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Optical Rotatory Dispersion Studies. XXVI.[1] α-Haloketones (Part 4).[2] Demonstration of Conformational Mobility in α-Halocyclohexanones[3]

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The preparation of optically active 2-chloro- and 2-bromo-5-methylcyclohexanone is reported. The optical rotatory dispersion curve of 2-chloro-5-methylcyclohexanone in the nonpolar solvent octane exhibited a negative Cotton effect curve which, on the basis of the earlier enunciated "axial α-haloketone rule," is only consistent with a predominance of that chair form in which both the chlorine and methyl substituents are axial. When the dispersion curve was measured in methanol solution, the sign of the Cotton effect was inverted demonstrating the presence of an appreciable amount of the other conformer in which both substituents are now equatorial. The large amplitude changes in the rotatory dispersion curves of 2-bromo-5-methylcyclohexanone in polar and nonpolar solvents are interpreted in a similar fashion.

Our extensive studies[2,5] of the optical rotatory dispersion of halogenated steroid ketones have led to an empirical generalization,[6] which permits the prediction of the sign of the Cotton effect. This offers an important means for determining absolute configurations[6] of cyclohexanones with known conformation, or of establishing the latter if information on the absolute configuration is available. Briefly, this rule states that the sign of the Cotton effect curve[7] of a given six-membered ketone (existing in the chair conformation)[8] is not altered by introduction of equatorial fluorine,[2] chlorine,[5] bromine,[5] or iodine.[2] On the other hand, when axial chlorine or bromine (but not fluorine[5]) is present in the α-position (to the left of observer looking down the O=C axis as indicated by arrow in I), the Cotton effect will be negative, while when it is in the α′-location (to the right of observer as in II), a positive Cotton effect curve will be observed. As noted recently,[2] appropriate application of this rule can also offer valuable information about the preferred existence of a given "free-rotational" isomer as for instance in 17α-halo-20-keto steroids.

The bulk of our earlier work was carried out with polycyclic ketones of rigid conformation and it was clearly desirable to examine the applicability of these empirical generalizations to monocyclic cyclohexanones, which are subject to conforma-

(1) Paper XXV, C. Djerassi, J. Osiecki, and W. Closson, *J. Am. Chem. Soc.*, **81**, 4587 (1959).

(2) Part 3, C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959).

(3) A preliminary communication concerning part of this work has already been published by C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958).

(4) Present address: Department of Chemistry, Stanford University, Stanford, Calif.

(5) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

(6) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957). This has proved to be a specific case of the general "octant rule" for predicting the sign of the Cotton effect of cyclohexanones (see: C. Djerassi, *Rec. Chemical Progress*, 20, 101 (1959); C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, Chap. 13, New York, McGraw-Hill, (1960); W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, in preparation.)

(7) For nomenclature and recording of experimental data see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(8) We have recently found that the rule is also applicable to cyclohexanones existing in the boat conformation; see C. Djerassi, N. Finch, and R. Mauli, *J. Am. Chem. Soc.*, **81**, 4997 (1959).

tional mobility. The most convenient optically active model ketone appeared to be (+)-3-methylcyclohexanone (III), since it is readily available from pulegone[9] and its absolute configuration has been established without any doubt.[9]

The mono-halogenation of 3-methylcyclohexanone (III) is rather complicated, since there are possible two position isomers, each of which can exist as two geometrical (*cis* or *trans* relationship of halogen atom to methyl group) isomers and each of these can in turn be accommodated in two non-equivalent chair conformations.[10] Consequently, there are at least eight plausible alternate representations for an α-halo-3-methylcyclohexanone and as will be shown in the sequel, rotatory dispersion offers a powerful tool for the solution of this problem.

Attention was first directed towards the monobromination of (+)-3-methylcyclohexanone (III), since this has been reported[11] to give a crystalline isomer (m.p. 83–85°) in unspecified yield. We have been able to secure the identical product in 21% yield by conducting the bromination in aqueous solution.[12] Kötz and Steinhorst[11b] have assigned the 2-bromo-5-methylcyclohexanone (IV) structure to this isomer since upon dehydrobromination with aniline, it afforded less than 1% of 5-methylcyclohex-2-en-1-one (Va). In view of the well known tendency towards rearrangement in such amine-promoted dehydrohalogenations, a structure proof based on such a poor yield is unacceptable and it was imperative to settle this point by an alternate procedure. For this purpose, we selected the dehydrobromination with 2,4-dinitrophenylhydrazine,[13] which has been shown not to involve any rearrangement[14] even in such cases where bases such as collidine or pyridine produce one. When the reaction was performed in acetic acid solution[14a] there was obtained in good yield the 2,4-dinitrophenylhydrazone of a methylcyclohexenone, which had to possess structure Vb since it exhibited $[\alpha]_D$ −219°. The alternate isomer, VII, derived from 2-bromo-3-methylcyclohexanone (VI) is, of course, optically inactive.

By settling the position of the bromine atom, only four representations[10,15] (IV *t,e;* IV *t,a;* IV *c,a;* IV *c,e*) have to be considered, two of them possessing a *trans* (IV *t,e;* IV *t,a*) and two a *cis* (IV *c,a;* IV *c,e*) relationship between the bromine atom and the methyl group. Corey[16]—on the basis of a number of model experiments with monobromocyclohexanones—has made the generalization that in the absence of 1,3-diaxial interactions between bromine (or chlorine) and an alkyl group, the halogen atom will assume the axial orientation, since electrostatic repulsion between the halogen atom and the carbonyl group is minimized over that existing in the equatorial isomer. Subsequent dipole moment measurements[17] have shown that this picture cannot hold for solvents of differing polarity and the situation has now been clarified by Allinger and Allinger,[12,18] who have demonstrated that there exists an equilibrium between the two conformational isomers (*e.g.* IV *c,a* ⇄ IV *c,e*). In a nonpolar solvent, this equilibrium lies substantially on the side of the axial conformer (*e.g.* IV *c,a*) and thus approximates the picture visualized by Corey,[16] but in polar solvents an appreciable amount of the equatorial conformer (*e.g.* IV *c,e*) may be present in solution.

The axial or equatorial character of a halogen atom in an α-halocyclohexanone can be recognized readily by infrared[19] or ultraviolet[20] spectral means. Such spectral measurements have now been conducted on the crystalline 2-bromo-5-methylcyclohexanone (IV) in a variety of solvents and these results, together with the dipole moment studies, are presented in the following paper.[21] The results are in accord with the earlier data obtained with 2-bromocyclohexanone[12] in that the proportion of equatorial isomer is augmented as the polarity of the solvent is increased. It should be noted that the spectral data do not differentiate between the two pairs (IV *t,e;* IV *t,a vs.* IV *c,a;* IV *c,e*) of conformational isomers and it was thus not possible to assign a *cis* (IV *c,a;* IV *c,e*) or *trans* (IV *t,e;* IV *t,a*) relationship to the bromine and methyl groups.

(+)-3-Methylcyclohexanone (III) exhibits a positive Cotton effect curve[22–24] in all of the sol-

(9) For leading references see E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

(10) We are ignoring in this case the existence of boat representations or intermediate forms.

(11) (a) N. Zelinsky and M. Roschdestwensky, *Ber.*, **35**, 2695 (1902); (b) A. Kötz and H. Steinhorst, *Ann.*, **379**, 18 (1911).

(12) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

(13) V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948) and later papers.

(14) (a) C. Djerassi, *J. Am. Chem. Soc.*, **71**, 1003 (1949); (b) M. Gates and G. M. K. Hughes, *Chem. & Ind. (London)*, 1506 (1956).

(15) As suggested to us by Dr. W. Klyne, we are using two suffixes: the first denotes configuration (*c* = *cis*, *t* = *trans*), while the second one refers to the orientation of the halogen atom (*e* = equatorial, *a* = axial). The equilibrium mixture of conformers bears only the configurational suffix.

