C_6H_3N_3O_7$: C, 41.5; H, 3.2; N, 17.6. Found: C, 41.7; H, 3.2; N, 17.5.

Nicotine-1′-oxide (II) is hygroscopic and attempted removal of traces of solvent by vacuum distillation results in extensive decomposition.

Nicotine-1,1′-dioxide (IV). Method (a). To a mixture of 954 g. of glacial acetic acid and 325 g. of nicotine contained in a 3 l. flask was added, with stirring, 590 g. of 30% hydrogen peroxide. The resulting mixture was heated in an oil bath (external temperature 50°) for 16 hr., and then for an additional 6 hr. at 80–90°. Concentration of the resulting amber-colored solution in a rotating film evaporator in the presence of platinum foil yielded 869 g. of a pale yellow viscous oil. An 87-g. aliquot of this oil was dissolved in 75 ml. of water and treated with 46 g. of picric acid in 4 l. of water to yield, after cooling, 72.9 g. of nicotine-1,1′-dioxide monopicrate. This represents an 86% conversion of I to IV. Recrystallization of the picrate from water yielded an analytical sample, m.p. 246° dec.

Anal. Calcd. for $C_{10}H_{14}N_2O_2.C_6H_3N_3O_7$: C, 45.5; H, 4.1; N, 16.5. Found: C, 45.3; H, 4.3; N, 16.2.

Although nicotine-1,1′-dioxide decomposes on attempted distillation, it can be prepared essentially free of solvents and pure enough for subsequent reactions, by heating the above viscous yellow oil at 70°/50 microns for several hours.

Method (*b*). A solution containing 32.5 g. of nicotine, 216 g. of perlauric acid[19] and 1.5 l. of petroleum ether was allowed to stand at room temperature for 40 hr. and then evaporated to dryness under reduced pressure. Treatment of the residue with water and filtration yielded 180 g. (90%) of lauric acid, while concentration of the aqueous filtrate at 40° *in vacuo* yielded a pale, straw-colored viscous oil which was shown to be essentially pure nicotine-1,1′-dioxide by conversion of an aliquot to the picrate, m.p. 246° dec. A mixture melting point determination with the product formed by method (a) showed no depression.

Nicotine-1-oxide (III). Gaseous sulfur dioxide was bubbled through a solution of 298 g. of nicotine-1,1′-dioxide in 700 ml. of water for 2.5 hr. The color of the reaction solution rapidly changed from pale yellow to red to dark brown, and the temperature rose to 65°. Occasional use of an ice bath was necessary to maintain the temperature below this point. The reaction mixture was allowed to stand overnight at room temperature and then concentrated at 30° in a rotating film evaporator to give a dark red, viscous, almost solid mass consisting largely of the sulfate of nicotine-1-oxide.

An aliquot was dissolved in water and carefully neutralized with aqueous sodium hydroxide. Evaporation below 30° under reduced pressure and addition of ethanol and ether to the residue yielded sodium sulfate, which was removed by filtration. Concentration of the filtrates then gave crude nicotine-1-oxide as an orange liquid which rapidly decomposed on attempted distillation. Treatment with picric acid in water yielded a dipicrate (66% yield based on nicotine-1,1′-dioxide), m.p. 155–156° dec., which was recrystallized from water.

(13) C. O. Badgett, A. Eisner, and H. A. Walens, *J. Am. Chem. Soc.*, **74**, 4096 (1952).

(14) L. Weil, *Science*, **107**, 426 (1948).

(15) W. G. Frankenburg, *Science*, **107**, 427 (1948).

(16) L. Weil, U.S. Patent **2,543,817**, March 6, 1951; *Chem. Abstr.*, **45**, 4566 (1951).

* NOTE ADDED IN PROOF: Since this paper was submitted for publication, two other papers describing the preparation and properties of the nicotine-*N*-oxides have appeared: (a) A. W. Johnson, T. J. King and J. R. Turner, *J. Chem. Soc.*, 3230 (1958); dipicrate of III, m.p. 147–148°; monopicrate of IV, m.p. >220° (b) Ya. L. Gol'dfarb and V. K. Zvorykina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 748 (1958); dipicrate of II, m.p. 168°; dipicrate of III, m.p. 161°; monopicrate of IV, m.p. 239–240°.

(17) All melting points are corrected. We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(18) This compound is reported to melt with decomposition at 154–158°,[4] 155–156°,[7] 168°,[8] and 169°.[9]

(19) F. P. Greenspan, R. J. Gall, and D. G. MacKellar, *J. Org. Chem.*, **20**, 215 (1955).

Anal. Calcd. for $C_{10}H_{14}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 41.5; H, 3.2; N, 17.6. Found: C, 41.6; H, 3.0; N, 17.7.

It should be pointed out that neither II, III, nor IV can be satisfactorily extracted from aqueous solution with organic solvents.

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Addition of Alkanethiolic Acids to $\Delta^{1,4,6}$-3-Oxosteroids

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Recently some selective additions to $\Delta^{1,4,6}$-3-oxosteroids have been reported. Nussbaum and coworkers[1] have reported the epoxidation of the 6,7-double bond, and Kirk and Petrow[2] recorded the addition of chlorine to the 1,2-double bond. We have observed mono- and di- additions of alkanethiolic acids to the $\Delta^{1,4,6}$-3-ketones. When 1,4,6-androstatriene-3,17-dione was heated with ethanethiolic acid, a monoadduct separated rapidly from the hot solution. The same product was obtained from a chloroform solution of equimolar amounts of triene and thiolic acid irradiated with an ultraviolet lamp. On the basis of its ultraviolet spectrum ($\lambda_{max}^{methanol}$ 287 mμ, ϵ 23,400) and of analogy to the addition of thiolic acids to $\Delta^{1,4}$-3-oxosteroids,[3] this product was assigned the structure, 1α-acetylthio-4,6-androstadiene-3,17-dione.

In the cases of 17β-acetoxy-1,4,6-androstatrien-3-one, 17α,21-dihydroxy-1,4,6-pregnatriene-3,11,20-trione 21-acetate, and 11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione 21-acetate, the products isolated were di-adducts (exhibiting maxima in the 240 mμ region characteristic of Δ^4-3-ketones). Again by analogy to monoadditions,[3] these compounds were assigned the 1α,7α-diacylthio structures.

EXPERIMENTAL[4]

1α-Acetylthio-4,6-androstadiene-3,17-dione. 1,4,6-Androstatriene-3,17-dione,[5] 2.00 g., was dissolved in 5.0 ml. of ethanethiolic acid and irradiated and heated with an ultraviolet light for 1 hr. During this time crystals formed. They were separated by filtration, washed with ether, and crystallized from methylene chloride-methanol. In this way 1.00 g. of 1α-acetylthio-4,6-androstadiene-3,17-dione, m.p. 229–229.5° (dec.), was obtained.

Anal. Calcd. for $C_{21}H_{26}O_2S$: C, 70.36; H, 7.31. Found: C, 70.38; H, 7.33. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 287 mμ, ϵ 23,400. $[\alpha]_D$ +68°.

1α,7α-Dithiol-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate 1,7-dipropionate. 11β,17α,21-Trihydroxy-1,4,6-pregnatriene-3,20-dione 21-acetate,[6] 0.87 g., dissolved in 1.0 ml. of propanethiolic acid, was heated on the steam bath for several hours. Most of the excess thiolic acid was removed under vacuum and the residue was chromatographed on silica gel. The column was washed with benzene and mixtures of 5 and 10% ethyl acetate in benzene. Then the column was eluted with 15% ethyl acetate in benzene and the eluants were concentrated to yield 0.20 g. of 1α,7α-dithiol-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate 1,7-dipropionate as a glass.

Anal: Calcd. for $C_{29}H_{40}O_8S_2$: C, 59.97; H, 6.94. Found: C, 59.91; H, 7.05. Ultraviolet spectrum $\lambda_{max}^{methanol}$ 239 mμ, ϵ 21,200; $[\alpha]_D$ +37°.

1α,7α-Dithiol-17β-hydroxy-4-androsten-3-one triacetate. 17β-Acetoxy-1,4,6-androstatrien-3-one,[5] 1.93 g., was mixed with 2.0 ml. of ethanethiolic acid and heated and irradiated with an ultraviolet light for 45 min. Some of the excess thiolic acid was distilled under vacuum, ether was added to the residue, and the solid which formed was separated by filtration. Two crystallizations of this material from acetone-ether yielded 0.91 g. of 1α,7α-dithiol-17β-hydroxy-4-androsten-3-one triacetate, m.p. 199–200° (dec.).

Anal. Calcd. for $C_{25}H_{34}O_5S_2$: C, 62.73; H, 7.16. Found: C, 62.68; H, 7.46. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 237.5 mμ, ϵ 20,100; $[\alpha]_D$ −46°.

1α,7α-Dithiol-17α,21-dihydroxy-4-pregnene-3,11,20-trione 1,7,21-triacetate. 17α,21-Dihydroxy-1,4,6-pregnatriene-3,11,-20-trione 21-acetate,[6] 0.54 g., was dissolved in 1.0 ml. of ethanethiolic acid and heated and irradiated with an ultraviolet light for 1 hr. Then part of the excess acid was removed under vacuum and ether was added. The solid which formed was separated by filtration and crystallized from acetone-ether to yield 0.38 g. of 1α,7α-dithiol-17α,21-dihydroxy-4-pregnene-3,11,20-trione 1,7,21-triacetate, m.p. 190–191° (dec.).

Anal. Calcd. for $C_{27}H_{34}O_8S_2$: C, 58.89; H, 6.22. Found: C, 59.05; 58.72; H, 6.70, 6.53. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 235.5 mμ, ϵ 18,500; $[\alpha]_D$ +80°.

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Synthesis of 1,2,4,5-Tetrachlorobenzene-1-Cl^{36}

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1,2,4,5-Tetrachlorobenzene has been under investigation in this laboratory for use as an agricultural chemical. The compound, labeled with chlorine-36, was desired for residue determinations using an isotope dilution procedure. Since it had not previously been prepared the synthesis was undertaken employing the Sandmeyer reaction.

EXPERIMENTAL

Cuprous chloride-Cl^{36}.[1] To a solution of cupric sulfate pentahydrate (187 mg., 0.75 mmole) and sodium chloride-Cl^{36} (44 mg., 0.75 mmole, specific activity 20.8 μc./mmole) in 0.6 ml. of water was added dropwise with shaking at room temperature, sodium sulfite (96 mg., 0.76 mmole) in 0.3 ml. of water. The mixture was centrifuged, the aqueous phase was removed with a dropper, and the precipitate of cuprous chloride-Cl^{36} was washed once with 0.5 ml. of water to which was added a very small amount of sulfurous acid to prevent oxidation. This aqueous phase was also removed by centrifugation.

The cuprous chloride-Cl^{36} was washed three times each with acetic acid, anhydrous ethanol, and anhydrous ether, centrifugation being used each time to separate the liquid phase. The product was used immediately in the next reaction.

The yield in preliminary runs was quantitative.

1,2,4,5-Tetrachlorobenzene-1-Cl^{36}. 2,4,5-Trichloroaniline (147 mg., 0.75 mmole) was diazotized in the following manner[2]: The aniline derivative was dissolved in 0.75 ml. of concentrated sulfuric acid. To this ice cold solution was added 1.88 ml. of a cold solution of sodium nitrite (1.125 mmole) in concentrated sulfuric acid. Cold 85% phosphoric acid (0.75 ml.) was then added and the dark colored solution was allowed to stand at room temperature for 1.5 hr. Initially and rather slowly, there was some precipitation, but the crystalline material gradually redissolved on intermittent shaking as the reaction progressed. The reaction solution was finally poured onto ice to give a solution with a volume of about 10 ml. The excess nitrous acid was destroyed by addition of small quantities of urea.

During the 1.5 hr. required for the diazotization reaction to take place, the cuprous chloride-Cl^{36} was prepared as described above. Following this, a solution of the cuprous chloride-Cl^{36} (0.75 mmole) and sodium chloride-Cl^{36} (65 mg., 1.13 mmole) in hydrochloric acid-Cl^{36} (0.6 ml. of 1.64 N acid, 0.98 mmole, specific activity 20.8 μc./mmole) was prepared. This solution contained a total of 2.86 mmole of chloride-Cl^{36}. Preliminary work had made it clear that a one-to-one stoichiometry, chloride to diazotized amine, gave a very poor yield of product.

The cuprous chloride-Cl^{36} solution was heated on the steam bath and the diazonium solution at room temperature was rapidly poured onto it with shaking. After 15 min. of intermittent shaking at room temperature, the product was isolated by hot benzene extraction. The benzene solution was placed in a porcelain crucible (3.3 cm. i.d. at the top) and the benzene was removed using the steam bath and a gentle stream of air. This evaporation was carried out carefully to prevent loss of product since tetrachlorobenzene sublimes very easily.

The product was purified by sublimation at atmospheric pressure in the following manner: The crucible containing the crude product was covered with a piece of Whatman No. 1 filter paper (4.25 cm.) through which were punched a large number of pin holes. This paper served to prevent sublimed product from falling back into the crucible and, more important, acted as a condensing surface for colored byproducts which do not sublime, but distill. The paper and crucible were covered with an inverted watch glass (4.2 cm.) which served as the condensing surface. The watch glass was cooled with a gentle stream of air. The crucible was heated at 275–285° for 1 hr. with the hot stage from a melting point apparatus. The tetrachlorobenzene condensed as long white needles, m.p. 137° (lit.[3] 137–141°). The yield was 92 mg. (57%); the specific activity was 20.8 μc./mmole. There was no depression in a mixed m.p. with an authentic sample of 1,2,4,5-tetrachlorobenzene.

The excess chloride-Cl^{36} used in this synthesis was recovered from the reaction mixture by treatment with barium hydroxide solution to precipitate the sulfate and phosphate, conversion to hydrochloric acid-Cl^{36} by means of Dowex-50 exchange resin in the acid form, and finally, titration of the eluate with dilute sodium hydroxide solution followed by evaporation to dryness.

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Stereochemistry of 8,10-Dimethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene

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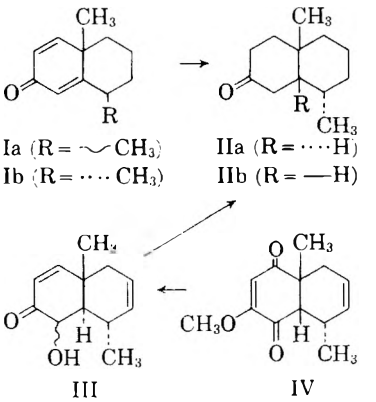
In the reported synthesis of 8,10-dimethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (Ia) the relationship between the methyl groups was unassigned.[1] The work described in this note establishes the missing stereochemical link and allows the assignment of (Ib) for the cyclohexadienone.



Reduction of the cyclohexadienone with lithium in ammonia gave an oily saturated ketone which is shown in the sequel to be identical with *trans*-2-keto-8α-10β-dimethyldecalin (IIa) synthesized from IV. The Diels-Alder adduct IV, in which the methyl groups are fixed in the desired manner, was made from the reaction of 4-methoxy-2,5-toluquinone with *trans*-1,3-pentadiene.[2,3] The adduct on

(1) S. M. Bloom, *J. Am. Chem. Soc.*, 80, 6280 (1958).

(2) The *trans*-1,3-pentadiene employed in this study was not separated from any *cis* contaminant (*vide infra*). Several prior investigations have shown that the *cis*-1,3-pentadiene does not give a normal Diels-Alder adduct. For example, *cis*-1,3-pentadiene gives only polymeric material on reaction with maleic anhydride. See D. Craig, *J. Am. Chem. Soc.*, 65, 1006 (1943); R. L. Frank, R. D. Emmick and R. S. Johnson, *J. Am. Chem. Soc.*, 69, 2313 (1947); S. J. Averill and H. L. Trumbull, *J. Am. Chem. Soc.*, 76, 1159 (1954) for a description of the dienophiles and the conditions employed. These facts led us to conclude that the *cis* isomer would give *only* polymeric material on reaction with 4-methoxy-2,5-toluquinone.

isomerization,[4] reduction with lithium aluminum hydride[5] and hydrolysis[5] was transformed into III. Acetylation, followed by deacetoxylation with zinc[5] and hydrogenation[5] gave IIa which was characterized by its semicarbazone and 2,4-dinitrophenylhydrazone.

The melting points of the semicarbazone and 2,4-dinitrophenylhydrazone of (IIa) synthesized *via* the adduct (IV) were in agreement with those obtained from the reduced cyclohexadienone. On admixture the derivatives from the two sources showed no melting point depressions. Lithium reduction of the cyclohexad enone (Ib) had led to (IIa).[6]

In the course of this work the semicarbazone and 2,4-dinitrophenylhydrazone of (IIb) were made and their melting points are recorded in the experimental section (*vide infra*).

EXPERIMENTAL[7]

Reduction of 8,10-dimethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene with lithium.[8] To 200 ml. of dry ethyl ether and 500 ml. of liquid ammonia sufficient lithium was added to give a persistent blue color to the reaction medium. Lithium, 700 mg., cut into small pieces was added at once. After 5 min. the cyclohexadienone, 1.7 g. dissolved in 45 ml. of dry ethyl ether, was added at once. The ketone was followed by excess ammonium chloride which was added until the blue color was discharged. The ammonia and ether were allowed to evaporate undisturbed and the residue was taken up in water and ethyl ether. The ether layer was washed with water, dried with magnesium sulfate and taken down *in vacuo* to a heavy slightly yellow oil. The *semicarbazone* made in the usual manner was recrystallized twice from absolute ethanol for analysis, fine needles, m.p. (in an evacuated soft glass capillary) 202.5–203.0°.

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77. Found: C, 65.62; H, 9.99.

The *2,4-dinitrophenylhydrazone* was made in the usual way and gave orange prisms, m.p. 151.0–152.5°, after two recrystallizations from cyclohexane.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.24; H, 6.80; N, 15.31.

Hydrogenation of 8,10-dimethyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene. The hydrogenation of the cyclohexadienone was conducted in the manner previously described,[1] with the single change that methanol was employed as the solvent. The theoretical uptake for the 206 mg. of dienone employed is 56 ml. of hydrogen while that observed was 59 ml. On work-up a pale oil was obtained which was converted to the semicarbazone in the usual manner. The derivative was crystallized three times from absolute ethanol, once from 95% ethanol, and finally from absolute ethanol, m.p. (in an evacuated soft glass capillary) 202.0–202.5°. On admixture with the *trans* isomer, m.p. (in an evacuated soft glass capillary) 196–199°.

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77; N, 17.71. Found: C, 65.63; H, 9.97; N, 17.94.

trans-1,4-Diketo-2-methoxy-8α,10β-dimethyl-$\Delta^{2,3;6,7}$-hexahydronaphthalene. 4-Methoxy-2,5-toluquinone,[9] 10 g., *trans*-1,3-pentadiene, 50 ml.,[10] benzene, 100 ml., and a trace of hydroquinone were heated in an autoclave at 110° for 5.5 days. The solvent was removed *in vacuo* and the thick yellow brown oil applied to Alcoa F-20 alumina, 200 g., employing ethyl ether–petroleum ether (b.p. 30–60°), 1:1. Elution with the same solvent gave after a small noncrystalline fraction, the crude semicrystalline adduct which on trituration with petroleum ether (b.p. 30–60°) melted from 90–91° and weighed 2.42 g. For analysis the adduct was taken up in a minimal of boiling dichloromethane, filtered from any insoluble material, and a large amount of petroleum ether (b.p. 30–60°) added. On concentration at the steam cone and slow cooling the compound was obtained as white leaflets. Recrystallization as above gave the adduct, m.p. 91.0–91.5°.

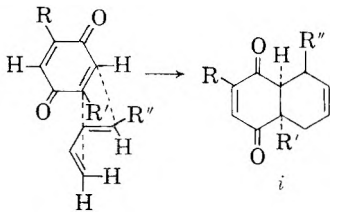
Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.03; H, 7.29.

trans-1,4-Dihydroxy-2-methoxy-8α,10β-dimethyl-$\Delta^{2,3;6,7}$-hexahydronaphthalene. The method of R. B. Woodward *et al.*,[5] was employed on 2.18 g. of adduct. The reaction product on crystallization from dichloromethane–petroleum ether (b.p. 30–60°) gave soft fine needles, m.p. 136.5–137.0°.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.74; H, 9.15.

trans-1-Hydroxy-2-keto-8α,10β-dimethyl-$\Delta^{3,4;6,7}$-hexahydronaphthalene. The method of R. B. Woodward *et al.*,[5] was employed on 659 mg. of diol. The crude product, which partially crystallized on scratching, weighed 530 mg. Crys-

(3) The assignment IV for the adduct is supported by the work of R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958) who detailed the theoretical reasons for expecting the adduct *i* (R = R′ = H, R″ = COOH) from the reaction of benzoquinone and *trans* vinylacrylic acid. In the case under discussion, the dienophile (R = OCH_3, R′ = CH_3) and the diene (R″ = CH_3) would lead to *i* (R = OCH_3, R′ = R″ = CH_3) which is the mirror image of (IV).



i

(4) While R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952) isomerized the *cis* adduct of 4-methoxy-2,5-toluquinone and butadiene by dissolving the compound in aqueous base followed by seeding with the *trans* isomer and acidification, we have found (unpublished results with Miss M. E. Kirtley that the isomerization occurs on Alcoa F-20 chromatographic alumina. In the case at hand the isomerization to the *trans* isomer was observed on purification of the crude reaction mixture (*vide infra*).

(5) R. B. Woodward, *et al.*, ref. 4, conducted a similar series of reactions, converting the adduct of 4-methoxy-2,5-toluquinone and butadiene to both *cis* and *trans*-2-keto-10-methyldecalin.

(6) The result of this study is in accord with the predictions of conformational analysis. An highly unfavorable 1:3 methyl:methyl interaction is avoided when the epimerizable C-8 methyl group assumes the equitorial (alpha) conformation.

(7) All melting points are corrected. Analyses are by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(8) The reduction was carried out by Miss M. E. Kirtley.

(9) A gift from Dr. W. S. Knowles (Monsanto Chemical Co., St. Louis, Mo.).

(10) The *trans*-1,3-pentadiene employed in an early reaction was synthesized by the method of M. A. Dolliver, *et al.*, *J. Am. Chem. Soc.*, **59**, 831 (1937) with modification. Potassium bisulfate was used to dehydrate the intermediate carbinol. This reagent was employed by L. F. Fieser and C. W. Wieghard, *J. Am. Chem. Soc.*, **62**, 153 (1940) to obtain 2,4-dimethyl-1,3-pentadiene. No effort was made to separate the *cis* isomer for the reasons outlined in footnote 2. The diene used in the above experiment was purchased from the Phillips Petroleum Co. The same adduct was isolated with either the synthesized or purchased diene.

tallization from petroleum ether (b.p. 30–60°) and then from methanol gave the ketol, m.p. 102.5–103.5°.[11]

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.97; H, 8.39. Found: C, 74.98; H, 8.61.

trans-2-Keto-8α,10β-dimethyldecalin. The method of R. B. Woodward *et. al.*,[5] was employed to acetylate 590 mg. of the ketol (III). The crude reaction product was deacetoxylated by method A of R. B. Woodward *et al.*,[5] and the oil so obtained hydrogenated with 66 mg. of prereduced platinum oxide in 20 ml. of methanol. In 55 min., 88 ml. of hydrogen had been absorbed, the theoretical amount for two moles of hydrogen being 112 ml. The catalyst was filtered off (pyrophoric) and the solvent evaporated *in vacuo* to give a colorless oil. On examination of the infrared spectrum of the oil taken in carbon tetrachloride, bands at 5.75 microns and 5.85 microns were observed. The oil was therefore taken up in 8 ml. of glacial acetic acid and refluxed with zinc dust, 3 g., for 20 min. The zinc was filtered from the acetic acid solution and washed with several portions of ethyl acetate, the ethyl acetate washes being added to the acetic acid solution. The ethyl acetate and acetic acid were removed *in vacuo* and the residue taken up in dichloromethane and water. The dichloromethane layer was washed successively with water, saturated sodium bicarbonate solution, and water and dried with anhydrous sodium sulfate. On concentration of the dried dichloromethane solution on the steam cone an oil, weighing 300 mg., was obtained. The semicarbazone was made in the usual manner and melted from 194.5–198°. After five recrystallizations from absolute ethanol the compound was obtained as fine short needles, m.p. 202.5–203.5° (taken in an evacuated soft glass capillary). No depression was observed on admixture with the semicarbazone made from the reduced cyclohexadienone, m.p. 202.5–203.5° (taken in an evacuated soft glass capillary concurrently with the pure semicarbazone synthesized above). The pure semicarbazone was converted to the 2,4-dinitrophenylhydrazone with hot 2,4-dinitrophenylhydrazine reagent (in sulfuric acid and methanol). The 2,4-dinitrophenylhydrazone crystallized out as fine orange needles, m.p. 138.5–140.0°. On recrystallization from cyclohexane yellow orange prisms, m.p. 151.0–152.5°, were obtained. No depression was observed on admixture with the 2,4-dinitrophenylhydrazone made from the reduced cyclohexadienone, m.p. 151.0–152.5° (taken concurrently with the pure 2,4-dinitrophenylhydrazone synthesized above).

Acknowledgment. The work described herein was in part supported by a grant from the National Science Foundation (NSF-G4873). The author is indebted to Dr. W. S. Knowles (Monsanto Chemical Co., St. Louis, Mo.) for a gift of the 4-methoxy-2,5-toluquinone.

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(11) This compound was first prepared by Miss M. E. Kirtley as a part of her M.A. thesis, Smith College, 1958.

Preparation and Hydrolysis of Crystalline Ferrocenoyl Chloride[1]

Hans H. Lau and Harold Hart

Received October 8, 1958

It was our original intent to study ferrocenyl free radicals by investigating the decomposition of ferrocenoyl peroxide. This effort was thwarted[2] by lack of success in synthesizing the peroxide. But during the course of the work, ferrocenoyl chloride was prepared pure for the first time, and this note describes its preparation and properties.

Ferrocenoyl chloride has been described several times[3–5] as a red oil prepared, often in rather poor yield, as an intermediate for certain ferrocenoyl derivatives. Ferrocenoyl chloride was obtained as pure red crystals, m.p. 49°; in 48% yield from reaction of the acid[6–8] with phosphorus pentachloride. Treatment with ammonia gave ferrocenamide, m.p. 167–168° (lit.[3] value 167–169°). The spectrum in absolute ethanol showed an appreciable bathochromic shift (λ_{max} 458 mμ; λ_{min} 398 mμ) compared with ferrocene itself (440 mμ and 360 mμ, resp.) or ferrocenoic acid (445 mμ and 386 mμ, resp.). The intense carbonyl band at 5.66μ in the infrared spectrum fell in the range expected[9] for an aromatic acid chloride.

The solvolysis rate of ferrocenoyl chloride was determined in 95% acetone–5% water at 25.0 ± 0.1°. The pseudo first order rate constant, over a concentration range 0.025*N* to 0.005*N* was 8.81 ± 0.22 × 10^{-5} sec.$^{-1}$, comparable to the value of 5.40 ± 0.03 × 10^{-5} sec.$^{-1}$ for benzoyl chloride determined under similar conditions.[10] Attention should be called to the similarity of the ionization constants of the corresponding acids,[11] suggesting that both processes are rather insensitive to electronic differences between the phenyl and ferrocenyl groups.[12]

Several attempts to convert ferrocenoyl chloride to the peroxide failed. Moist ether with sodium peroxide gave only unreacted chloride and acid, by hydrolysis. Reflux with sodium peroxide in anhydrous ether gave what is presumably ferrocenoic anhydride, m.p. 141–142°, with carbonyl bands at 5.62μ and 5.80μ.[13] An attempt to prepare

(1) We are indebted to the National Science Foundation (NSF-G 3289) for financial support of this work.

(2) Although many avenues to such radicals are undoubtedly available, they have hitherto received little attention.

(3) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

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(5) M. Rausch, P. Shaw, D. Mayo, and A. M. Lovelace, *J. Org. Chem.*, **23**, 505 (1958).

(6) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954).

(7) R. A. Benkeser, D. Goggin and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

(8) D. W. Mayo, P. D. Shaw and M. Rausch, *Chem. and Ind. (London)*, 1388 (1957).

(9) L. J. Bellamy, *Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, pp. 109–110.

(10) D. A. Brown and R. F. Hudson, *J. Chem. Soc.* 883 (1953).

(11) *M. Rosenblum*, Thesis, Harvard, 1953.

(12) Ferrocene is known to be more reactive toward electrophilic substitution than either benzene or anisole; see P. L. Pauson, *Quart. Rev.*, **9**, 391 (1955).

(13) See ref. 9, pp. 110–111.

this anhydride from the acid and *N,N'*-dicyclohexylcarbodiimide gave a substance which analyzed correctly for *N,N'*-dicyclohexyl-*N*-ferrocenoylurea, m.p. 161°. Neutral, acidic, or weakly alkaline hydrogen peroxide caused oxidation of the iron in the acid chloride. Reaction of the chloride in pentane-pyridine with *t*-butyl hydroperoxide also resulted in oxidation of the iron.

EXPERIMENTAL[14]

Ferrocenoic acid, prepared by metallation and carbonation of ferrocene,[7,8] melted at 208–210° (*cf.* 208.5°,[15] 195–205°,[6] 225–230°[16]). Potentiometric titration in 95% aqueous acetone gave N.E. 232, Calcd. 230, with the equivalence point at *p*H reading 8.75 on a Beckman *p*H meter with glass and calomel electrodes. This *p*H reading was used when following the kinetics of solvolysis of ferrocenoyl chloride as described below.