(16) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); *Experientia*, **9**, 329 (1953).

(17) W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956).

(18) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

(19) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(20) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(21) N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, **25**, accompanying paper (1960).

(22) H. S. French and M. Naps, *J. Am. Chem. Soc.*, **58**, 2303 (1936).

(23) C. Djerassi, *Bull. Soc. Chim. France*, 741 (1957).

(24) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 237 (1959).

vents examined and application of our earlier generalizations[6] from the steroid series would predict a similar positive Cotton effect for the two equatorial isomers IV *t,e* and IV *c,e*,[25] and especially for the axial isomer IV *c,a*. On the other hand, a strong negative Cotton effect curve would be predicted for the axial conformer IV *t,a* and such a curve was found experimentally (Fig. 1) for the crystalline

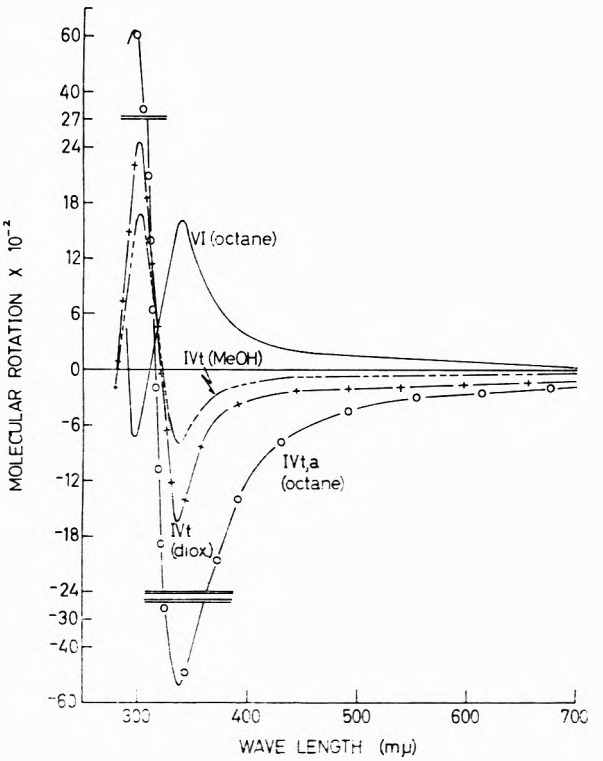
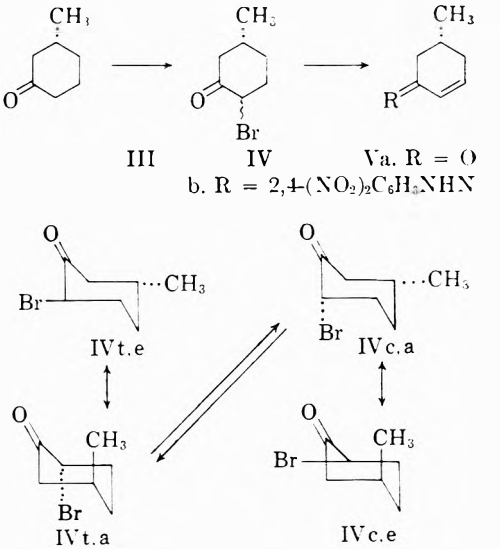


Fig. 1. Optical rotatory dispersion curves of *trans*-2-bromo-5-methylcyclohexanone (IV *t*) and 2-bromo-3-methylcyclohexanone (VI)

bromoketone IV. The amplitude of this negative Cotton effect is greatly reduced as the polarity of the solvent is augmented — indicating the presence of increasing amounts of the equatorial conformer IV *t,e* with its positive Cotton effect. The quantitative aspects of the rotatory dispersion shifts summarized in Fig. 1 and their relationship to the spectral and dipole moment studies are discussed in detail in the accompanying communication.[21]

The rotatory dispersion results offer a decisive answer in favor of the *trans* relationship between the methyl and bromine substituents and this has now been confirmed independently by x-ray studies[26] which show that IV *t,a* represents the correct expression in the crystal lattice.

The demonstration of structure IV *t,a* for 2-bromo-5-methylcyclohexanone does not necessarily mean that it represents the initial product of the bromination of (+)-3-methylcyclohexanone (III), since on the basis of earlier work[16] one would anticipate that bromination of the enol of 3-methylcyclohexanone (III) would lead originally to the axial conformer IV *c,a*, of *cis*-2-bromo-5-methylcyclohexanone. As demonstrated in the following paper[21] by rotatory dispersion and infrared spectroscopic means, the *trans*-isomer IV *t,a* (negative Cotton effect) is readily isomerized to the *cis*-isomer IV *c,a* (positive Cotton effect) in carbon tetrachloride solution containing some hydrogen bromide. While the position of this equilibrium lies predominantly on the side of the *cis*-isomer IV c,*a*, in carbon tetrachloride solution the isolation of the less favored *trans*-isomer IV *t,a* is due to the fact that under the conditions of the bromination (of III) it crystallizes out of solution and thus continuously shifts the equilibrium in the direction ofI V *t.a*. In carbon tetrachloride solution,[21] no crystallization is observed and IV *c,a*, is largely obtained.



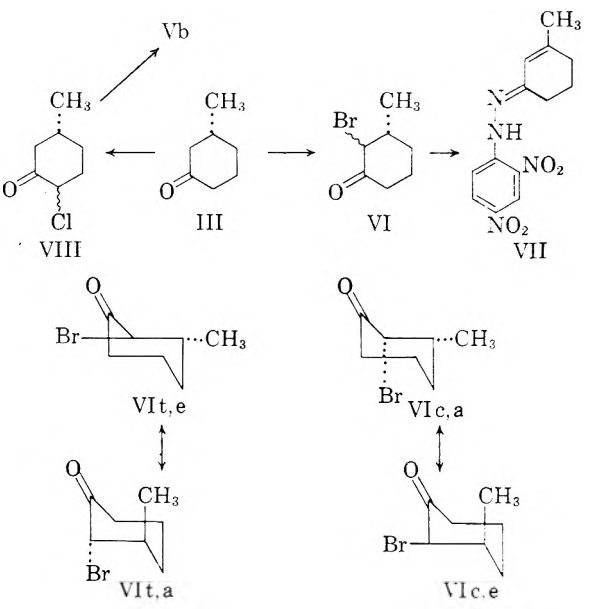
After separation of the crystalline *trans*-2-bromo-5-methylcyclohexanone isomer (IV *t,a*), the filtrate was distilled and yielded a liquid isomer of the same analytical composition. Dehydrobromination of this material with 2,4-dinitrophenylhydrazine gave a difficultly separable mixture of the 2,4-

(25) On the basis of the refinements introduced by the octant rule (see ref. 6) which also considers the contribution of substituents in the position β to the carbonyl group, a negative Cotton effect would also be assumed for the equatorial isomer IV, *c,e*, since this is now based on a conformation (see ref. 27) different from that existing in our parent ketone III—a situation which did not exist in the steroid reference ketones (ref. 2,5). Nevertheless, we can exclude this possibility, because the corresponding axial isomer IV *c,a* definitely possesses a strong positive Cotton effect curve (see Fig. 3 in ref. 21) and consequently a shift in sign from the positive to the negative side would be expected in increasing the polarity of the solvent. In actual fact, the reverse shift was observed (see Fig. 1) and this is even more noticeable with the corresponding chloroketone (VIII) (see Fig. 2), where the sign of the Cotton effect was actually inverted—an observation which is only consistent with the pairs IV *t,e*–IV *t,a* and VIII *t,e*–VIII *t,a*.

(26) Private communication from Prof. R. Pepinsky, Pennsylvania State University, University Park, Pa.