Ferrocenoyl chloride. Ferrocenoic acid (2.3 g.) in 30 ml. of benzene was allowed to react with 2.5 g. of phosphorus pentachloride (nitrogen atmosphere) as described.[4] The residue, after removal of solvent and phosphorus oxychloride, was dissolved in pentane, washed with dilute base, water, then dried over anhydrous magnesium sulfate. Evaporation (cold) of the solvent gave a solid m.p. 46–47° which, after careful recrystallization from pentane, gave 1.2 g. of red crystals, m.p. 49°.

Anal. Calcd. for $C_{11}H_9ClFeO$: C, 53.69; H, 3.65; Fe, 22.70. Found: C, 53.79; H, 3.99; Fe, 22.73. The compound gave a strong Beilstein test. Its spectrum showed λ_{max} 458 mμ(ϵ = 200) and λ_{min} 398 mμ(ϵ = 120). Bands for the carbonyl (5.66μ), unsubstituted ferrocene ring[17] (6.94, 9.02, 10.00, 12.16μ) and a monosubstituted ferrocene ring[15] (10.69μ) were present. Concentrated aqueous ammonia converted the chloride to the amide, m.p. 167–168° (lit.[3] value, 167–169°).

The chloride (0.8 g.) was refluxed with an excess of sodium peroxide (0.5 g.) in 50 ml. of anhydrous ether (3 drops of water added) for 5 hr. After decomposing the excess of sodium peroxide by water under ice-cooling, enough ether was added to dissolve the insoluble part between the two layers. The ether layer was washed with water, dried, and the solvent evaporated. The yellow solid (0.5 g.) was recrystallized from pentane, m.p. 141–142°, and presumed to be *ferrocenoic anhydride*.

Anal. Calcd. for $C_{22}H_{18}O_3Fe_2$: C, 59.77; H, 4.10; Fe, 25.27. Found: C, 59.43; H, 4.41; Fe, 25.62. The infrared spectrum showed carbonyl (5.62, 5.80μ), and other bands at 6.89, 8.05, 9.02, 9.40, 9.58, 9.99, and 11.02μ.

N,N'-dicyclohexyl-N-ferrocenoylurea. Ferrocenoic acid (0.5 g.) and 0.5 g. of *N,N'*-dicyclohexylcarbodiimide in 20 ml. of tetrahydrofuran were allowed to stand (dry nitrogen atmosphere) at room temperature for 15 hr. The solvent was removed and the residue washed with ether and recrystallized twice from hexane, m.p. 161°.

Anal. Calcd. for $C_{24}H_{31}O_2N_2Fe$: C, 66.20; H, 7.18; N, 6.44; Fe, 12.85. Found: C, 65.87; H, 7.49; N, 6.58; Fe, 12.62.

Rate measurements. Acetone was carefully purified[18] and conductivity water was used. The solvent was prepared by diluting 50 ml. of water to 1 l. with acetone. For duplicate experiments, 0.852 g. of ferrocenoyl chloride was dissolved in 100 ml. of solvent and the solution divided between two stoppered flasks, maintained at 25.0 ± 0.1°. At convenient intervals, 5 ml. aliquots were withdrawn, quenched by running into 50 ml. of pure cold acetone, then titrated immediately with 0.0128*N* sodium hydroxide, using *p*H 8.75 on a Beckman instrument (*vide supra*) for the end point. The total titers (26.72, 26.85 ml.) were in good agreement with the calculated (26.8 ml.). Typical data are given in Table I.

TABLE I

SOLVOLYSIS OF FERROCENOYL CHLORIDE IN 95% AQUEOUS ACETONE, 25.0°

t, Min.	Ml. of 0.0128*N* Base/5 Ml. Aliquot	$k_1 \times 10^{-5}$, sec.$^{-1}$
0[a]	4.12	...
28	7.27	8.88
42	8.86	9.31
67	10.92	8.87
90	12.48	8.59
126	15.05	8.85
252	20.35	8.39
end	26.72	...
	Av. k = 8.81 ± 0.22 × 10^{-5} sec.$^{-1}$	

[a] Zero time is taken as time first aliquot was removed.

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(14) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Clark Microanalytical Laboratory, Urbana, Ill.

(15) K. L. Rinehart, Jr., K. L. Motz and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

(16) V. Weinmayr, U. S. Patent **2,683,157** (1954).

(17) Ref. 12, p. 402.

(18) R. F. Hudson and J. E. Wardill, *J. Chem. Soc.*, 1729 (1950).

Benzhydryl Ethers of *N*-2-Hydroxyethyl-*O,N*-dialkylhydroxylamines

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The discovery that diphenhydramine, *N*-2-diphenylmethoxyethyl-*N,N*-dimethylamine hydrochloride, $(C_6H_5)_2CHO\text{-}CH_2CH_2N(CH_3)_2\cdot HCl$ is a useful antihistaminic drug with a high incidence of sedation in full therapeutic doses led to an extensive study of this amine and related compounds.[1]

Utilizing methods similar to those used in the synthesis of the corresponding amines,[1b,c] namely, the interaction of benzhydryl bromide and *N*-2-hydroxyethyl-*O,N*-dialkylhydroxylamines in presence of potassium carbonate according to the equation

$$(C_6H_5)_2CHBr + HOCH_2CH_2N(R)OR \xrightarrow{K_2CO_3} (C_6H_5)_2CHO\text{—}CH_2CH_2N(R)OR$$

two *N*-2-diphenylmethoxyethyl-*O,N*-dialkylhydroxylamines have been prepared.

Some of the pharmacological properties of the following compounds have been determined by Dr. C. A. Stone of the Merck Institute for Thera-

(1) (a) American Medical Association, "New and Nonofficial Remedies," J. B. Lippincott Co., Philadelphia, 1956, p. 10. (b) G. Rieveschl, U. S. Patents **2,421,714**; **2,427,878**; Brit. Patent **743,495**. (c) J. B. Wright, H. G. Kolloff and J. H. Hunter, *J. Am. Chem. Soc.*, **70**, 3098 (1948).

peutic Research, West Point, Pa.: *N*-2-diphenylmethoxyethyl - *O,N* - dimethylhydroxylamine (I) and its iodomethylate (II) and the hydrochloride of *N* - 2 - diphenylmethoxyethyl - *O,N* - diethylhydroxylamine (III).

Administration of a dose of 100 mg. per kg. of I to monkeys intramuscularly, produced signs of restlessness, hyperactivity and piloerection. The signs were slow to appear. With intraperitoneal doses of 134 mg. per kg. of I the duration of hexobarbital-induced hypnosis in mice was increased 5.7 fold. Because of the magnitude of the dosage and the order of barbiturate potentiation induced by the compound, it seems more likely that the barbiturate potentiation may be due to the inhibition of the metabolic degradation of the hexobarbital.

Intravenous doses of 3.5 to 7.0 mg. per kg. of II produced weak atropinelike actions, antihistaminic and ganglionic blocking effects in the dog. Again, this compound is not particularly potent.

Compound III markedly prolonged the depressant effects of barbiturates in mice. The use of this agent with a barbiturate did not decrease the dose of barbiturate required to produce hypnosis, such as occurs with chlorpromazine.

EXPERIMENTAL[2]

N-2-hydroxyethyl-O,N-diethylhydroxylamine. To 42 g. (0.47 mole) *O,N*-diethylhydroxylamine in 30 ml. methanol was added a cold solution of 30 g. (0.68 mole) ethylene oxide in 90 ml. methanol. The mixture was refluxed for 7 hr. on a water bath with stirring (condenser temperature lower than 10°). During this time the reaction temperature rose to 65°. The reaction mixture was cooled, concentrated under reduced pressure, and the residue distilled; the fraction b.p. 85–90° (at 38 mm.) was collected; yield, 42 g. (66%). Upon redistillation, b.p. 65–66° (11 mm.). Jones and Burns[3] reported b.p. 63° (10 mm.)

N-2-diphenylmethoxyethyl-O,N-dimethylhydroxylamine (I). A mixture of 40 g. benzhydryl bromide[4] (0.16 mole), 18.7 g. *N*-2-hydroxyethyl-*O,N*-dimethylhydroxylamine[5] (0.18 mole), 24 g. finely powdered anhydrous potassium carbonate (0.18 mole), and 60 cc. dry toluene was heated with stirring on a water bath. If the evolution of carbon dioxide did not start immediately some drops of water were added. After 6 to 10 hr. the gas evolution ceased. The mixture was cooled and acidified with 100 cc. diluted hydrochloric acid. The aqueous layer was washed with ether and alkalinized with potassium hydroxide solution. An oil separated and was extracted with ether; upon evaporation of the dried extract 21.0 g. of crude I (48%) was left as a yellowish oil. Redistillation furnished 15.5 g. pure product, b.p. 138–141° (0.2 mm.).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 74.97; H, 7.66.

The *hydrochloride* was obtained with etheral hydrochloric acid as an oil which did not crystallize.

The *picrate* was prepared in isopropanol and crystallized in 93% yield as yellow prisms, m.p. 102–103°.

Anal. Calcd. for $C_{23}H_{24}N_4O_9$: C, 55.20; H, 4.83. Found: C, 55.43; H, 4.93.

The *iodomethylate* (II) was separated slowly from an ethereal solution of the base after treatment with excessive methyl iodide. Recrystallization from ethanol/ether furnished 80% yield of colorless needles, m.p. 112°.

Anal. Calcd. for $C_{18}H_{24}INO_2$: C, 52.31; H, 5.85. Found: C, 52.61; H, 5.72.

N-2-diphenylmethoxyethyl-O,N-diethylhydroxylamine was prepared as described above in 41% yield, b.p. 155–157° (0.65 mm.).

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.41; H, 8.08.

The *hydrochloride* (III) was obtained with etheral hydrochloric acid and recrystallized from ethyl acetate/ether; m.p. 81–83°.

Anal. Calcd. for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.83. Found: C, 68.25; H, 7.89.

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(2) Melting points and boiling points are uncorrected; microanalyses by Mrs. J. Jensen of this Laboratory.

(3) L. W. Jones and G. R. Burns, *J. Am. Chem. Soc.*, **47**, 2972 (1925).

(4) C. H. Courtot, Anales de Chemie, **5**, 80 (1916).

(5) R. T. Major and L. H. Petersen, *J. Org. Chem.*, **22**, 579 (1957).

Triphenylphosphoniumfluorenylide[1]

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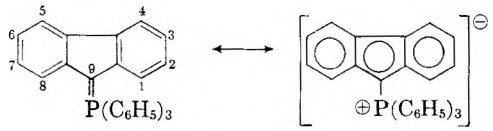
In connection with another problem the reaction of triphenylphosphoniumfluorenylide (I)[2] with symmetrical ketones was examined as a potential



Ia Ib

method of introducing a disubstituted carbon into the C_9-position of fluorene. The failure to obtain a reaction between I and either dimethyl acetonedicarboxylate or acetone prompted us to examine the chemistry of I in detail as it represented a unique electronic system.

Ramirez[3] has suggested that the color, stability, and ability to react with carbonyl compounds reflects the distribution of negative charge in phosphinemethylenes (II).[1] In agreement with this

$$(C_6H_5)_3\overset{+}{P}—\overset{-}{R}$$

IIa R = cyclopentadienyl
b CH_2
c CHC_6H_5
d $CHCOC_6H_5$
e $CHCOOC_2H_5$

postulate, he found that triphenylphosphoniumcyclopentadienylide (IIa), a stable and high melting solid, failed to react with aldehydes or

(1) For nomenclature of these compounds see reference 10, footnote 1.

(2) L. A. Pinck and G. A. Hilbert, *J. Am. Chem. Soc.*, **69**, 723 (1947).

(3) F. Ramirez and S. Levy, *J. Am. Chem. Soc.*, **79**, 67 (1957).

ketones in the usual manner and resisted alkaline hydrolysis. The added resonance stabilization afforded by delocalization of the electrons in the carbon 2*p*-orbital throughout the cyclopentadienyl ring together with the usual overlap with a 3*d*-orbital of phosphorus[4] may account for this unusual stability.

The chemistry of fluorene is similar to that of cyclopentadiene but the former is considerably less reactive. In many cases this is due to a decreased tendency for electron delocalization in the fluorenyl anion compared to that in the cyclopentadienyl anion. An examination of the chemistry of I when compared to that of IIa was expected to reflect this difference.

Triphenylphosphoniumfluorenylide (I), one of the few known stable phosphinemethylenes,[5] was isolated as a yellow solid, m.p. 258–260. It was dissolved in dilute mineral acid forming a colorless solution from which it could be reprecipitated unchanged upon the addition of alkali. The ultraviolet absorption spectrum of I in chloroform solution resembled that of other fluorenylidene compounds (*e.g.*, benzalfluorene and 9-ethylidenefluorene) below 300 mμ. It was hydrolyzed in only mediocre yield by refluxing an aqueous ethanol but in high yield in alcoholic sodium hydroxide solution to triphenylphosphine oxide and fluorene. The electric dipole moment, measured in benzene solution at 25°, was 7.09 D.,[6] indicating nearly equal contributions of structure Ia and structures summarized in Ib to the resonance hybrid. Hence, the P–C bond must contain nearly 50% double bond character.

The condensation of I with several carbonyl compounds was studied and the results are summarized in Table I.

TABLE I

CONDENSATION OF I WITH CARBONYLS

Reaction	Recovered I	Yield[a]	Expected Product
Acetone[b]	97%	0	IIIa
Dimethyl acetonedicarboxylate	98	0	IIIb
Cyclohexanone	95	0	IIIc
Benzaldehyde	0	84	IIId
Anisaldehyde	60	93	IIIe
p-Dimethylaminobenzaldehyde	94	0	IIIf
p-Nitrobenzaldehyde	0	96	IIIg
Fluorenone	100	0	IIIh
2,4,7-Trinitrofluorenone	0	100	IIIk

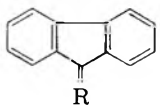
[a] Based on I consumed. [b] Tetrahydrofuran solvent.

(4) (a) *Ann. Reports*, **53**, 137 (1956). (b) See W. von E. Doering and L. K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955) and succeeding papers for evidence concerning *d*-orbital resonance in an analogous sulfur case.

(5) See ref. 3 for a complete list of stable phosphinemethylenes.

(6) We thank Dr. Max T. Rogers of Michigan State University for measuring and interpreting the electric dipole moment.

On the basis of Wittig's mechanism[7] for this reaction involving the initial attack of the electron pair at C_9 on a carbonyl carbon, aldehydes would be expected to be more reactive than ketones. It was, in fact, observed that acetone, dimethyl acetonedicarboxylate, cyclohexanone[8] and fluorenone all failed to react under the test conditions whereas benzaldehyde reacted in high yield, affording benzalfluorene (IIId). Alkyl triphenyl-



R

IIIa	R = $C(CH_3)_2$	IIIf	R = $CHC_6H_4N(CH_3)_2$(p)
b	$C(CH_2CO_2CH_3)_2$	g	$CHC_6H_4NO_2$(p)
c	C_6H_{10}	h	Fluorenylidene
d	CHC_6H_5	k	2,4,7-trinitrofluorenylidene
e	$CHC_6H_4OCH_3$ (p)		

phosphinemethylenes (*e.g.*, IIb) fail to distinguish between and react equally well with both aldehydes and ketones.[9a] Even triphenylphosphoniumbenzylide (IIc) reacts in good yield with both aldehydes and ketones.[9b]

Several *p*-substituted benzaldehydes were then condensed with I in order to examine the electronic effect of substituents and to provide evidence for or against the proposed mechanism. Reaction of I with *p*-dimethylaminobenzaldehyde and anisaldehyde proceeded to 0% and 40% conversion, respectively, whereas reaction with *p*-nitrobenzaldehyde proceeded to 100% conversion very rapidly. While fluorenone failed to react with I, 2,4,7-trinitrofluorenone reacted in high yield to afford 2,4,7-trinitrodifluorenylidene (IIIk). Regardless of the per cent of conversion in the reactions, the yields of pure products, based on the amount of I consumed, were extremely high in all cases.

Triphenylphosphoniumfluorenylide (I) is thus intermediate in reactivity between the alkyl (IIb) and cyclopentadienyl (IIa) derivatives. It may be concluded that the π-orbitals of the fluorenyl portion of the molecule compete favorably with the 3*d*-orbital of phosphorus for the available electron pair in the carbon 2*p*-orbital and this interaction affords added stability to the molecule. It is also evident that the attack of a negative carbon at the positive carbonyl carbon must indeed be the controlling step in the reactions of phosphinemethylenes with carbonyls since substitution by a group (*e.g.*, nitro group) which increased the polarization of the carbonyl group in benzaldehyde facilitated the reaction and vice versa. The effect of the electronic structure of the phosphinemethylene (in terms of the degree of localization of charge at the

(7) (a) G. Wittig, *Angew. Chem.*, **68**, 505 (1956). (b) G. Wittig, *Experientia*, **12**, 41 (1956).

(8) Cyclohexanone also failed to react when heated under reflux for 24 hours.

(9) (a) G. Wittig and U. Schollkopf, *Ber.*, **87**, 1318 (1954). (b) G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

attacking carbon) on the reaction is also in accord with this postulate.

Triphenylphosphinebenzoylmethylene[10] (IId) and triphenylphosphinecarbethoxymethylene[9b,11] (IIe) have recently been prepared and their reactions with carbonyl compounds examined. Both reacted with benzaldehyde but failed to react with cyclohexanone in the usual manner. In both examples there is an available "electron sink" to compete with the 3*d*-orbital of phosphorus for the electron pair on carbon, thereby increasing the stability and decreasing the reactivity of these reagents in a manner analogous to that operating in I.

An examination of the mechanism of the reaction of phosphinemethylenes with carbonyl compounds reveals that the more reactive and less stable reagent should possess the largest double bond character (*i.e.*, the largest concentration of negative charge on the carbon next to phosphorus). It is of interest to note that the measured electric dipole moments of I and IIa indicated that the P—C bond in both possessed roughly 50% double bond character, whereas they differed considerably in their reactivity.

EXPERIMENTAL[12]

Triphenylphosphoniumfluorenylide. Triphenylfluorenylphosphonium bromide, m.p. 289–291°, was prepared in 94% yield according to the procedure of Pinck and Hilbert.[2] It was then converted to I, m.p. 258–260, $\lambda_{max}^{CHCl_3}$ 250 mμ(log ε 4.6), 258 (4.6), 284 (4.3), and 382 (3.6), in 88% yield.

Anal. Calcd. for $C_{31}H_{23}P$: C, 87.3; H, 5.4; P, 7.3. Found: C, 87.6; H, 5.4; P, 7.3.

Reaction of I with carbonyl compounds. The general procedure used in all reactions is described below. To a solution of 1.0 g. (2.35 mmoles) of I in 30 ml. of chloroform was added 2.35 mmoles of the carbonyl compound. After heating the orange solution under reflux for 3 hr. the solvent was evaporated on the steam bath. To the residual oil or solid was added 25 ml. of absolute ethanol and any unchanged I which precipitated was removed by filtration. The filtrate was diluted with water and the precipitated dibenzofulvene derivative was filtered and dried.

A. Benzaldehyde (0.3 g., 2.35 mmoles) and I were reacted as described above. No unchanged I precipitated upon the addition of absolute ethanol. The addition of a few ml. of water precipitated 0.5 g. (84%) of benzalfluorene (IIId), m.p. 71–74°. Recrystallization from ethanol-water afforded colorless leaflets, m.p. 74.5–76.0,° λ_{max}^{EtOH} 227 mμ(log ε 4.6), 248 (4.3), 256 (4.4), and 325 (4.1). (Lit.,[13] m.p. 76°.)

Anal. Calcd. for $C_{20}H_{14}$: C, 94.5; H, 5.5. Found: C, 94.9; H, 5.4.

The filtrate remaining after the removal of the benzalfluorene was quenched with water and exhaustively extracted with ether. The ethereal layer was dried and evaporated to a colorless solid. Hexane was added and the residual precipitate of triphenylphosphine oxide (0.5 g., 77%) was filtered and dried to m.p. 152–154°.

B. Anisaldehyde (0.32 g., 2.35 mmoles) and I were allowed to react as described here. The addition of absolute ethanol to the evaporation residue afforded 0.6 g. of unchanged I as a yellow precipitate. The filtrate remaining after the removal of I was treated with a few ml. of water resulting in the precipitation of 0.25 g. (93%) of *p*-methoxybenzalfluorene (IIIe), m.p. 129.5–131°, which was recrystallized from 95% ethanol as pale yellow plates, m.p. 130–131°, λ_{max}^{EtOH} 232 mμ(log ε 4.5), 247 (4.4), 257 (4.4), and 342 (4.2). (Lit.,[14] m.p. 128–129°.)

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.7; H, 5.7. Found: C, 88.9; H, 5.6.

C. p-Nitrobenzaldehyde (0.36 g., 2.35 mmoles) and I were mixed in 30 ml. of chloroform as described here. Almost immediately the characteristic orange color of I was replaced by a very pale yellow color. Heating under reflux for 3 hr. effected no visible color change. Evaporation of the solvent left a pale yellow oil. The addition of ethanol afforded 0.64 g. (96%) of *p*-nitrobenzalfluorene (IIIg), m.p. 167–168°, which was recrystallized from absolute ethanol as fine yellow needles, m.p. 167–168°, λ_{max}^{EtOH} 224 mμ(log ε 4.5), 258 (4.5), and 354 (4.1).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.3; H, 4.3; N, 4.6.

D. 2,4,7-Trinitrofluorenone (0.74 g., 2.35 mmoles) and I were mixed in chloroform solution as described above resulting in the immediate formation of a deep red coloration. Heating for 3 hr. under reflux effected no visible change. The solution was cooled and a deep red-brown precipitate (1.1 g.) was removed by filtration and dried to m.p. 272–276°. All attempts at recrystallization failed. No unchanged I could be recovered upon evaporation of the chloroform filtrate and the addition of ethanol.

Hydrolysis of I. A slurry of 0.7 g. (1.6 mmoles) of I in 60 ml. of 30% aqueous ethanol was heated under reflux for 24 hr. The fluorenylide was initially insoluble in the solvent but dissolved with apparent reaction only after 18 hr. of reflux. Water, 200 ml., was added and the resulting solution was extracted with ether. Removal of the ether afforded 1.2 g. of a pale yellow solid which was in turn extracted with hexane. Evaporation of this extract left 0.20 g. (73%) of a colorless solid which crystallized from ethanol as colorless plates, m.p. 113–115°, undepressed on admixture with authentic fluorene.

To 100 ml. of a 70% ethanolic sodium hydroxide solution was added 0.93 g. (2.2 mmoles) of I and the mixture was heated under reflux for 18 hr. The solution was worked up as above to afford 0.32 g. (90%) of fluorene, m.p. 113–114.5°.

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(10) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

(11) M. Vilkas and N. A. Abraham, *Compt. rend.*, **246**, 1434 (1958).

(12) Melting points are uncorrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York. Ultraviolet spectra were recorded in 95% ethanol with a Cary model 11 spectrophotometer by W. B. White.

(13) J. Thiele, *Ber.*, **33**, 851 (1900).

(14) J. Thiele and F. Henle, *Ann.*, **347**, 290 (1906).

Reaction of Mesityl Oxide with Peroxyacetic Acid

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The principal product usually obtained from the reaction of an α,β-unsaturated ketone with a peracid is an enol ester.[1] The ketones used, how-

(1) See H. M. Walton, *J. Org. Chem.*, **22**, 1161 (1957) for a recent discussion of the possible products which might be expected from this reaction.

ever, have generally been those having a phenyl group in the β-position.[1,2]

We have observed that mesityl oxide, 4-methyl-3-pentene-2-one (I), having two alkyl groups in the β-position, on treatment with peroxyacetic acid afforded *no* enol ester, II. Instead, there was obtained in 53% yield (based on peroxyacetic acid) crude 3,3-dimethyl-2-acetoxyoxirane (III), contaminated with about 20% of what appeared to be the epoxy ketone, IV. The latter material has the same boiling point as III[3] and could not be separated by distillation. Gas chromatography also failed to give a separation. The presence of IV was indicated (a) by carbon and hydrogen analysis, (b) by ketone carbonyl absorption in the infrared, and (c) by virtue of its removal through water-washing of the mixture.[4] The latter procedure afforded III, in analytical purity, although in reduced yield due to loss to the water.

The epoxy ester III was undoubtedly formed *via* the enol ester II,[1] since, in a blank experiment, the epoxy ketone IV underwent less than 5% reaction with peroxyacetic acid. The fact that no enol ester II was isolated indicates that it must have reacted much more rapidly with the peracid than did the starting material. The failure of the reaction rate to decrease with time (as determined by a plot of *log* peracid concentration *vs.* time) over 90% of the reaction was evidence in support of this view.

The reaction of III with hot acidic ethanol afforded 2-methylpropenal (VII), presumably formed by way of intermediates V and VI; it was isolated as the 2,4-dinitrophenylhydrazone.

When methyl isopropenyl ketone and methyl vinyl ketone, compounds containing neither aryl nor alkyl substitution at the β-carbon, were treated with peroxyacetic acid, very slow reaction rates were encountered.[5] Whereas mesityl oxide was oxidized in 4.5 hr. at room temperature, methyl isopropenyl ketone required 5 days for 95% reaction and methyl vinyl ketone required 26 days for 92% reaction. The product isolated in 22% yield from the methyl isopropenyl ketone reaction was the epoxy ketone, 3-methyl-3,4-epoxy-2-butanone, apparently contaminated with about 10% of the corresponding epoxy ester, 2-methyl-2-acetoxyoxirane. The presence of the latter was inferred from carbon and hydrogen analysis, saponification value, and infrared analysis.

In view of the low recovery of epoxy derivatives obtained in the reaction of methyl isopropenyl ketone with peroxyacetic acid (undoubtedly due to the hydrolysis of primary products to water-soluble fragments during the 5-day reaction period), the reaction mixture from methyl vinyl ketone was not investigated.

EXPERIMENTAL

Reaction of mesityl oxide with peroxyacetic acid. To a stirred solution of 49 g. (0.50 mole) of mesityl oxide (n_D^{20} 1.4401) in 250 ml. of chloroform was added 0.50 mole of 45% peroxyacetic acid[6] (previously treated with sodium acetate to neutralize the sulfuric acid present). The mixture was stirred at 20–25° using a water bath held at 15–20° by the periodic addition of ice, and the rate of disappearance of peroxyacetic acid was followed iodometrically[7]:

Time (Hr.)	% Peroxyacetic Acid Consumed
1	53
2.5	89
3.5	93
4.5	96

The mixture was treated with 150 ml. of water followed by the portionwise addition of 125 g. of sodium bicarbonate. When carbon dioxide was no longer evolved, excess solid was removed by filtration and the organic layer was washed with 100 ml. of half-saturated ammonium sulfate solution. After drying over magnesium sulfate, the bulk of the chloroform was removed at atmospheric pressure using a 10-tray Oldershaw column. When the kettle temperature reached 120°, distillation was continued under vacuum through a 0.5 × 60 cm. glass spiral-packed column. The following fractions were obtained. Fraction 1: 54–70° (100 mm.), 1.8 g.; Fraction 2: 70–72° (100 mm.), 20.7 g., n_D^{20} 1.4402; Frac-

(2) J. Boeseken and A. Kramer, *Rec. trav. chim.*, **50**, 827 (1931); J. Boeseken and A. L. Soesman, *Rec. trav. chim.*, **52**, 874 (1933); J. Boeseken and J. Jacobs, *Rec. trav. chim.*, **55**, 786 (1936).

(3) R. S. Wilder and A. A. Dolnick, U. S. Patent 2,431,718 (Dec. 2, 1947).

(4) Epoxy ketone IV, prepared by alkaline epoxidation of mesityl oxide (reference 3), is soluble in an equal volume of water while III is less water-soluble.

(5) This would be expected on the basis of a mechanistic interpretation advanced for this general reaction by W. Wenkert and M. Rubin, *Nature*, **170**, 708 (1952).

(6) F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).

(7) F. P. Greenspan and D. G. Mackellar, *Anal. Chem.*, **20**, 1061 (1948).

tion 3: 72–82° (100–50 mm.), 3.8 g.; Fraction 4: 82–83° (50 mm.), 17.3 g.; Residue, 3 g.

Fraction 2 was recovered mesityl oxide (0.21 mole); its refractive index indicated the absence of any enol ester (II).[8] Analysis of Fraction 4 indicated it to be a mixture composed of 78% w. 3,3-dimethyl-2-acetoxyoxirane and 22% w. 4-methyl-3,4-epoxy-2-pentanone.

Anal. Calcd. for 78% $C_6H_{10}O_3$ and 22% $C_6H_{10}O_2$: C, 57.1; H, 8.0. Found: C, 57.1; H, 8.0.

The infrared spectrum showed ester carbonyl absorption at 5.73μ with a shoulder at 5.84μ. A sample of 4-methyl-3,4-epoxy-2-pentanone[3] exhibited carbonyl absorption at 5.84μ.

Fraction 4 (15 g.) was washed with three 25-ml. portions of water, dried over magnesium sulfate and Claisen distilled to give 7 g. of 3,3-dimethyl-2-acetoxyoxirane, b.p. 60° (20 mm.), n_D^{20} 1.4128, which, by analysis, was substantially free of the ketone epoxide.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.4; H, 7.7. Found: C, 55.8; H, 7.9.

A 2,4-dinitrophenylhydrazone was prepared[9] from Fraction 4 and recrystallized from ethyl acetate, m.p. 199–200° (dec.). The same derivative was prepared from freshly distilled 2-methylpropenal, m.p. 200–201° (dec.). The mixed m.p. was 199–200° (dec.). The derivative from Fraction 4 was subjected to analysis.