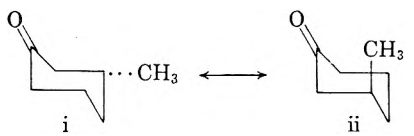
dinitrophenylhydrazone Vb of 5-methylcyclohex-2-en-1-one and of the 2,4-dinitrophenylhydrazine VII of 3-methylcyclohex-2-en-1-one, thus establishing that the liquid product consists of a mixture of 2-bromo-5-methylcyclohexanone (IV) and 2-bromo-3-methylcyclohexanone (VI). Since the 2,4-dinitrophenylhydrazone Vb has a rotation of *ca.* −220°, while the isomer VII is optically inactive, a fairly accurate estimate of the quantitative composition of the liquid mixture can be deduced from the optical rotation of the *total*, crude 2,4-dinitrophenylhydrazone obtained from the liquid; this proved to be 45% IV and 55% VI as an average of several experiments.

2-Bromo-3-methylcyclohexanone (VI) can again exist in four isomeric forms[10,15] (VI *t,e;* VI *t,a;* VI *c,a;* VI *c,e*) and application of the "axial haloketone rule" as refined by the "octant rule"[6] would predict a positive Cotton effect for the pair VI *t,e;* VI *t,a* and a negative one[27] for the pair VI *c,a;* VI *c,e*. As shown in Fig. 1, the rotatory dispersion curve of the liquid mixture in octane exhibits a positive Cotton effect and in this solvent of low polarity, the axial conformers (with Cotton effects of increased amplitude as compared to those of the corresponding equatorial conformers) will play the dominant role. As far as the contribution of the 2-bromo-5-methylcyclohexanone (IV) component of the mixture is concerned, the crystalline *trans*-isomer in the axial orientation IV *t,a* has been shown above to exhibit a large negative Cotton effect and while a small amount of it may still be present in the liquid mixture due to incomplete crystallization, it must represent a very minor portion in view of the observed positive Cotton effect, which can be attributed largely to conformer IV *c,a*. No such distinction can be made among the four isomeric representations VI *t,e;* VI *t,a;* VI *c,a;* VI *c,e* or even the two axial ones (VI *t,a* and VI *c,a*) of the 2-methyl-3-bromocyclohexanone (VI) component of the liquid mixture. It will be noted from Fig. 1 that the amplitude of the negative Cotton effect of the crystalline isomer IV in octane is much greater than that of the liquid mixture in the same solvent. While the pure axial isomer IV *t,a* would be expected to have the greatest amplitude of any of the eight conformers of IV and VI— the axial bromine atom and the axial methyl group both contributing strongly towards a negative Cotton effect according to the postulates of the "octant rule"[6]— the conformational equilibrium IV *t,e* ⇄ IV *t,a* would not be expected[21] to lie as far on the axial side as that of the pair IV *c,a* ⇄ IV *c,e*. As long as the "octant rule" is not placed on a quantitative basis by assigning fairly accurate parameters to the contribution of the various substituents, the amplitude differences shown in Fig. 1 between the Cotton effect curves (octane solution) of the pure, crystalline isomer IV *t,a* and that of the liquid mixture, can be interpreted at the present time equally well in terms of the liquid consisting of *ca.* 40% of the axial conformer IV *c,a* of *cis*-2-bromo-5-methylcyclohexanone (IV *c*) and 55% of a mixture of any one of the isomers of VI, VI *c,a* presumably being favored on energetic grounds.[21]



Since chlorination of 3-methylcyclohexanone (III) has also been reported[11b] to produce a crystalline monochloro derivative—presumably 2-chloro-5-methylcyclohexanone (VIII)—we have repeated its preparation using sulfuryl chloride in carbon tetrachloride solution as the chlorinating agent.[28] No attempt was made to develop optimum conditions for the preparation of the crystalline isomer (m.p. 68–69°) which was shown to be 2-chloro-5-methylcyclohexanone (VIII) by dehydrochlorination with 2,4-dinitrophenylhydrazine to the above described 5-methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone (Vb) with $[\alpha]_D$ −211°. This substance can exist in four possible representations[10,15] (VIII *t,e;* VIII *t,a;* VIII *c,a;* VIII *c,e*), the pre-

(27) The octant rule (ref. 6) predicts a positive Cotton effect for 3-methylcyclohexanone in conformation (i) but a strongly negative one for the alternate conformation (ii). In the conformer VI *t,a*, the strongly positive contribution (ref. 6) of the axial bromine atom will offset the negative contribution of the axial methyl group (corresponding to ii) and the compound will exhibit a positive Cotton effect, although its amplitude is bound to be reduced over that of IV *c,a*. On the other hand in VI *c,e*, the equatorial bromine atom is not expected to make a large contribution and the negative Cotton effect of the substance should be due largely to the axial methyl group.



(28) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1954).

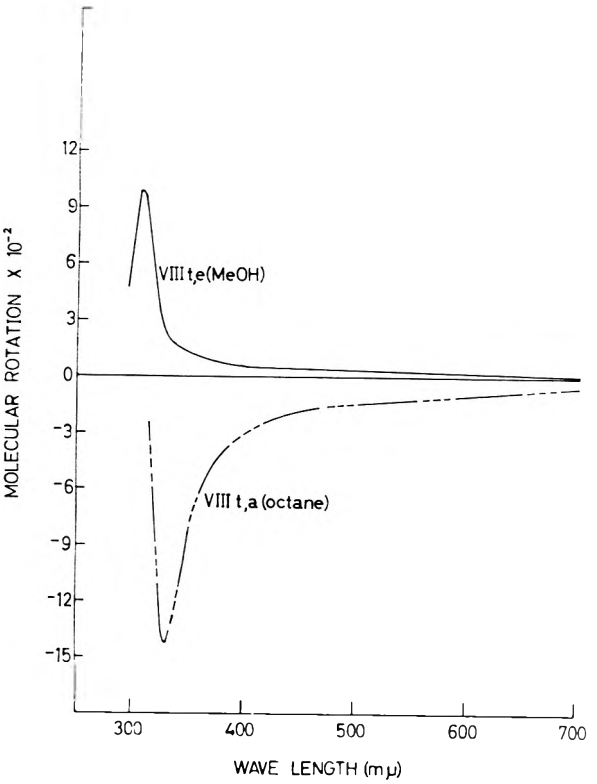
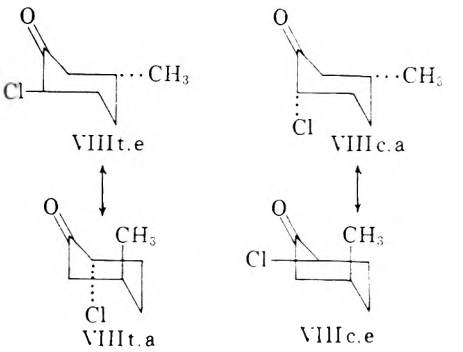


Fig. 2. Optical rotatory dispersion curves of *trans*-2-chloro-5-methylcyclohexanone (VIII *t*) in octane and in methanol

dicted signs of their Cotton effects paralleling those of the corresponding 2-bromo-5-methyl analogs (IV). In this instance, an assignment could be made rapidly and decisively by rotatory dispersion measurements. As reproduced in Fig. 2, the chloroketone exhibited a negative Cotton effect in the nonpolar solvent octane, which is only consistent with the presence of an appreciable amount of the axial conformer VIII *t,a* of *trans*-2-chloro-5-methylcyclohexanone. In the polar solvent methanol, where an increased proportion of the corresponding equatorial conformer VIII *t,e* (predicted[6] to have a positive Cotton effect) is to be expected,[12] there was not observed just a diminution in amplitude (see Fig. 1 for IV *t,a* ⇄ IV *t,e*), but actually a reversal in sign. This striking inversion of the Cotton effect curve upon altering the dielectric constant of the medium is only compatible with the conformational change VIII *t,a* ⇄ VIII *t,e*, since the alternate *cis* pair (VIII *c,e* ⇄ VIII *c,a*) would have exhibited exactly the opposite sign. The unlikely alternate explanation that *trans*-2-chloro-5-methylcyclohexanone (VIII *t*) is isomerized in methanol solution to *cis*-2-chloro-5-methylcyclohexanone (VIII *c*) which would then be responsible for the observed positive Cotton effect (Fig. 2) in methanol solution, was excluded by the following experiment.

A sample of *trans*-2-chloro-5-methylcyclohexanone (VIII *t*), exhibiting a negative Cotton effect curve in octane solution, was dissolved in methanol solution and kept at room temperature for forty-five minutes. The solvent was then removed under reduced pressure and the rotatory dispersion run immediately in octane solution, starting at 330 mμ. Essentially the same negative Cotton effect curve was obtained as is reproduced in Fig. 2.

The results outlined in this paper illustrate once more the wide applicability of rotatory dispersion measurements to a variety of organic chemical problems.[23] Further work is in progress in this laboratory with optically active cyclohexanones, especially those in which conformational mobility is inhibited by suitably situated bulky substituents.



EXPERIMENTAL[29]

Bromination of (+)-*3-methylcyclohexanone* (III). Bromine (11.79 g.) was added dropwise over a 2-hr. period to a vigorously stirred biphasic system consisting of 25 cc. of water and 8.25 g. of (+)-3-methylcyclohexanone (III) prepared[9] from pulegone. The reaction flask was cooled with tap water to prevent the temperature rising above 20° and the mixture was stirred for an additional 3 hr. at which time both layers were colorless. Extraction with ether, washing of the organic phase with water, drying over anhydrous sodium sulfate and evaporation left 12.38 g. of a pale yellow oil. Freezing in a Dry Ice–acetone bath and filtration of the various crops (followed each time by washing with pentane, evaporation of the solvent and repeated freezing) gave a total of 3.2 g. of *trans*-2-bromo-5-methylcyclohexanone (IV *t, a*). Recrystallization from petroleum ether or sublimation at 28° and 0.05 mm. gave the colorless bromoketone, m.p. 83.5–84°, $[\alpha]_D$ −64.4° (*c* 1.06 in toluene); lit.,[11a] m.p. 83–85°, $[\alpha]_D$ −47.9° (in toluene). R.D. (Fig. 1) in *methanol* (*c* 0.117): $[\alpha]_{700}$ −26°, $[\alpha]_{589}$ −32°, $[\alpha]_{337.5}$ −423°, $[\alpha]_{305}$ +1200°, $[\alpha]_{270}$ −670°. R.D. (Fig. 1) in *dioxane* (*c* 0.0686): $[\alpha]_{700}$ −66°, $[\alpha]_{589}$ −67°, $[\alpha]_{335}$ −862°, $[\alpha]_{300}$ +1285°, $[\alpha]_{280}$ −58°. R.D. (Fig. 1) in *octane* (*c* 0.133): $[\alpha]_{700}$ −96°, $[\alpha]_{589}$ −140°, $[\alpha]_{337.5}$ −2820°, $[\alpha]_{295}$ +3730°. R.D. in *carbon tetrachloride* (*c* 0.0475): $[\alpha]_{700}$ −84°, $[\alpha]_{589}$ −150°, $[\alpha]_{335}$ −2630°, $[\alpha]_{320}$ −1055°.

Anal. Calcd. for $C_7H_{11}BrO$: C, 43.97; H, 5.76; Br, 41.88; O, 8.38. Found: C, 44.03; H, 6.05; Br, 41.76; O, 8.58.

After removal of the crystalline bromoketone IV, *t, a* by freezing, 3.3 g. of the liquid residue was fractionated with a Podbielniak column. The portion (2.01 g.) boiling at 71–74°/3.6 mm. was redistilled to yield 1.9 g. of colorless liquid, b.p. 72°/3.6 mm. representing a mixture of *ca.* 45% of 2-bromo-5-methylcyclohexanone (IV) and 55% of 2-bromo-3-

(29) Melting points were determined on the Kofler block; boiling points are uncorrected. We are indebted to Mrs. V. Halpern and Mrs. B. J. Mitscher for several of the rotatory dispersion measurements. The microanalyses were performed by Mr. Joseph Alicino, Metuchen, N. J. and by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

methylcyclohexanone (VI) as shown below by dehydrobromination with 2,4-dinitrophenylhydrazine. R.D. in *methanol* (*c* 0.0895): $[\alpha]_{700}$ +18.5°, $[\alpha]_{539}$ +36°, $[\alpha]_{335}$ +634°, $[\alpha]_{290}$ −319°, $[\alpha]_{265}$ +313°. R.D. (Fig. 1) in *octane* (*c* 0.046): $[\alpha]_{700}$ +126°, $[\alpha]_{589}$ +147°, $[\alpha]_{337.5}$ +832°, $[\alpha]_{295}$ −381°.

Anal. Calcd. for $C_7H_{11}BrO$: C, 43.97; H, 5.76; Br, 41.88; O, 8.38. Found: C, 44.08; H, 5.69; Br, 41.53; O, 8.26.

5-Methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone (Vb). To a solution of 300 mg. of *trans*-2-bromo-5-methylcyclohexanone (IV *t*) in 10 cc. of glacial acetic acid,[14a] which was heated on a hot plate in a current of nitrogen, was added 339 mg. of 2,4-dinitrophenylhydrazine and heating was continued for 10 min. Water was added, the product was extracted with benzene, the latter was concentrated and then filtered through a short column of Fischer activated alumina. The resulting 2,4-dinitrophenylhydrazone was recrystallized from ethanol–ethyl acetate to provide 240 mg. of orange-red crystals, m.p. 143–145°. $[\alpha]_D$ −219° (*c* 0.06 in chloroform), $\lambda_{max}^{CHCl_3}$ 380 mμ,[30] log ε 4.45.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 54.00; H, 5.03; N, 19.77.

Dehydrobromination of the liquid bromo-3-methylcyclohexanone mixture with 2,4-dinitrophenylhydrazine. The above liquid bromoketone mixture (320 mg.) was dehydrobrominated in acetic acid solution with 365 mg. of 2,4-dinitrophenylhydrazine exactly as described in the preceding experiment. The total 2,4-dinitrophenylhydrazone obtained after filtration through a small column of alumina but *before* recrystallization exhibited m.p. 132–156°, $[\alpha]_D$ −100° (*c* 0.27 in chloroform) from which a composition of *ca.* 45% IV and 55% VI can be calculated.

This mixture of 2,4-dinitrophenylhydrazones was chromatographed on 20 g. of Fischer activated alumina using hexane-benzene (6:4) as the developing agent and collecting fourteen 50-cc. fractions. The separation was followed by determining the rotation of various eluates and the first six fractions were combined and recrystallized from ethanol–ethyl acetate to provide 5-methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone (Vb), m.p. 138–142°, $[\alpha]_D$ −221°. After some intermediate fractions ($[\alpha]_D$ −105°), there appeared optically inactive hydrazone and the last five fractions were combined and recrystallized from ethanol–ethyl acetate to yield 50 mg. of 3-methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone (VII), m.p. 178–179.5°, $[\alpha]_D$ ±4° (*c* 0.144 in chloroform).