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.0; H, 4.0; N, 22.4. Found: C, 47.8; H, 4.2; N, 22.3.

Reaction of methyl isopropenyl ketone with peroxyacetic acid. A solution of 84 g. (1.0 mole) of methyl isopropenyl ketone[10] (b.p. 98–99°; 98% purity by bromine number) and 1.0 mole of 45% peroxyacetic acid in 500 ml. of chloroform was allowed to stand at room temperature for 5 days. Iodometric titration at that time indicated that 96% of the theoretical amount of peracid had been consumed. The mixture was worked up as above and distilled through a 10-tray Oldershaw column to give, after removal of solvent and 10.0 g. of crude starting material, b.p. 50–54° (150 mm.), 22.2 g. (22% yield) of product, b.p. 58–59° (50 mm.); n_D^{20} 1.4171. Analysis of the product indicated it to be a mixture containing 89% of 3-methyl-3,4-epoxy-2-butanone[11] and 11% of 2-methyl-2-acetoxyoxirane.

Anal. Calcd. for 89% $C_5H_8O_2$ and 11% $C_5H_8O_3$: C, 59.2; H, 7.9. Found: C, 59.1; H, 8.0.

A 1.96 g. sample of the product was allowed to stand overnight with 50.0 ml. of 0.102*N* sodium hydroxide. Back titration with standard acid indicated the presence of 10.8% by weight of ester calculated as 2-methyl-2-acetoxyoxirane.

The infrared spectrum of the product was virtually identical with that of the epoxy ketone obtained from the alkaline epoxidation of methyl isopropenyl ketone[11]: maxima at 5.84, 7.35, 8.87, 9.92, 10.56, 10.88, and 11.92μ. The only significant difference was a shoulder at 5.71μ, consistent with the presence of small amount of ester impurity.

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(8) A. P. Terent'ev, A. N. Kost, A. M. Yurkevich, and E. E. Khaskina (Moscow State University) *Zhur. Obshchei Khim.* **23**, 746 (1953); *Chem. Abstr.* **48**, 4430 (1954) report b.p. 121–124°, n_D^{20} 1.4106 for isobutyraldehyde enol acetate (II).

(9) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley & Sons, Inc., New York 1948, p. 143.

(10) Prepared by liquid phase alkali-catalyzed condensation between methyl ethyl ketone and formaldehyde (Shell Development Co., unpublished results).

(11) Wilder and Dolnick (reference 3) report b.p. 130–138°; n_D^{20} 1.4192. We repeated their alkaline epoxidation and found b.p. 58–59° (50 mm.); n_D^{20} 1.4182.

7α-Hydroxy-Reichstein's Substance S

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During an extensive investigation of the microbiological transformation of Reichstein's substance S (I) with a variety of organisms, several monohydroxylated products were obtained.[1] The fermentation of this substrate with *Cephalosporium sp.* (Lederle No. Z-164) to form 7α-hydroxy-Reichstein's substance S (IIa)[2] and the tentative proof of its structure is elaborated in this paper.

The structure of IIa was assigned on the basis of the following considerations. Elemental analysis indicated the addition of one oxygen to the parent compound. Treatment of IIa in pyridine with acetic anhydride (one equivalent or an excess over two equivalents) at room temperature provided a monoacetate IIb or a diacetate IIc, respectively, which indicated the addition of an acylable hydroxyl group. Furthermore, reaction of IIa in methanol with 8% (v/v) sulfuric acid at reflux temperature gave in 79% yield 17α,21-dihydroxy-4,6-pregnadiene-3,20-dione (IIIa). An attempt to prepare the 3-monoketal of the monoacetate IIb by treatment with ethylene glycol (benzene reflux, *p*-toluenesulfonic acid) led only to the known 21-acetoxy-17α-hydroxy-4,6-pregnadiene-3,20-dione (IIIb).[3] It is interesting to note that the $\Delta^{4,6}$-3-one moiety is apparently unreactive under these conditions to ethylene glycol.

Since the physical constants of IIa did not agree with either 6α- or 6β-hydroxy-Reichstein's substance S,[4] it seemed obvious that the new group must be on the C7 carbon atom in order to permit

(1) The microbiological synthesis of 15α- and 15β-hydroxy substance S has been announced by this laboratory: S. Bernstein, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *Chem. & Ind. (London)*, 111 (1956).

(2) Other observed microbiological hydroxylations at C7 of various steroids have been reported: (a) A. Krámli and J. Horváth, *Nature*, 162, 619 (1948); **163**, 219 (1949); (b) F. W. Kahnt, Ch. Meystre, R. Neher, E. Vischer, and A. Wettstein, *Experientia*, **8**, 422 (1952); (c) Ch. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955); (d) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progress in Hormone Research*, 11, 157 (1955); (e) H. C. Murray and D. H. Peterson, U. S. Patent **2,702,809** (Feb. 22, 1955); (f) W. J. McAleer, M. A. Kozlowski, T. H. Stoudt, and J. M. Chemerda, Meeting-in-Miniature of the American Chemical Society, New York Section, March 14, 1958; (g) W. J. McAleer, M. A. Kozlowski, T. H. Stoudt, and J. M. Chemerda, *J. Org. Chem.*, **23**, 958 (1958).

(3) F. Sondheimer, C. Amendola, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5932 (1953).

(4) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. Marian Leigh, A. Weintraub, and L. M. Reineke, *J. Am. Chem. Soc.*, **75**, 412 (1953); K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1331 (1954).

dehydration to the $\Delta^{4,6}$-3-one IIIa under acidic conditions. Moreover, in accordance with the observation[5] that the $[M]_D$ (7-hydroxy steroid) $-[M]_D$ (parent steroid) is negative for a 7α-hydroxyl substituent and positive for a 7β-hydroxyl substituent, the ΔM_D (IIa — Reichstein's substance S[6]) was calculated to be -110 suggestive that IIa is 7α,17α,21-trihydroxy-4-pregnene-3,20-dione. Thus, it follows that IIb is 21-acetoxy-7α,-17α-dihydroxy-4-pregnene-3,20-dione and IIc is the 7α,21-diacetate. Further support of the configurational assignment was furnished by sodium bismuthate[7] treatment of IIa to form 7α-hydroxy-4-androstene-3,17-dione (IV). The ΔM_D (IV — 4-androstene-3,17-dione[8]) is -30 again suggestive that the added hydroxyl group at C7 is in the α-configuration.

The absorption spectrum of IIa in sulfuric acid[9] showed a new maximum at *ca.* 340 mμ which could indicate the introduction of a $\Delta^{4,6}$-3-one system similar to the case of the 6β-hydroxy-3-ones. However, it should be mentioned that the sulfuric acid spectrum of 7α-hydroxy-4-androstene-3,17-dione (IV) was essentially similar to that of 4-androstene-3,17-dione in the 2-hr. period used as a standard time. Consequently, some caution must be observed in anticipating a typical acid reaction (*i.e.*, dehydration) under the conditions of determining the sulfuric acid spectrum.

Concurrent with the microbiological hydroxylation experiments, an investigation was carried out to introduce by chemical means an oxygen function in the C7 position of Reichstein's substance S. According to an already published procedure[10] 21-acetoxy-3,20-bisethylenedioxy-5-pregnene-17α-ol (V)[11] was brominated in the allylic position (C7) with *N*-bromosuccinimide. The bromination product VI (not purified) was treated with alumina to give 21-acetoxy-3,20-bisethylenedioxy-5-pregnene-7α,17α-diol (VII). The latter was ozidized with chromic acid–pyridine reagent to 21-acetoxy-3,20-bisethylenedioxy-17α-hydroxy-5-pregnene-7-one (VIII).

In one run, a collection of the mother liquors from the alumina treatment of the bromination product VI gave after oxidation a compound whose ultraviolet spectrum revealed the presence of a $\Delta^{4,6}$-3-one moiety. Accordingly, the product was assigned the structure 21-acetoxy-20-ethylenedioxy-17α-hydroxy-4,6-pregnadiene-3-one (IX), although it could never be brought to a satisfactory elemental analysis. Saponification of IX followed by acid hydrolysis furnished 17α,21-dihydroxy-4,6-pregnadiene-3,20-dione (IIIa) identical to the sample described above. It is most probable that in this particular run an accidental hydrolysis of

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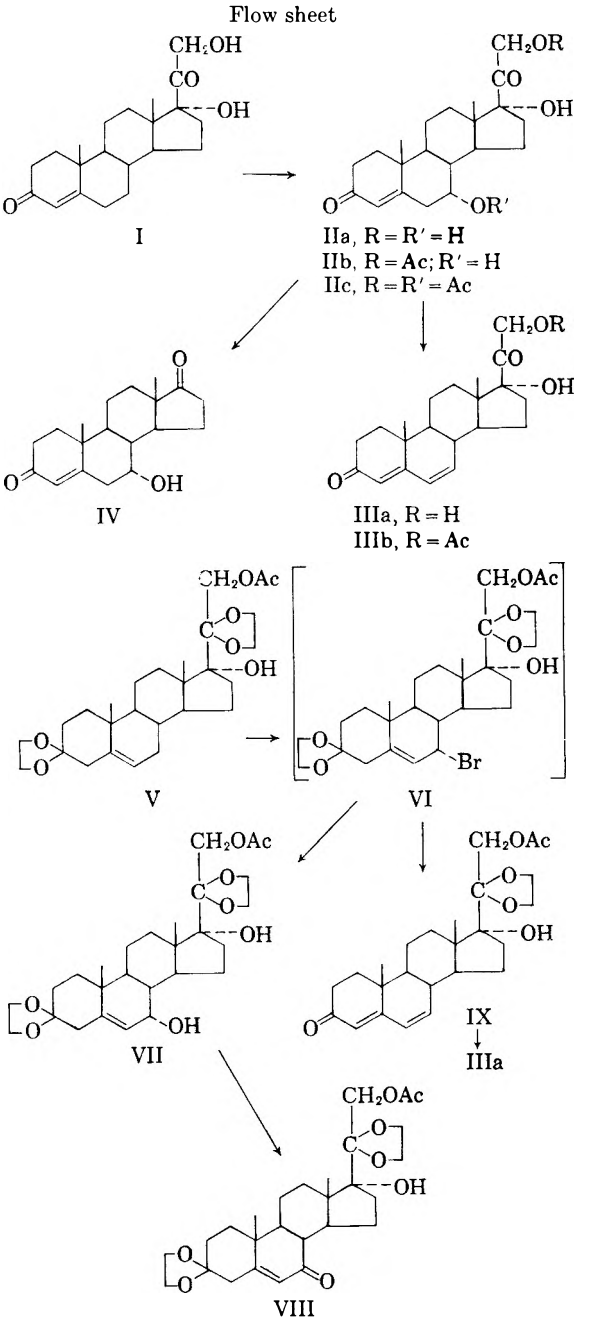

(5) (a) H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 3318 (1952); (b) A. E. Bide, H. B. Henbest, E. R. H. Jones, and P. A. Wilkinson, *J. Chem. Soc.*, 1788 (1948); (c) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2375 (1952), and (d) Ch. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955).

(6) The molecular rotation of Reichstein's substance *S* in methanol as determined in this Laboratory was +450.

(7) C. J. W. Brooks and K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(8) The molecular rotation of 4-androstene-3,17-dione in chloroform is +567 as reported in J. P. Mathieu and A. Petit, *Tables de Constantes et Données Numeriques 6. Constantes Selectionnées Pouvoir Rotatoire Naturel I. Steroides*, Masson & Cie, Editeurs, Paris, 1956, p. 15.

(9) S. Bernstein and R. H. Lenhard, *J. Org. Chem.*, **19**, 1269 (1954).

(10) R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 989 (1956).

(11) R. Antonucci, S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **76**, 2956 (1954).

the 3-ketal function followed by dehydrobromination occurred possibly in the *N*-bromosuccinimide treatment or work-up. The alumina treatment and the oxidation most likely did not contribute to the structure of the final product.

In view of the unlikely possibility of obtaining a 7α-ol-Δ⁴-3,20-dione by a strictly chemical method[10] no further work was done on this approach.

Bioassays.[12] In the electrolyte assay (K/Na) ratio on adrenalectomized rats 7α-hydroxy-Reichstein's substance S (IIa) showed no activity at total dose levels of 15 and 60 μg. In the same assay desoxycorticosterone gave significant responses at 6 and 25 μg. dose levels.

In the thymus involution assay (adrenalectomized and ovariectomized mice) IIa was inactive at a total dose level of 600 μg., whereas hydrocortisone acetate gave significant responses at 75 and 150 μg. dose levels.

7α-Hydroxy-4-androstene-3,17-dione (IV) was inactive in the baby chick comb test for androgenic activity (inunction method, propylene glycol, daily dose of 20 μg. for 7 days). Dehydroisoandrosterone at the same dose level showed significant activity.

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Optical rotations. The rotations are for chloroform solutions (unless otherwise noted), and were determined at 24–25°.

Absorption spectra. The ultraviolet spectra were determined in absolute alcohol; the infrared spectra were determined in a potassium bromide disk (unless otherwise indicated).

Petroleum ether. The fraction used had a b.p. 60–70° (Skellysolve B).

7α-Hydroxy-Reichstein's substance S (7α,17α,21-trihydroxy-4-pregnene-3,20-dione) (IIa). A 5-gal. fermentation bottle containing a paddle stirrer and aerating assembly was charged with 12 l. of the following medium: Edamin lactalbumin digest (Sheffield), 2%; cerelose, 2%; corn steep liquor, 0.6%; *p*H adjusted to 7.0. The bottle was sterilized by autoclaving at 120° for 1 hr. The fermentation vessel was inoculated with 300 ml. of a 72-hr. mycelial growth of *Cephalosporium sp.* and incubated at 28° with a stirring rate of 200 r.p.m. and an aeration rate of 0.2 vol. of air/vol. of medium/min. Forty-eight hr. after inoculation, 6 g. of Reichstein's substance S (I) dissolved in 120 ml. of methanol was added to the mash. The bottle was harvested 125 hr. later when paper chromatography showed an almost complete conversion of Reichstein's substance S to the more polar product. The mash was filtered, and the mycelial cake was washed with 2 l. of acetone. The acetone extract and mash filtrate were pooled, and the acetone was removed by distillation. The resulting aqueous mixture was extracted with four successive 2-l. portions of methylene chloride which were subsequently combined, washed with saturated saline, and evaporated. This furnished 5 g. of a gummy solid which was subjected to partition chromatography on Celite[13] (320 g.) in the following manner. The stationary phase consisted of 6 parts of methanol and 4 parts of water, whereas the mobile phase consisted of 8 parts of ethyl acetate and 3 parts of petroleum ether (b.p. 90–100°). Both phases were equilibrated with each other. The gummy solid was dissolved in 20 ml. of the stationary phase and mixed with 40 g. of diatomaceous earth, and the mixture was added to the column. Chromatography was then initiated with the mobile phase, and 160 fractions of 20-ml. vol. each were collected. Fractions 76–120 (inclusive) contained the desired product as shown by paper chromatographic analysis, and were combined and evaporated. The residue consisted of 4.5 g. of a gummy solid which was slurried with cold chloroform and filtered. This afforded 0.99 g. of crystalline crude IIa, m.p. 197–200°. Crystallization from acetone–petroleum ether raised the melting point to 209–211°; λ_{max} 242–243 mμ (ε 14,800); ν_{max} 3420, 1720, 1667, 1628, and 1034 cm.$^{-1}$; $[\alpha]_D$ +94° (*c*, 0.839 in methanol), $[M]_D$ +340.