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 54.16; H, 5.11; N, 19.36.

trans-2-Chloro-5-methylcyclohexanone (VIII *t*). A mixture of 16.5 g. of sulfuryl chloride and 16.5 cc. of carbon tetrachloride was added dropwise at room temperature with stirring to 13.73 g. of (+)-3-methylcyclohexanone (III) dissolved in 65 cc. of carbon tetrachloride. No heat was evolved and when addition was completed, the pale yellow solution was washed successively with water, sodium bicarbonate solution, and finally with saturated salt solution. After drying and removing the carbon tetrachloride by careful distillation through a Vigreux column, the residue was fractionally distilled at 12 mm., seven fractions being collected. The residue from the distillation was semisolid and after sublimation at 61°/1.3 mm. furnished 215 mg. of chloroketone. Similarly, storage of the last two distillate fractions (b.p. 91°/12 mm. and 74°/3 mm.) in the ice box provided additional crystalline material and combination of these, followed by sublimation, furnished a total of 1.54 g. of *trans*-2-chloro-5-methylcyclohexanone (VIII *t*), m.p. 67–69°. The analytical sample was recrystallized from petroleum ether and sublimed, whereupon it exhibited m.p. 68–69°, $[\alpha]_D$ +6.4° (*c* 0.88 in chloroform). R.D. (Fig. 2) in *methanol* (c 0.096): $[\alpha]_{700}$ +9.3°, $[\alpha]_{589}$ +10°, $[\alpha]_{305}$ +755°, $[\alpha]_{295}$ +354°. R.D. (Fig. 2) in *octane* (c 0.0825): $[\alpha]_{700}$ −41°, $[\alpha]_{589}$ −81° $[\alpha]_{330}$ −1092°, $[\alpha]_{315}$ −191°. R.D. in *carbon tetrachloride* (c 0.051): $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −20°, $[\alpha]_{332.5}$ −1002°, $[\alpha]_{300}$ +795°.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.55; Cl, 24.19; O, 10.92. Found: C, 56.97; H, 7.71; Cl, 23.80; O, 11.07.

The position of the chlorine atom was established by dehydrochlorination with 2,4-dinitrophenylhydrazine exactly as described for the corresponding bromoketone IV *t*, and afforded orange-red needles of 5-methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone (Vb), m.p. 140–142°, $[\alpha]_D$ −211°.

Acknowledgment. We are indebted to the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, for a research grant (No. CY-2919).

DETROIT, MICH.

(30) See C. Djerassi and E. Ryan, *J. Am. Chem. Soc.*, **71**, 1000 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Conformational Analysis. VI.[1a] Optical Rotatory Dispersion Studies. XXVII.[1b] Quantitative Studies of an α-Haloketone by the Rotatory Dispersion Method

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The equilibrium between the conformational isomers of *trans*-2-bromo-5-methylcyclohexanone (I t) has been examined in a variety of solvents by measurements of dipole moments, and infrared and ultraviolet spectra. Under all conditions used in this work, the halogen atom was found to be predominantly in the equatorial conformation. A study of the rotatory dispersion curves of I t and of equilibrium mixtures of I c and I t in various solvents shows that such curves can be used in a quantitative manner for the determination of conformational equilibria.

INTRODUCTION

The qualitative usefulness of rotatory dispersion curves in establishing the conformations and absolute configurations of α-haloketones has been well established.[3] A quantitative study of con-

(1) (a) Paper V, ref. 13; (b) Paper XXVI, ref. 4.

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(3) (a) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957); (b) C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958); (c) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959).

formational equilibria by this method is also possible and forms much of the subject of this paper. The approach used is strictly empirical and although the quantitative aspects of the theory of the rotatory dispersion Cotton effect are not yet completely understood, such an understanding is not essential to the present work.

For these studies an α-halocyclohexanone was desired which could be obtained optically active and which would exist as a mixture containing comparable amounts of two conformers. The compound chosen was *trans*-2-bromo-5-methylcyclohexanone (I t), the synthesis of which has been described.[4]

As the methyl group in I t[5] prefers to be equatorial while the bromine atom prefers to be axial, the opposed and nearly balanced forces will cause the compound to exist in solution as a mixture containing both the I t,e and I t,a conformers. The Cotton effect is positive for (+)-3-methylcyclohexanone in which the carbon atom bearing the methyl group is known[6] to have the R[7] configuration. Consequently I t,e and I t,a are expected, from the "axial α-haloketone rule",[3a] to show positive and negative Cotton effects, respectively. The observed Cotton effect curve of I t is then a resultant of two opposing curves, and should be a measure of the point of equilibrium between the two conformers. As an unfavorable electrostatic repulsion exists between the bromine and oxygen atoms, I t,e will become more stable relative to I t,a as the effective dielectric constant of the solvent is increased.[8] Qualitatively then, the observed Cotton effect of I t should become increasingly positive as the solvent becomes increasingly polar, and this is what is found experimentally.

RESULTS AND DISCUSSION

One of the objectives of the present work was to establish the quantitative applicability of rotatory dispersion measurements to conformational problems. The second principal objective was to show that the energy of an α-bromine atom in a cyclohexanone ring, as found from earlier work,[8,9] could be used, together with the known conformational energy of a methyl group (a 3-alkylcyclohexanone[10] in this case), to calculate the equilibrium constant for a simple system such as I t, and the variation of this constant with solvent. The correctness of these calculated equilibrium constants was checked by measurements of the dipole moment, and infrared and ultraviolet spectra, as functions of solvent.[8,11]

The energy of an axial methyl group (3-alkylcyclohexanone) relative to the corresponding equatorial form is 0.80 kcal./mol. The energy of an equatorial bromine atom relative to the axial one (2-bromocyclohexanone) varies with solvent and is assigned the following values from the earlier dipole moment work of Kumler and Huitric[8,9]: 0.45 kcal./mole in heptane, 0.24 kcal./mole in benzene, and 0.02 kcal./mole in dioxane. From these numbers it was possible to calculate the energy[12] of I t,a relative to I t,e. From the relationship $E = -RT \ln K_t$, the equilibrium constants for the conformational change and the percentages of the axial conformer in I t were also calculated and the values are given in Table I.

Of the various methods which have been used for determining conformational composition in systems similar to the one at hand, the dipole moment usually has yielded the most accurate results.[8,9,13] The dipole moment of I t was, therefore, measured in heptane, benzene and dioxane solution. The conformational compositions of I t were calculated from the observed moments in the usual way, and the percentages of axial isomer thus obtained are also included in Table I. The agreement between the conformational equilibrium predicted and that found from the dipole moments is satisfactory, the variation being 0.1–0.2 kcal.

TABLE I

DATA FOR CONFORMATIONAL ISOMERS OF *trans*-2-BROMO-5-METHYLCYCLOHEXANONE (I t)

	Calculated		Per Cent I t,a by Various Methods				
Solvent	$E_{I\,t,a} - E_{I\,t,e}$ Kcal./Mole	K_t	Calcd.	μ	I.R.	U.V.	R.D.
Heptane	0.35	1.82	36	45	39	37	44
Carbon tetrachloride	—	—	—	—	36	36	38
Chloroform	—	—	—	—	32	—	—
Benzene	0.56	2.57	28	29	30	—	—
Dioxane	0.77	3.70	21	19	26	18	20
Ethanol	—	—	—	—	—	16	18
Methanol	—	—	—	—	—	11	17

The high-resolution infrared spectrum of the carbonyl region of I t was obtained in various solvents, and the curves are reproduced in Fig. 1.

(4) C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *J. Org. Chem.*, preceding paper.

(5) As suggested to us by Dr. W. Klyne, we are using two suffixes: the first denotes configuration (c = *cis*, *t* = *trans*), while the second one refers to the orientation of the halogen atom (*e* = equatorial, *a* = axial). The equilibrium mixture of conformers bears only the configurational suffix.

(6) For leading references see E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

(7) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experi.*, **12**, 81 (1956).

(8) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

(9) W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956).

(10) W. Klyne, *Experi.*, **12**, 119 (1956).

(11) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

(12) Energy and free energy are taken to be interchangeable here.