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.40; H, 8.56.

21-Acetoxy-7α,17α-dihydroxy-4-pregnene-3,20-dione (IIb). A solution of 7α-hydroxy-Reichstein's substance S (IIa, 100 mg.) in pyridine (1 ml.) was treated with acetic anhydride (0.026 ml.), and the mixture was allowed to stand at room temperature overnight. Water was added, and the resultant crystals were collected and washed with water; 60 mg. (54%), m.p. 197–203°. Recrystallization from acetone–petroleum ether provided the analytical sample, m.p. 210–211.5°; λ_{max} 242 mμ (ε 15,300); ν_{max} 3510, 1740, 1712, 1688, 1630, 1240, and 1070 cm.$^{-1}$; $[\alpha]_D$ +111° (c, 1.146), $[M]_D$ +448.

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97. Found: C, 67.92; H, 8.15.

7α,21-Diacetoxy-17α-hydroxy-4-pregnene-3,20-dione (IIc). A mixture of IIa (60 mg.), pyridine (5 ml.) and acetic anhydride (2 ml.) was allowed to stand overnight at room temperature. The solution was poured into ice water, and the resultant crystals were collected and washed with water; 60 mg. (81%), m.p. 253–256°. Recrystallization from acetone–petroleum ether changed the melting point to 246–248°; λ_{max} 238 mμ (ε 16,100); ν_{max} 3550, 1754 (shoulder), 1740, 1660, 1632, 1235, and 1042 cm.$^{-1}$; $[\alpha]_D$ +107° (*c*, 0.936), $[M]_D$ +478.

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68; OAc, 19.3. Found: C, 67.50; H, 7.90; OAc, 19.3.

17α,21-Dihydroxy-4,6-pregnadiene-3,20-dione (IIIa). *A.* A solution of IIa (0.1 g.) in methanol (15 ml.) and 8% (v./v.) sulfuric acid (10 ml.) was refluxed for 1 hr. Water was added to the cooled solution, and the methanol was evaporated. The residual gummy mixture was neutralized with sodium bicarbonate, and the product was extracted with chloroform. The extract was washed with saturated saline, dried, and evaporated to afford crystals which were recrystallized from acetone–petroleum ether to afford 75 mg. (79%) of IIIa, m.p. 218.5–221°. Further recrystallization furnished pure diene IIIa, m.p. 223.5–225°; λ_{max} 283 mμ (ε 26,400); ν_{max} 3580, 1726, 1656, 1631, 1602, and 1096 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.10, 73.16; H, 8.52, 8.48.

B. The 21-acetate IX (150 mg.) was saponified by refluxing for 0.5 hr. with 5 ml. of 2.5% alcoholic potassium hydroxide. The addition of water to the cooled reaction mixture yielded 115 mg. of the presumed free alcohol, m.p. 250–253°. Recrystallization from acetone (petroleum ether wash) did not alter the melting point. A solution of 100 mg. of the free alcohol in 8 ml. of methanol and 0.8 ml. of 8% sulfuric

(12) We are indebted to the following and their associates for the bioassays; Dr. R. I. Dorfman, Worcester Foundation for Experimental Biology (electrolyte and thymus assays), and Dr. F. I. Dessau, Experimental Therapeutics Research Section of these Laboratories (androgen assay).

(13) The adsorbent was specially treated Celite 545 diatomaceous earth which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and washed with water, followed by 3 A alcohol and/or acetone. Finally, it was dried at 100°. Celite is the trade-mark of Johns-Manville Co. for diatomaceous silica products.

acid (v./v.) was refluxed for 30 min. Water was added to the cooled solution and it was allowed to stand overnight at 5°. The product was filtered and washed with water to afford 68 mg. of the dione IIIa, m.p. 222.5–225.5°. Recrystallization from acetone–petroleum ether gave 56 mg., m.p. 225–228°. One additional crystallization from the same solvent pair did not alter the melting point; λ_{max} 283.5 mμ (ε 26,800); $[\alpha]_D$ +88° (*c*, 0.614). The infrared spectrum was identical to that of the sample prepared above.

21-Acetoxy-17α-hydroxy-4,6-pregnadiene-3,20-dione (IIIb). A mixture of the 7α-hydroxy-21-acetate IIb (0.3 g.), benzene (125 ml.), ethylene glycol (8 ml.), and *p*-toluenesulfonic acid (25 mg.) was refluxed and stirred for 5 hr. with constant water removal. The mixture was cooled, neutralized with sodium bicarbonate, and extracted with chloroform. The extract was washed with saturated saline, dried, and evaporated. The crystalline residue was recrystallized from acetone–petroleum ether to give 240 mg. (83%) of IIIb, m.p. 219–221°; λ_{max} 283 mμ (ε 29,000). Further crystallization raised the m.p. to 223.5–224.5°[11]; ν_{max} 3484, 1757, 1650, 1623, 1592, 1236, and 1095 cm.$^{-1}$.

7α-Hydroxy-4-androstene-3,17-dione (IV). A solution of IIa (0.5 g.) in glacial acetic acid (50 ml.) was shaken with sodium bismuthate (5 g.) for 25 min. After the addition of water, a solution of potassium hydroxide (35 g.) in water (30 ml.) was added, and the mixture was finally neutralized with solid sodium bicarbonate. The product was extracted with chloroform, and the extract was washed once with saturated sodium bicarbonate solution, and three times with saturated saline, dried, and evaporated. The residue was crystallized from acetone–petroleum ether to furnish 107 mg. of crude IV, m.p. 214–215°. Further recrystallization raised the m.p. to 220–222.5°; λ_{max} 241–242 mμ (ε 16,800); ν_{max} 3390, 1748, 1652, and 1087 cm.$^{-1}$; $[\alpha]_D$ +178° (*c*, 1.205), $[M]_D$ +537.

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.40): C, 75.46; H, 8.67. Found: C, 75.71; H, 8.91.

21-Acetoxy-3,20-bisethylenedioxy-5-pregnene-7α,17α-diol (VII). A mixture of the bisethylene ketal of Reichstein's substance S acetate (V, 1.0 g.), *N*-bromosuccinimide (0.46 g.) and anhydrous potassium carbonate (0.2 g.) in carbon tetrachloride (30 ml.) and petroleum ether (b.p. 62–64°) (10 ml.) was refluxed and irradiated for 4 min. by the heat and light of a photospot lamp (Type RSP-2A, General Electric Co.). The filtered solution was stirred at room temperature for 2 hr. with ethyl acetate washed alumina (8 g.), filtered, and evaporated to a glass which was crystallized from ether–petroleum ether to afford 167 mg. of material having a negative Beilstein test, m.p. below 110°; λ_{max} 241 and 285 mμ. The alumina was stirred for 20 min. with approximately 150 ml. of acetone, filtered, and evaporated to a white crystalline solid. Crystallization of the residue from acetone–petroleum ether gave 433 mg. of product, m.p. 193.5–196° with previous softening. Four additional crystallizations from the same solvent pair afforded 190 mg. of the pure diol VII, m.p. 201.5–203.5°; λ_{max} none; ν_{max}^{Nujol} 3550, 3450, 1755, 1680, 1265, 1245, and 1103 cm.$^{-1}$; $[\alpha]_D$ −71° (c, 0.973).

Anal. Calcd. for $C_{27}H_{40}O_8$ (492.59): C, 65.83; H, 8.19. Found: C, 65.75; H, 8.12.

21-Acetoxy-3,20-bisethylenedioxy-17α-hydroxy-5-pregnen-7-one (VIII). *A.* A solution of 240 mg. of VII (obtained by evaporation of the mother liquors of the preceding experiment) in 10 ml. of pyridine was added to a slurry of 170 mg. of chromic anhydride in 17 ml. of cold pyridine. After standing at room temperature for 16 hr., the reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with 10% acetic acid (v./v.) and with water, dried, and evaporated. The residue was crystallized from ether–petroleum ether to afford 130 mg. of product, m.p. 185–186.5°; λ_{max} 240 mμ (ε 12,700). Recrystallization from ether–petroleum ether gave 98 mg., m.p. 186–187.5°. Two additional crystallizations from the same solvent pair did not alter the melting point; λ_{max} 240 mμ (ε 13,000); ν_{max}^{Nujol} 3650, 1761, 1683, 1642, 1242, and 1093 cm.$^{-1}$; $[\alpha]_D$ −63° (c, 0.590).

Anal. Calcd. for $C_{27}H_{38}O_8$ (490.57): C, 66.10; H, 7.81. Found: C, 66.43; H, 7.96.

B. In another run, the 7α-hydroxy-bis-ketal VII (685 mg.) was oxidized in the same manner as above and the residue obtained from a benzene extract was crystallized from acetone–ether–petroleum ether to afford 495 mg. of product, m.p. 183–185°. An additional 74 mg., m.p. 179–182°, was obtained by concentration of the mother liquor to bring the total yield to 83%.

21-Acetoxy-20-ethylenedioxy-17α-hydroxy-4,6-pregnadien-3-one (IX). In an attempt to salvage more of the 7-keto analog VIII, several mother liquors from the alumina hydrolysis of the 7α-bromo compound VI were evaporated and the residue (3.8 g.) was oxidized in the same manner as above. The benzene extract was evaporated and the oily residue was treated with acetone–ether–petroleum ether to give a semisolid. After decanting the supernatant liquid, the semisolid residue was triturated with ether to afford 0.22 g. of solid, m.p. 183–187°. Addition of petroleum ether to the decantate precipitated 0.50 g. which was recrystallized from acetone–petroleum ether to give 0.35 g., m.p. 182.5–187.5°. The latter fraction was combined with the above 0.22 g. and recrystallized from acetone–petroleum ether to afford 0.33 g., m.p. 184–189.5°; ν_{max}^{Nujol} 3550, 1737, 1682, 1633, 1600, and 1102 cm.$^{-1}$ One recrystallization from ether–petroleum ether, one from aqueous methanol and two from acetone–petroleum ether gave 0.18 g. of the 4,6-diene-3-one IX, m.p. 191.5–194°; λ_{max} 283–284 mμ (ε 25,100); $[\alpha]_D$ +39° (*c*, 0.536).

Anal. Calcd. for $C_{25}H_{34}O_6$(430.52): C, 69.74; H, 7.96. Found: C, 68.49, 68.82; H, 7.75, 7.97.

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(14) Ref. 3 gives m.p. 220–222°, λ_{max} 284 mμ, log ε 4.47 (95% ethanol).

p-Thiolcinnamic Acid and S-Acyloxy Derivatives[1]

C. G. OVERBERGER, H. BILETCH,[2] AND F. W. ORTTUNG[3]

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During work relating to the preparation of poly-*p*-thiolstyrene by Overberger and Lebovits,[4] *p*-

(1) This note comprises portions of the Ph.D. dissertation of H. Biletch, Polytechnic Institute of Brooklyn, 1953, and of a thesis submitted by F. W. Orttung in partial fulfillment of the requirements for the degree of Master of Science in the Graduate School of the Polytechnic Institute of Brooklyn, June 1959.

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(4) C. G. Overberger and A. Lebovits, *J. Am. Chem. Soc.*, **77**, 3675 (1955); **78**, 4792 (1956).

thiolcinnamic acid and three *p*-thioacyloxycinnamic acids were prepared.

The thiol acid (m.p. 288–290° dec.) was obtained nearly quantitatively by reducing *p*-chlorosulfocinnamic acid[5] with stannous chloride and hydrogen chloride in acetic acid. Reduction of *p*-chlorosulfocinnamic acid with zinc and acetic acid gave a low yield, while zinc and sulfuric acid appeared to attack the double bond as well. Low yields and less pure products also resulted from many other attempts to prepare the thiol acid from either *p*-iodocinnamic acid or diazotized *p*-aminocinnamic acid. Some of these experiments gave a lower melting (210–211°) product which was apparently the *cis* isomer but which was not fully characterized.

Acylation of the thiol group of *p*-thiolcinnamic acid required different conditions for each of three compounds prepared. *p*-Thioacetoxycinnamic acid was obtained in good yield by the action of a tenfold excess of acetic anhydride in either pyridine at reflux or aqueous potassium hydroxide at room temperature, but the use of acetyl chloride failed. However, benzoyl chloride in aqueous potassium hydroxide did yield *p*-thiobenzyloxycinnamic acid. Myristoyl chloride gave no product in aqueous potassium hydroxide, but in pyridine at room temperature a fair yield of *p*-thiomyristoxycinnamic acid was obtained.

Attempted decarboxylations of the *p*-thioacyloxycinnamic acids under a variety of conditions (Cu, Cu-quinoline, $CuSO_4$-quinoline, aq. HBr) gave in some cases evidence of formation of the desired *p*-thiolacyloxystyrenes, but pure monomeric compounds were never obtained.

EXPERIMENTAL[6,7]

p-Chlorosulfocinnamic acid. A solution of 5.0 g. (0.034 mole) of cinnamic acid in 30 g. (0.264 mole) of chlorosulfonic acid was held at 55° for 30 min., cooled, and poured onto 500 g. of cracked ice. The white precipitate was collected and recrystallized from glacial acetic acid, yielding 5.4 g. (66%) of product, m.p. 221–224° dec. A second recrystallization gave 4.8 g. of white flakes, m.p. 224–225° (226°, no yield given).[5]

p-Thiolcinnamic acid. 1. *Reduction of p-chlorosulfocinnamic acid.*

(a) *Stannous chloride–hydrochloric acid.* This procedure is a convenient modification of a general procedure described by Bogert and Bartlett.[8] *p*-Chlorosulfocinnamic acid, 10.0 g. (0.0404 mole) was dissolved in 300 ml. of boiling glacial acetic acid and the solution, after cooling to 75°, was mixed with a solution of 45 g. (0.200 mole) of stannous chloride decahydrate in 40 ml. (0.480 mole) of concentrated hydrochloric acid. The reaction mixture was shaken for 30 min., periodically allowing the escape of gas and then poured into 1000 ml. of water containing 50 ml. of conc. hydrochloric acid. The yellow precipitate was collected, washed free of acid, and vacuum-dried. The product was extremely insoluble but could be recrystallized from acetone after several hours of Soxhlet extraction to effect solution, m.p. 277–280° (dec.). Additional recrystallization yielded 6.9 g. (96%) of yellow powder, m.p. 288–290° (dec.).