(13) J. Allinger and N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5736 (1959).

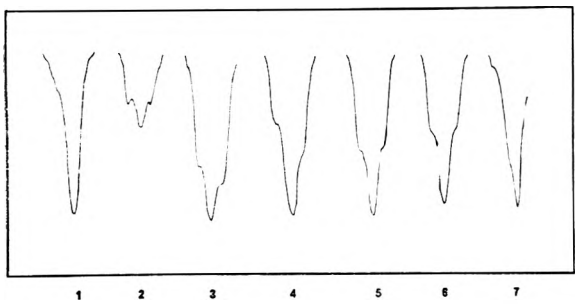


Fig. 1. The infrared carbonyl absorption spectra of I t in various solvents. The numbers correspond to the following solvents: 2, heptane; 3, carbon tetrachloride 4, chloroform; 5, benzene; 6, dioxane; 7, dimethyl sulfoxide. The band numbered 1 is the parent 3-methylcyclohexanone

Three bands were usually seen. Two of these bands had the approximate relative intensities and showed frequency shifts relative to the unbrominated parent ketone of the proper magnitude (5 cm.$^{-1}$ and 10-25 cm.$^{-1}$) to be assigned to the conformers I t,a and I t,e respectively.[8,11,14] The "extra" band was variable in intensity and was found at a frequency 15 to 30 cm.$^{-1}$ higher than that of the parent ketone. The extra band occurred at 1754 cm.$^{-1}$ (in carbon tetrachloride), and there was present a strong band at 865 cm.$^{-1}$, which suggests that the former is an overtone of the absorption at 865 cm.$^{-1}$, intensified by Fermi resonance. Evidence for a similar situation in the case of 2-bromo-4-cyclopentenone was recently obtained by Yates and Williams.[15] Because of the incomplete resolution of the bands due to the two conformers it was not possible to establish their relative integrated intensities. What could be done easily was to measure the relative apparent extinction coefficients of the two conformers. In this way a rough measure of the ratio of the conformers was found. The approximate conformational composition thus determined is in satisfactory agreement with the calculated values (Table I).

TABLE II

ULTRAVIOLET SPECTRA OF 3-METHYLCYCLOHEXANONE, AND *trans*-2-BROMO-5-METHYLCYCLOHEXANONE

	3-Methylcyclohexanone		*trans*-2-Bromo-5-methylcyclohexanone	
Solvent	λ_{max}	ϵ	λ_{max}	ϵ
Methanol	283	17	292	22
Ethanol	285	18	294	28
Dioxane	287	16	301	30
Carbon tetrachloride	294	14	310	50
Octane	290	14	310	51

The ultraviolet spectra in different solvents were also examined for the bromo compound and for the parent ketone. The data are summarized in Table II.

The wave length shifts are qualitatively consistent with an increasing amount of equatorial isomer[11,16] with increasing solvent polarity. The magnitude of the extinction coefficient is quantitatively more useful. If the reasonable assumptions are made that the extinction coefficients are 20 and 120 at the maxima for the equatorial and axial conformers respectively,[11] and that the extinction coefficient of the equatorial isomer at the wave length where the axial one has its maximum is 10, the approximate conformational composition can be calculated (see Table I). Again the agreement is very good.

It seems clear then that each of these methods is capable of yielding within the experimental limitations imposed by the particular systems, the conformational composition of such a simple α-bromocyclohexanone.

As is shown in Table I, conformer I t,e always predominates in solution, yet x-ray crystallography has shown that the compound exists in the other conformation, I t,a, in the crystal lattice.[17] Although it is generally recognized[18] that there exists the possibility of a flexible cyclohexane ring having a different preferred conformation in solution from that in the crystal, this is one of the very few cases known where this situation has been demonstrated experimentally.

For a quantitative determination of conformational composition from the rotatory dispersion curves, certain requirements must be satisfied.

One which appears to be met is that it must be experimentally possible to measure the amplitude of the curve to the desired accuracy. Another requirement is that ideal solutions must exist. In the present study, 10^{-3} M concentrations of I t were employed so this condition was probably realized. Finally, the amplitude of the curve $[a]$ for each pure conformer (x and y) must be known, and the peaks and troughs must occur at nearly the same wavelength. If each of these conditions is satisfied, then from the observed amplitude $[a]$[19] and the relationship $[a] = Nx[a_x] + (1-Nx)[a_y]$, the mole fraction (Nx) of conformer x can be found. The difficulty encountered in the present study arises from the fact that the amplitudes of the molecular rotations of pure I t,a and I t,e cannot be directly determined.

(14) (a) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 2828 (1952); (b) E. J. Corey, *J. Am. Chem. Soc.*, 75, 2301, 3297 (1953).

(15) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, 80, 5896 (1958).

(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(17) Private communication from Dr. R. Pepinsky, Pennsylvania State University.

(18) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 10, 44 (1956).

(19) For basic nomenclature see C. Djerassi and W. Klyne, *J. Chem. Soc. (Proc.)*, 55 (1957). For convenience the symbol $[a]$ will be used to indicate the amplitude of the molecular rotation prefaced usually by a plus or minus sign to indicate the sign of the Cotton effect.

The relationships of the axial haloketone rule[3a] offer a possible solution to this dilemma. When an equatorial halogen is introduced adjacent to a keto group, no essential change in the amplitude of the curve occurs. Introduction of an axial halogen, however, produces a large change in the amplitude, the sign of which is predictable from the absolute configuration of the parent ketone. For I t, it is necessary to make the approximation that the amplitude change from I t,e to I t, a is only negligibly influenced by the conformational change associated with the methyl group and that the major influence on the amplitude is due to the concurrent change of the bromine substituent. The magnitude of this amplitude change might be expected to be relatively constant from one α-haloketone to another. If such were the case, an approximate value for $[a]_{I\ t,a}$ could be estimated.

Values of $[a]$ for several α-bromo keto steroids in which the bromine substituent is axial and secondary and those of the parent keto steroids are available[20] and the changes ($\Delta[a]$) in the molecular amplitude associated with the introduction of the bromine atom are presented in Table III.

TABLE III

CHANGES IN MOLECULAR AMPLITUDES ON INTRODUCTION OF AXIAL BROMINE

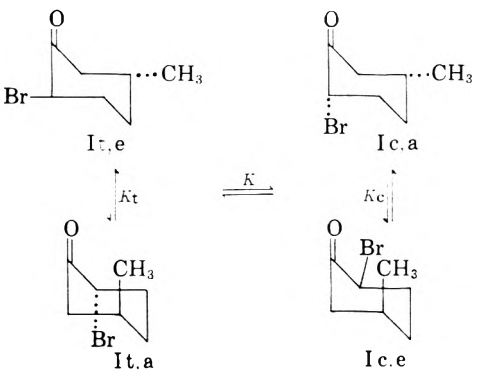
Compound	$\Delta[a]^a$
2α-Bromofriedelin	−15,600°
7α-Bromocholestan-3β,5α-diol-6-one 3-acetate	+19,200°
7α-Bromocholestan-3β,5α-diol-6-one 3,5-diacetate	+24,500°
Methyl 11β-Bromo-3α-acetoxy-12-ketocholanate	−19,600°
6β-Bromo-3β-acetoxycholestan-7-one	+15,700°
12α-Bromo-3β-acetoxyergostan-11-one	−16,100°
3α-Bromoandrostan-2-one-17β-ol propionate	+19,400°

[a] $\Delta[a]$ is the change in molecular amplitude (see ref. 19) which occurs when the axial bromine atom is introduced into the parent ketone.