Anal. Calcd. for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 60.04; H, 4.34; S, 17.69.

(b) *Zinc–sulfuric acid.* Cracked ice (20 g.) and 3.7 ml. of concentrated sulfuric acid were mixed at −5°, and 1.7 g. (0.0068 mole) of *p*-chlorosulfocinnamic acid was introduced slowly during 30 min., after which 2.4 g. (0.037 mole) of zinc dust was added during an additional 30 min. without allowing the temperature to exceed 0°. The system was allowed to warm slowly and was then refluxed for 3 hr. Filtration and recrystallization from acetone as above gave 0.3 g. (26%) of yellow powder, m.p. 277–280° dec.; a mixed melting point with the *p*-thiolcinnamic acid prepared by the first reduction, m.p. 277–280° (dec.) melted at 277–280° (dec.).

When 7 instead of 3 hr. heating was allowed, as recommended by Adams and Marvel[9] for the reduction of benzenesulfonyl chloride, the only product was a small amount of white plates of *p*-thioldihydrocinnamic acid, m.p. 119–120° after two recrystallizations from a methylene chloride–ligroin mixture.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.25; H, 5.58; S, 17.73.

(c) *Zinc–Acetic acid. p*-Chlorosulfocinnamic acid, 3.4 g. (0.014 mole), in a mixture of 16 ml. of glacial acetic acid and 40 ml. of water, was stirred at room temperature and treated with 5.0 g. (0.077 mole) of zinc dust added in portions during 15 min. After stirring for 2 hr. and refluxing for 6, a yellow solid was obtained upon dilution with water. Successive washings with methylene chloride and hot acetone gave extracts which, on concentrating, gave, respectively, 0.04 g. of a solid, m.p. 216–220° and 0.32 g. (13%) of yellow powder, m.p. 277–281° (dec.); a mixed melting point with a sample of *p*-thiolcinnamic acid prepared above, m.p. 277–280° (dec.) melted at 277–280° (dec.). The residue after both extractions gave an additional 0.22 g. (9%) of product.

2. *Reaction of potassium ethyl xanthate with diazotized p-aminocinnamic acid. p*-Aminocinnamic acid,[10] 1.63 g. (0.010 mole) was dissolved in 5 ml. of water and 2 ml. of concentrated hydrochloric acid, treated at 0° with 0.7 g. of sodium nitrite and then neutralized to Congo Red with sodium carbonate as described in the procedure of Tarbell and McCall[11] for introducing the sulfhydryl group of 3,5-dichlorothiosalicylic acid. A small amount of excess sodium carbonate was then added and the cold solution was added dropwise during 15 min. to a rapidly stirred solution of 2.57 g. (0.016 mole) of potassium ethyl xanthate in 10 ml. of water kept at 65–70° during the addition and raised to 85° for 15 min. after the addition. Sodium hydroxide solution (2.5 g. in 20 ml. of water) was added and the red solution refluxed under nitrogen for 4 hr. Aqueous hydrochloric acid (1:1) was added until the thick yellow slurry was acid to Congo Red. The solids were filtered off, redispersed in warm dilute hydrochloric acid and treated with a few granules of zinc. When the zinc had disappeared the yellow solids were again filtered, washed, and dried, yielding 0.62 g. (30%) of a fine yellow powder, m.p. 285–287° identical to the previous product prepared by reduction—its ultraviolet spectrum in methanol showed $\lambda_{max} = 296$ mμ, $\log \epsilon = 4.23$.

p-Thioacetoxycinnamic acid. p-Thiolcinnamic acid, 7.2 g. (0.040 mole) in 200 ml. of 20% aqueous potassium hydroxide

(5) J. Stewart, *J. Chem. Soc.*, 2555 (1922).

(6) Analyses were performed by Dr. F. Schwarzkopf, Elmhurst, N. Y., and Drs. Weiler and Strauss, Oxford, England.

(7) All melting points are corrected.

(8) M. T. Bogert and J. H. Bartlett, *J. Am. Chem. Soc.*, **53**, 4046 (1931).

(9) R. Adams and C. S. Marvel, *Org. Syntheses*, Coll. Vol. I, 504 (1948).

(10) E. R. Blout and D. C. Silverman, *J. Am. Chem. Soc.*, **66**, 1442 (1944).

(11) D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.*, **74**, 48 (1952).

was treated with 35 g. (0.343 mole) of acetic anhydride, added portionwise while vigorously shaking and cooling to keep the temperature below 40°. Precipitation was completed by adding 50 ml. of 6*N* hydrochloric acid. The solids were removed by filtration, dried and taken up in 500 ml. of hot methanol. After filtering off inorganic salts and cooling, 5.8 g. of yellow needles were obtained, m.p. 216–217.5°; concentration of their filtrate to 50 ml. yielded an additional 1.9 g. Recrystallization of these combined crops from methanol gave 6.7 g. (75%) of small yellow needles, m.p. 218–219°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.53; S, 14.43. Found: C, 59.68; H, 4.46; S, 14.16.

p-Thiomyristoxycinnamic acid. p-Thiolcinnamic acid, 11.8 g. (0.066 mole) and 1 g. of potassium hydroxide were dissolved in 200 ml. of dry pyridine and the reaction mixture was stirred for 1 hr. Myristoyl chloride, 22.7 g. (0.092 mole) was added dropwise during 1 hr. below 30°, and stirring was continued for 3 additional hr. The solids obtained upon dilution with 500 ml. of water and 100 ml. of 6*N* hydrochloric acid were removed by filtration and then shaken with 200 ml. methanol to remove excess myristic acid. The residue was recrystallized from benzene with the aid of charcoal, 6.8 g. (27%) light yellow plates, m.p. 166–167°.

Anal. Calcd. for $C_{23}H_{34}O_3S$: C, 70.70; H, 8.77; S, 8.21. Found: C, 70.55; H, 8.88; S, 8.00.

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Structure of the Side Chain of Cucurbitacin B

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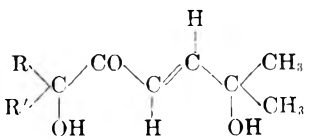
In two recent Communications,[1,2] Lavie and his co-workers have proposed the partial structure I

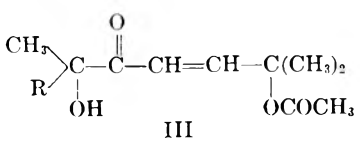


I

$$RCH(CH_3)COCH{=}CHC(OH)(CH_3)_2$$

II

for elatericin A and α-elaterin. Structure II was proposed by Rivett and Enslin[3] for elaterin and for cucurbitacins A and C. Still more recently[4] partial structure III has been proposed for elaterin



III

and cucurbitacins A, B, and C. From our work we also have concluded that curcurbitacin B (formerly called fabacein II[5]) has structure III, and we wish to report results which confirm this structure and which clarify the results of catalytic hydrogenation.

Cucurbitacin B has been assigned the molecular formula $C_{32}H_{48}O_8$[6] and is a monoacetate, containing an α,β-unsaturated carbonyl group.[5,7] Analyses of an apparently identical product isolated from the juice of *Echinocystis fabacea* were reported[5,8] to agree with the formulas $C_{30}H_{44-46}O_8$ (Calcd. for $C_{30}H_{44}O_8$: C, 67.64; H, 8.33; for $C_{30}H_{46}O_8$: C, 67.39; H, 8.67. Found: C, 67.38; H, 8.40; average of 12 analyses). However the formulas $C_{32}H_{46-48}O_8 \cdot 0.5\ H_2O$ (Calcd.: C, 67.70; H, 8.34; or C, 67.46; H, 8.67) also are equally satisfactory and agree better with the analyses of derived products.

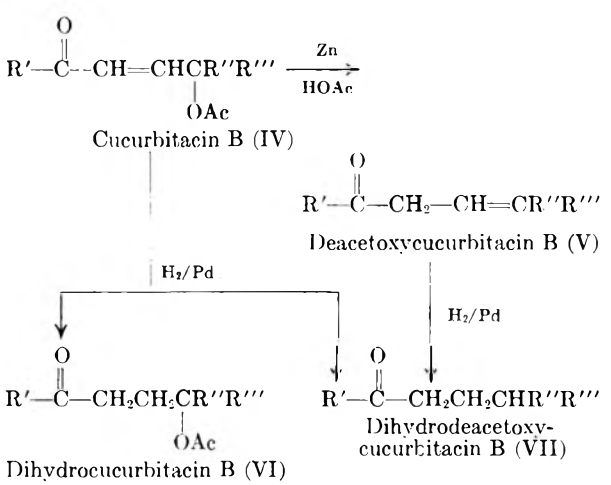
When cucurbitacin B was hydrogenated in 95% ethanol using 10% palladium on carbon as catalyst, from 1.3 to 1.6 moles of hydrogen was absorbed.[8] The resulting solution contained acetic acid, and titration indicated that 0.3 to 0.6 mole of acetic acid was formed. Evidently hydrogenolysis as well as hydrogenation had occurred. The paper chromatogram of the hydrogenated material showed that two products were present which could be separated readily. One product is dihydrocucurbitacin B (VI) (Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63; for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96. Found: C, 68.38; H, 8.80); m.p. 163–164° from acetone-hexane; $[\alpha]_D^{25}$ +57° (c = 0.91 in $CHCl_3$); UV (ethanol) λ_{max} 282 mμ, log ε 2.32; IR ($CHCl_3$): 2.92 (OH), 5.79 w(AcO), 5.85 sh (C=O), 5.89 (C=O), 8.10 (AcO). The other product is dihydrodeacetoxycucurbitacin B (VII) (Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22; for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.59; H, 9.37); m.p. 208–210° from ether; $[\alpha]_D^{25}$ +57° (c = 0.93 in $CHCl_3$); UV (ethanol) λ_{max} 279 mμ, log ε 2.46; IR ($CHCl_3$): 2.92 (OH), 5.85 sh (C=O), 5.90 (C=O). In both products the α,β-unsaturated carbonyl system present in cucurbitacin B[5,7] has disappeared.

When cucurbitacin B in acetic acid was treated with zinc dust for 4 hr. at room temperature, a new product was obtained. The ultraviolet and infrared spectra showed that the α,β-unsaturated carbonyl system had disappeared. Although cucurbitacin B gave only a pale yellow color with tetranitromethane, the new compound gave an orange color, indicating the production of a highly alkylated isolated double bond. Analysis showed that the new

(1) D. Lavie and Y. Shvo, *Proc. Chem. Soc.*, 220 (1958).
(2) D. Lavie, Y. Shvo, and D. Willner, *Chem. and Ind.*, 1361 (1958).
(3) D. E. A. Rivett and P. R. Enslin, *Proc. Chem. Soc.*, 1958, in press. We wish to thank Dr. Enslin for sending us a copy of this Communication.
(4) Private communication from Dr. P. R. Enslin summarizing a note sent to Chemistry and Industry in December, 1958.
(5) W. O. Eisenhut and C. R. Noller, Abstracts of paper presented at the San Francisco meeting of the American Chemical Society, April 1958.
(6) D. E. A. Rivett and F. H. Herbstein, *Chemistry and Industry*, 393 (1957).
(7) P. R. Enslin, S. Rehm, and D. E. A. Rivett, *J. Sci. Food Agr.*, **8**, 673 (1957).
(8) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

compound was a deacetoxycucurbitacin B (V) (Calcd. for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86; for $C_{30}H_{46}O_8$: C, 71.68; H, 9.22. Found: C, 71.72; H, 9.05); m.p. 178–179°; $[\alpha]_D^{25}$ +78° (c = 0.76 in ethanol); UV (ethanol) λ_{max} 292 mμ, log ε 2.66; IR ($CHCl_3$) 2.91 (OH), 5.87 (C=O), 5.90 (C=O). Thus, by this reaction not only has the acetoxy group been removed, but the double bond no longer is in conjugation with the carbonyl group. Hydrogenation of this product converted it quantitatively into a single compound which was identical in all respects with dihydrodeacetoxycucurbitacin B (VII).

These results can be explained by partial formula IV for cucurbitacin B. The easy loss of acetic acid from curcurbitacin B by mild saponification[5] or hydrogenolysis indicates that either an enol acetate



or allyl acetate grouping is present. The former is excluded by the lack of absorption around 5.68 μ, which is typical of enol acetates. It should be noted that hydrogenation of cucurbitacin B stops completely when considerably less than two moles of hydrogen is absorbed. Thus hydrogenolysis of some molecules takes place previous to hydrogenation of the double bond, and hydrogenation of the double bond without hydrogenolysis occurs simultaneously (VII and VI). Once the double bond is hydrogenated, hydrogenolysis no longer occurs. Facile deacylation of cucurbitacin by reduction with zinc and migration of the double bond out of conjugation with the carbonyl group to give deacetoxycucurbitacin B (V) is analogous to the easy removal by zinc reduction of a hydroxyl or acetoxyl group α to a carbonyl group and undoubtedly occurs by a similar mechanism.[7]

Oxidation of dihydrodeacetoxycucurbitacin B (VII) in aqueous dioxane with sodium periodate gave about equal amounts of neutral and acidic products. The latter were converted to the methyl esters with diazomethane and steam distilled. Gas chromatography using a Carbowax-impregnated column identified the chief component of the volatile esters as methyl isocaproate. Methyl isocaproate was obtained also when alkaline hydrogen peroxide was used as an oxidizing agent. Thus the carbon skeleton of isocaproic acid is present as a side chain. The presence of a 1,2-diketo or α-hydroxy keto grouping at the sixth and seventh carbon atoms of the side chain also is indicated.

Acetylation of cucurbitacin B and of its hydrogenation products with acetic anhydride in pyridine gave only amorphous compounds which appeared to be homogeneous on paper. They were purified for analysis by selecting a narrow cut when passed through a chromatographic column. Cucurbitacin B gave a tetraacetate (VIII) (Calcd. for $C_{38}H_{52}O_{11}$: C, 66.65; H, 7.65; O, 25.70; for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; O, 25.63. Found: C, 66.42; H, 7.83; O, 25.38); m.p. 125–130°; $[\alpha]_D^{25}$ +4.4 (c = 0.95 in $CHCl_3$); UV (ethanol) λ_{max} 228 mμ, log ε 4.33; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.92 (C=O), 6.13 (C=C), 8.10 (AcO). Thus cucurbitacin B contains three acetylatable hydroxyl groups and at least one nonacetylatable hydroxyl group which probably is tertiary.

Dihydrocucurbitacin B also gave a tetraacetate (IX) (Calcd. for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; for $C_{38}H_{56}O_{11}$: C, 66.26; H, 8.19. Found: C, 66.52; H, 8.16); m.p. 120–125°; $[\alpha]_D^{25}$ −16.3 (c = 0.92 in $CHCl_3$); UV (ethanol) λ_{max} 286 mμ, log ε 2.28; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.90 sh (C=O), 8.10 (AcO). As expected, dihydrodeacetoxycucurbitacin B (VII) gave a triacetate (X). (Calcd. for $C_{36}H_{52}O_9$: C, 68.76; H, 8.34; for $C_{36}H_{54}O_9$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.46); m.p. ~130°; $[\alpha]_D^{25}$ −20.4° (c = 1.37 in $CHCl_3$); UV (ethanol) λ_{max} 282 mμ, log ε 2.44; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.90 (C=O), 8.10 (AcO).