It is seen that $\Delta[a]$ varies somewhat and this can probably be attributed to the different types and numbers of asymmetric centers in each compound. If only very similar systems were compared, a more consistent $\Delta[a]$ would probably be realized. Nevertheless, the rough value for $\Delta[a]$ of 19,000 could be used to obtain the magnitude of the molecular rotation of I t,a and this would allow at least a crude approximation of the conformer composition of I t. A more accurate value for $[a]_{I\ t,a}$ was available from the dipole measurement of I t in dioxane which estimated 19% of I t,a to be present in this solution. If the value +2690° is taken[21] for $[a]_{I\ t,e}$ then from the amplitude of the observed Cotton effect curve of I t in dioxane ($[a]$ = −3,940°) $[a]_{I\ t,a}$ is calculated to be −32,200°. Employing these amplitudes for I t,a and I t,e along with the measured amplitudes of the Cotton effect curves of I t in various solvents the percent of axial conformer present in the various media was calculated. The results are presented in Table I and the agreement with the values obtained by other methods is good.

Rotatory dispersion measurements thus provide a useful method for the determination of conformational equilibria. The application of this analytical procedure to simple α-halo ketones is limited largely by the necessity of having optically active compounds.

The equilibrium I t $\rightleftarrows$ I c can be readily established by hydrogen bromide treatment of the *trans* isomer (I t). Furthermore, the *cis* isomer (I c) allows the most energetically favorable conformations for each substituent (methyl, equatorial; bromine, axial) and the equilibrium constant K is therefore anticipated to be greater than one in any of the solvents of the present study. As *cis* I, analogous to *trans* I, would exist as a mixture of two conformers, I c,e and I c,a, the proportion of which would be described by a solvent-dependent equilibrium constant K_c, the equilibrium mixture of I t,c would contain four conformers.[22] The equilibrium situation is described as follows. (As a generalized thermodynamic treatment of two isomers, each having two conformers, is straightforward



(20) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

(21) Actually the conformational composition of 3-methylcyclohexanone is expected to be the same in any inert solvent. Consequently the amplitude of the Cotton effect curve of this compound should be solvent-independent, and this was found experimentally. It was found that $[a]$ had the value 2690° ± 40° in methanol and octane. Lack of solvent transparency prevented measurement of the complete curve in dioxane, but the observed portion of the curve was identical with the other two, and the same value of $[a]$ is assumed. It has now been found (C. Djerassi, E. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org. Chem.* in press) that introduction of a bromine into the equatorial position at carbon 5 in optically active 3-*t*-butylcyclohexane causes a small change (1220°) in $[a]$. This small change supports the assumption of negligible change made above. If this value is taken into account in calculating the quantities in the R. D. column of Table I, these quantities would be changed by about 3–4% in heptane and carbon tetrachloride and 0–1% in the other solvents. These changes are less than the probable errors in the quantities listed.

(22) The amount of flexible forms is quite small, and is ignored. (See N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

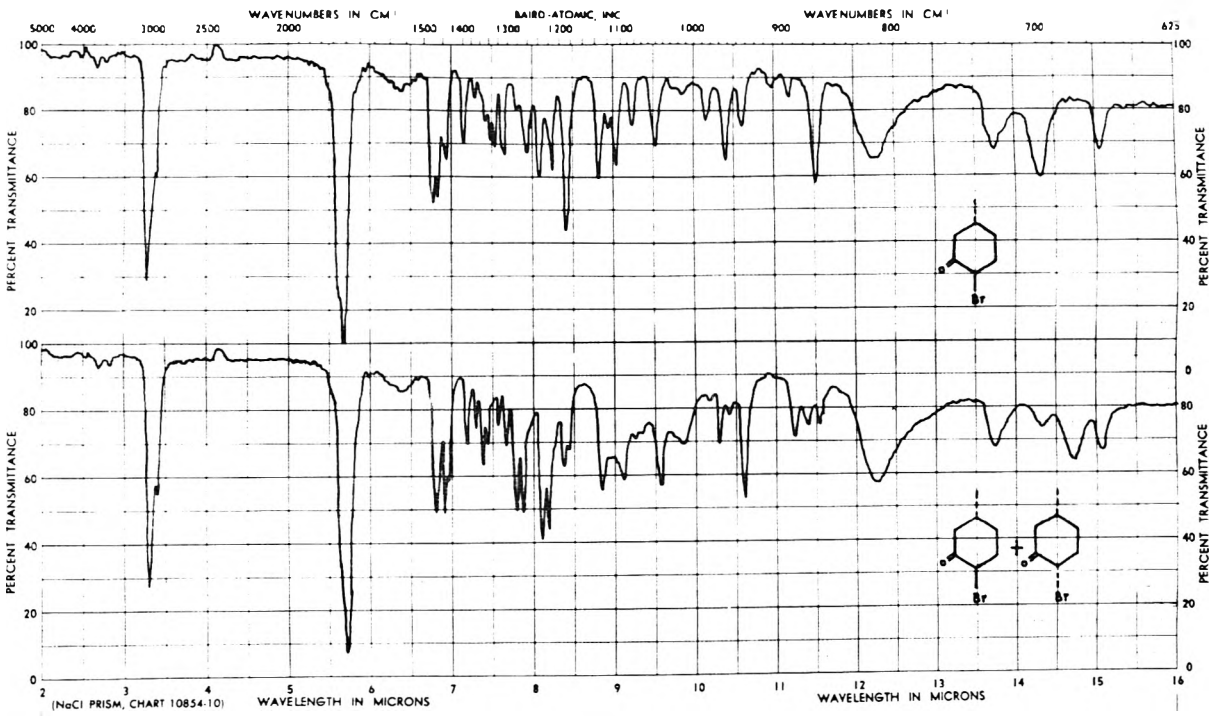


Fig. 2. Infrared absorption spectra of *trans*-2-bromo-5-methylcyclohexanone (It) and of hydrogen bromide catalyzed equilibrium mixture of It ⇄ Ic in carbon tetrachloride solution

but laborious, the equilibrium relationships have been found using the method of Eliel and Ro.[23])

The symmetry number is one for each conformer, and it is assumed that there is no entropy effect due to restricted rotation of the methyl group in any conformation.[24] If K is designated as the equilibrium constant for the isomerization *trans* I ⇄ *cis* I, the relationships between the equilibrium constants are:

(1) By definition:

$$K = \frac{I\,c,a + I\,c,e}{I\,t,a + I\,t,e},\ K_c = \frac{I\,c,e}{I\,c,a},\ K_t = \frac{I\,t,e}{I\,t,a}$$

Substituting:

$$K = \frac{I\,c,a + K_c\,I\,c,a}{I\,t,a + K_t\,I\,t,a}$$

(2) Therefore:

$$K = \frac{I\,c,a}{I\,t,a} \times \frac{1 + K_c}{1 + K_t}$$

The quantity $\frac{I\,c,a}{I\,t,a}$ is the equilibrium constant for the conformational change axial 3-methyl→equatorial 3-methylcyclohexanone and as such has the value 3.86 and is solvent-independent. K_c is solvent-dependent and the same type of theoretical treatment employed to obtain K_t gave calculated values for K_c of 0.121, 0.172, 0.251[25] in heptane, benzene and dioxane, respectively. The theoretical values of K_t in benzene and dioxane (Table I) were employed but since a value of $K_t = 1.27$ for heptane solution was available from rotatory dispersion and dipole moment data, this experimental number was used in that case. The calculated values for K are 1.92 (heptane), 1.29 (benzene) and 1.10 (dioxane); in other words, 38%, 44%, and 49% of I t are predicted to be present at equilibrium in the respective solvents. Pure I t was treated with dry hydrogen bromide in both carbon tetrachloride and benzene solution and the infrared spectrum of each acid-freed solution was obtained and compared with that of the pure *trans* isomer (I t) in each solvent. The amount of I t in an equilibrated sample was estimated using the available strong bands (see Fig. 2) and assuming that I c did not absorb at these wave lengths. The percentage of *trans* isomer calculated from various bands was as follows: carbon tetrachloride 17.1% (14.3μ), 18.2% (11.55μ), 24.4% (8.43μ); benzene 22.8% (11.55μ), 29.4% (10.40μ), 42.8% (8.48μ), 48% (7.59μ).