Oxidation of all three acetates with chromium trioxide in acetic acid at room temperature gave a mixture of volatile acids and a large neutral fraction. From 0.5 to 1.5 moles of carbon dioxide also was evolved. Examination of the volatile acids by paper chromatography and of their methyl esters by gas chromatography showed that the acetate of dihydrodeacetoxycucurbitacin B (X) gave chiefly isocaproic acid. The acetate of cucurbitacin B (VIII), however, gave chiefly β,β-dimethylacrylic acid. These facts together with the observations concerning the hydrogenation products of cucurbitacin B, prove that its acetoxy group must be in the side chain and that R″ and R‴ are methyl groups. The neutral products of the oxidations appear to be methyl ketones (positive iodoform reaction), which, coupled with the results of periodate oxidation, indicates that R′ in formula IV may be replaced by the group  , leading to the partial formula III for cucurbitacin B. The formation of β,β-dimethylacrylic acid would

(7) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4225 (1952).

thus involve an allylic shift of the acetoxyl group. An allylic shift of a hydroxyl group previously has been postulated for the formation of senecioaldehyde by oxidation of cucurbitacin B.[3]

The neutral fractions from the oxidations of all of the acetylated compounds appear to be identical and to consist of a mixture of at least six substances. The component present in largest quantity, which for the present is designated as ketone A, appears to have the formula $C_{28}H_{38}O_8$ (Calcd.: C, 66.91; H, 7.62. Found: C, 67.10; H, 7.47); m.p. 219–221° from acetone-hexane; $[\alpha]_D^{25}$ +86.6 (c = 0.96 in $CHCl_3$); UV (ethanol): λ_{max} 243 mμ, log ε 4.1; 335 mμ, log ε 2.0; IR ($CHCl_3$) 5.77 (AcO), 5.85 (C=O), 6.00, 6.15 (C=C—C=O), 8.12 (AcO). Analyses of the component present in next largest amount, designated as ketone B, indicate the formula $C_{28}H_{36}O_8$ (Calcd.: C, 67.18; H, 7.25; Found: C, 67.09; H, 7.15); m.p. 154–157° from acetone hexane; $[\alpha]_D^{25}$ −84.9 (c = 1.14 in $CHCl_3$); UV (ethanol) λ_{max} 295 mμ, log ε 2.37; IR ($CHCl_3$) 5.78 (AcO), 5.91 (C=O), 8.10 (AcO). Both compounds gave a positive iodoform reaction, indicating the possible presence of methyl ketone groups.

The remaining four neutral products, which are present in smaller amounts, have been isolated in a fairly pure state but have not yet been further investigated. Inasmuch as they do not appear when the oxidations are carried out for longer periods, it is possible that they are intermediates in the formation of ketones A and B.

Enslin and Rivett report the isolation of two methyl ketones designated as cucurbitones A and C from the chromic acid oxidation products of the diacetates of cucurbitacins A and C.[3] Their analyses and molecular weight determination on cucurbitone A, m.p. 210°, $[\alpha]_D$ +100° ($CHCl_3$), λ_{max} 245 mμ (log ε 4.04), correspond to the molecular formula $C_{30}H_{38}O_{10}$. Their analyses of cucurbitone C, m.p. 246–247°, $[\alpha]_D$ +153 ($CHCl_3$) λ_{max} 241 (log ε 4.1), support the molecular formula $C_{30}H_{40}O_9$. The physical constants of our methyl ketone A and cucurbitone A are similar, but the analyses are very different. The other important product of our oxidations, ketone B, is certainly different than any previously reported.

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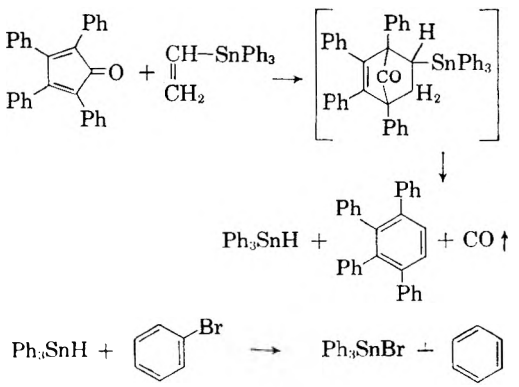
Communications TO THE EDITOR

Hydrogenolysis of Bromobenzene with Triphenyltin Hydride

Sir:

In attempting to prepare organometallic compounds *via* the Diels-Alder reaction, the reaction of tetracyclone (tetraphenylcyclopentadienone) with triphenylvinyltin in refluxing bromobenzene was examined. Among the products isolate were tetraphenyltin, m.p. 228–229° (reported:[1] 229.2°), 1,2,3,4-tetraphenylbenzene (I), m.p. 192.5–193.5° (reported:[2] 193–194°), 2,3,4,5-tetraphenylcyclopent-2-enone, m.p. 160–162° (reported:[3] 160–162° and 162–163°), and triphenyltin bromide (II), m.p. 121.5–122.5° (reported:[4] 121–122°)—all well-known compounds. A reducing gas was evolved throughout the course of the reaction. When tetracyclone was omitted from the boiling bromobenzene solution, tetraphenyltin was isolated, but no triphenyltin bromide.

To rationalize the appearance of these products, it was assumed that tetracyclone underwent the Diels-Alder reaction with triphenylvinyltin affording a transient adduct which eliminated carbon monoxide (the reducing gas?) and triphenyltin hydride to give fully aromatic I. The triphenyltin hydride then reacted with bromobenzene to give II and benzene.



To test this assumption a solution of triphenyltin hydride in bromobenzene was refluxed and afforded II in yields of 61–72% and benzene in yields of 60–75%.

This first example of the hydrogenolysis of an aromatic bromide with triphenyltin hydride is important in view of the recently reported hydrogenolyses of allyl bromide[5] and saturated bromides.[6,7] We have also determined that iodobenzene reacts more rapidly than bromobenzene and that chlorobenzene is least reactive.

Additional work to outline the scope of the hydrogenolysis of aromatic halogen is under way.

Acknowledgment. We are glad to thank the Metal and Thermit Corp. for the gift of generous supplies of triphenylvinyltin and triphenyltin chloride.

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(1) H. D. K. Drew and J. K. Landquist, *J. Chem. Soc.*, 1480 (1935).

(2) W. Dilthey and G. Hurtig, *Ber.*, 67B, 495 (1934).

(3) N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Am. Chem. Soc.*, 75, 2283 (1953).

(4) O. H. Johnson and J. R. Holum, *J. Org. Chem.*, 23, 738 (1958).

(5) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem. (London)*, 7, 356 (1957).

(6) G. J. M. van der Kerk, J. G. A. Luijten, and J. G. Noltes, *Angew. Chem.*, 70, 298 (1958).

(7) After this Communication had been submitted, we found that J. G. Noltes and G. J. M. van der Kerk in the course of their extensive investigation of organotin chemistry independently discovered the hydrogenolysis of bromobenzene with triphenyltin hydride in 54% yield. See "Functionally Substituted Organotin Compounds," report to the Tin Research Institute, June, 1958.

A New Potent Synthetic Analgesic

Sir:

The substitution of phenethyl for methyl on the nitrogen of several well known analgesics has generally produced a marked increase in potency.[1] Well established also is the fact that one optical isomer (usually *levo*) of a racemate contains, with few exceptions, practically all of the analgesic activity.[2] Accordingly, we have synthesized (±)-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) and its optical isomers from (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) (an effective analgesic in mice)[3] by a route previously described.[4] Acetylation of I with acetic anhydride gave the crude *O*-acetyl derivative

(1) J. Weijlard, P. D. Orahovats, A. P. Sullivan, Jr., G. Purdue, F. K. Heath, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, 78, 2342 (1956); T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, 21, 125 (1956); A. Grüssner, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, 40, 1232 (1957); L. F. Small, N. B. Eddy, J. H. Ager, and E. L. May, *J. Org. Chem.*, 23, 1387 (1958).

(2) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, 13, 937 (1955).

(3) This compound is comparable to morphine in analgesic effectiveness, E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

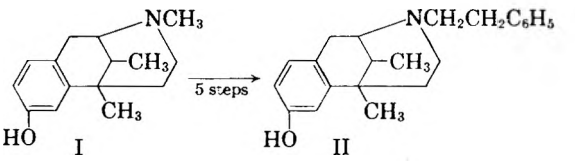
(4) E. L. May, *J. Org. Chem.*, 21, 899 (1956).

which was *N*-demethylated by the method of von Braun.[5] Phenylacetylation of the resultant secondary amine produced the amide which, on reduction with ethereal lithium aluminum hydride, yielded (±)-2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) isolated as the *hydrobromide* salt, m.p. 166–170°[6] (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.40; H, 7.00). The free *base* (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.27; H, 8.48) melted at 180–181°.

Treatment of the hydrochloride salt of I in water with (±)-α-bromocamphor-π-sulfonic acid [(+)-3-bromo-8-camphorsulfonic acid] ammonium salt[7] gave, after fractional crystallization of the diastereoisomeric salts and neutralization of these salts with aqueous ammonium hydroxide, (−)-I, m.p. 183–184.5°, $[\alpha]_D^{20}$ −84.8° (*c*, 0.92, abs. alcohol) (*Anal.* Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.91; H, 8.97); *hydrobromide*, m.p. 238–241°, $[\alpha]_D^{20}$ −52.0 (*c*, 2.00, water) (*Anal.* Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.66; H, 7.34) and (+) -I, m.p. 183–184.5°, $[\alpha]_D^{20}$ +84.3 (*c*, 0.83, abs. alcohol) (*Anal.* Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.75; H, 9.25); hydrobromide, m.p. 238–242°. $[\alpha]_D^{20}$ +52.1° (*c*, 1.46, water) (*Anal.* Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.93; H, 7.18).

As described in the preparation of (±) - II, (−)-I and (+)-I gave, respectively, (−)-II *hydrobromide*, m.p. 284–287°, $[\alpha]_D^{20}$ −84.1° (*c*, 1.12, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.82; H, 7.02); base, m.p. 159–159.5°, $[\alpha]_D^{20}$ =121.6° (*c*, 0.74, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.95; N, 8.44) and (+)-II *hydrobromide*, m.p. 284–287°, $[\alpha]_D^{20}$ +84.4° (*c*, 1.47, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.65; H, 7.15); *base* m.p. 159–160°, $[\alpha]_D^{20}$ +120° (*c*, 0.60, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.35; H, 8.41).

In mice (subcutaneous administration) (−)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) proved to be almost twice as effective (ED_{50} 1.7 mg./kg.) and less than half as toxic (LD_{50}>400 mg./kg.) as (+)-I while the *dextro*-isomer was inactive at 20 mg./kg., a convulsant dose. The (−)-2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) (ED_{50} 0.11 mg./kg.) is 12–15 times more potent than (−)-I, almost 20 times more so than morphine. The (+) -II is also surprisingly effective (ED_{50} 6.7). Finally (±)-II (ED_{50} 0.25) has shown low physical dependence potency in the monkey.[8] Addiction studies in man[9] are in progress. Initial clinical experiments[10] with this racemate show it to be a promising agent for the relief of both acute and chronic pain.



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(5) J. von Braun, O. Kruber, and E. Aust, *Ber.*, **47**, 2312 (1914).

(6) After about a year the melting point had risen to 247–250°. Analysis and infrared data proved the new crystals to be another crystalline modification of II.

(7) From the Aldrich Chemical Co., Inc.

(8) G. Deneau, personal communication.

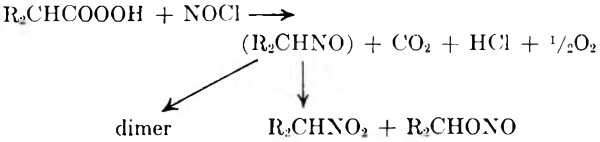
(9) Research Addiction Center, National Institute of Mental Health, Lexington, Ky.

(10) Large-scale preparation of this compound and clinical studies are due to the Smith Kline & French Laboratories, Philadelphia.

A New Reaction of Organic Peroxyacids

Sir:

If a primary or secondary peroxyacid is allowed to react with a nitrosating agent in an appropriate solvent in the cold, an instantaneous reaction occurs. The solution becomes deep blue or green, colors characteristic of monomeric C-nitroso compounds. Upon working up the crude products bis-nitroso compounds have been isolated, as well as nitro compounds and nitrite esters. The following equation approximates the reaction:



We will illustrate it by the results obtained in a typical experiment with peroxyphenylacetic acid.

Peroxyphenylacetic acid (12 g.) prepared by a modification of the method of Swern and coworkers[1] (purity by titration for active oxygen 95%, m.p. 76–77°), was allowed to react with nitrosyl chloride in petroleum ether at 0°; the solution became deep green in color. Three products were isolated from the reaction mixture: (a) bis-α-nitrosotoluene, an ether-insoluble solid, m.p. 120–121.5°[2,3]; crude yield 0.7 g. λ_{max} 295 mμ, lit. 296 mμ.[3] *Anal.* Found C, 69.23; H, 5.83; N, 11.46. The infrared spectrum showed a strong peak at 8.53μ in chloroform and 8.55μ in a Nujol mull (lit.[3] 8.58μ), and the absence of the 6.25 and 6.45μ

(1) W. E. Parker, C. Ricciuti, C. L. Ogg, and D. Swern, *J. Am. Chem. Soc.*, **77**, 4037 (1955).

(2) R. Behrend and E. König, *Ber.*, **23**, 1776 (1890); *Ann.*, **263**, 210 (1891).

(3) E. Müller and H. Metzger, *Chem. Ber.*, **88**, 165 (1955).

peaks characteristic of the monomeric material.[4] (b) Benzyl nitrite, b.p. 31–32° at 1 mm., $n_D^{24.8°}$ 1.4986; crude yield 5 g. The ultraviolet and infrared spectra were identical with a sample synthesized by a different route.[5] (c) α-Nitrotoluene, b.p. 62–63° at 0.6 mm, $n_D^{24.8°}$ 1.5320; crude yield 4 g. The infrared spectrum was identical with a sample prepared by a different route.[5]

No tertiary carboxylic acid from which we have been able to make the peroxyacid has reacted with a nitrosating agent. We are currently investigating the mechanism, and the extensions to other reagents and peroxygen compounds. Preliminary results indicate that other electrophilic agents behave similarly. Dinitrogen tetroxide reacting with peroxyacid gives a nitro compound as the major product. The mechanism may be analogous to that indicated by Barry and Hartung[6] for the nitrosation of malonic acid involving the addition of nitrosyl chloride to an enol form of the acid.

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(5) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Am. Chem. Soc.*, **78**, 1497 (1956).

(6) R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947).