The data are only fair but appear to indicate 20 ± 4% of the *trans* form (I t) in carbon tetrachloride and 35 ± 10% in benzene solution. Within the sizeable limits of experimental error, the calculated and found values agree for the solution in benzene but not in carbon tetrachloride. The possibility exists that a complex between the ke-

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

(24) Such was the case with the 1,3- and 1,4-dimethylcyclohexanones (C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, 69, 977. 2488 (1947).

(25) These equilibrium constants give values for $E_{I\,c,e} - E_{I\,e,a}$ of +1.25, +1.04 and +0.82 kcal./mole in heptane, benzene and dioxane, respectively.

tone and hydrogen bromide is formed in carbon tetrachloride, the existence of which would be expected to influence strongly the position of conformer and isomer equilibria. Such a complex was looked for in an earlier similar case, but no evidence for its existence could be found.[11] It was shown that the hydrogen bromide treatment of I t did not cause any rearrangement to 2-bromo-3-methylcyclohexanone by preparing the 2,4-dinitrophenylhydrazone of the equilibrated mixture (which yielded only 5-methylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone), and by measuring the rotatory dispersion curve of the mixture. The presence of rearranged bromide would have led to a diminution in amplitude which was not observed.

More sensitive measurements of these equilibria were made by means of the rotatory dispersion curves. The rotatory dispersion curve of I t in carbon tetrachloride is shown in Fig. 3. Also shown

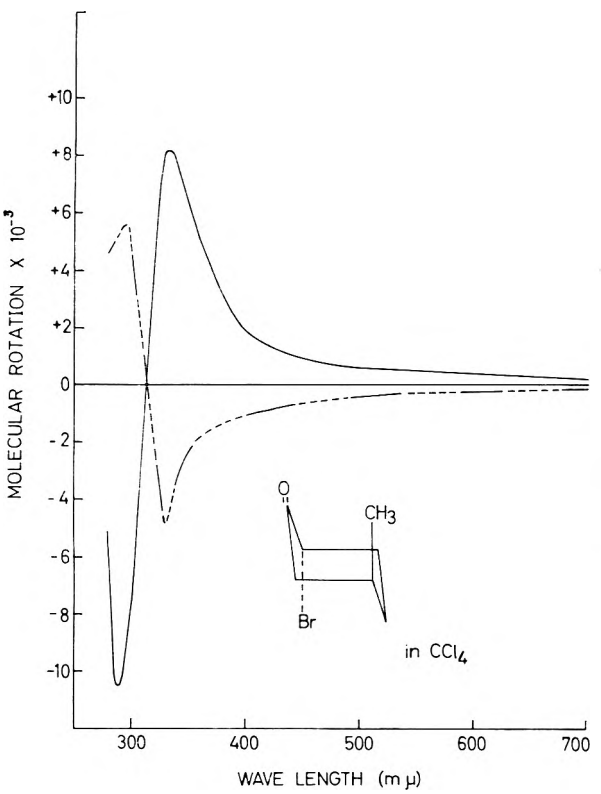


Fig. 3. Optical rotatory dispersion curves of *trans*-2-bromo-5-methylcyclohexanone (I t) and of hydrogen bromide catalyzed equilibrium mixture of I t ⇄ I c in carbon tetrachloride solution

is the curve obtained from the hydrogen bromide catalyzed equilibrium mixture I t ⇄ I c, the difference between the curves being noteworthy. Analysis of the isomer composition proceeded as follows:

The amplitudes assigned to conformers I t,e and I c,e were the same as for the parent ketone, +2690°, while to I t,a and I c,a there were assigned the value −32,200° and +32,200°, respectively. Knowing the value of [α] for each conformer and the equilibrium constants involved, the molecular amplitudes for I t and I c were calculated to be −12,500° and +29,000° in heptane solution. Using these parameters as reasonable approximations for carbon tetrachloride (on the basis of the similarity of the value of [α] of I t in both heptane and carbon tetrachloride), the observed value of [α] = +18,360° for the equilibrated mixture in that solvent indicated that the mixture contained 21% of I t. This value is in excellent agreement with that obtained (20%) by infrared analysis.

EXPERIMENTAL[26]

trans-2-Bromo-5-methylcyclohexanone (I t). The synthesis of this optically active ketone, m.p. 83.5–84°, was described earlier.[4] The infrared carbonyl spectra were obtained with a Beckmann IR-4 instrument with a scanning time of 0.02 μ/min. The data are summarized in Table I and the absorption spectra are reproduced in Fig. 1. The ultraviolet spectra were obtained with a Beckmann Spectrophotometer, model DU, with a Spectracord attachment. More or less fine structure appeared in the n → π^* band. The constants λ_{max} and ϵ are given (Table II) for a smoothed curve in which the fine structure is averaged out. The rotatory dispersion measurements were performed as described else-

TABLE IV

DIPOLE MOMENT DATA FOR *trans*-2-BROMO-5-METHYLCYCLOHEXANONE (I t)

Solvent—Heptane		
N_2	d_{12}	ϵ_{12}
0.0078106	0.683786	1.9896
0.0054452	0.682235	1.9659
0.0042453	0.681418	1.9535
0.0029712	0.680599	1.9407
0.0015456	0.679620	1.9261
0.0000000	0.678579	1.9114
α = 10.1385	β = 0.66671	$P_{2\infty}$ = 325.47 cc.
ϵ_1 = 1.9105	d_1 = 0.678593	μ = 3.74 D
Solvent—Benzene		
N_2	d_{12}	ϵ_{12}
0.0057103	0.877178	2.3962
0.0035907	0.875366	2.3490
0.0027275	0.874776	2.3296
0.0013474	0.873630	2.3007
0.0011227	0.873395	2.2966
0.0003330	0.872782	2.2775
0.0000000	0.872482	2.2716
α = 21.814	β = 0.81726	$P_{2\infty}$ = 361.38 cc.
ϵ_1 = 2.2710	d_1 = 0.872498	μ = 3.96 D
Solvent—Dioxane		
N_2	d_{12}	ϵ_{12}
0.0061965	1.030456	2.3479
0.0035127	1.028849	2.3279
0.0026912	1.028432	2.2653
0.0018567	1.027908	2.2450
0.0010017	1.027420	2.2245
0.0000000	1.026777	2.2024
α = 23.583	β = 0.59111	$P_{2\infty}$ = 382.96 cc.
ϵ_1 = 2.2017	d_1 = 0.973497	μ = 4.09 D

(26) Pure samples of heptane and octane were used interchangeably as solvents in this work.

where.[27] The values of [α] in various solvents are as follows[4]: methanol, −3,100°; ethanol, −3,700°; dioxane, −4,100°; carbon tetrachloride, −10,440°; octane, −12,500°.

Equilibration experiments. A 1.0-g. sample of *trans*-2-bromo-5-methylcyclohexanone (I t)[4] was dissolved in a solution prepared from 0.32 g. of anhydrous hydrogen bromide and 40 ml. of carbon tetrachloride. The mixture was allowed to stand at room temperature for 2 hr., after which time it was washed with water, dilute sodium bicarbonate solution and water. After drying, the infrared spectrum was obtained directly on the solution.

A similar isomerization was carried out in benzene solution. To show the absence of bromine migration under these conditions, 97 mg. of the bromoketone I t was dissolved in 1 ml. of carbon tetrachloride which had been saturated with dry hydrogen bromide. The solution was allowed to stand overnight at room temperature, after which time 108 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of acetic acid was added. The solution was warmed under nitrogen for 10 min. and was diluted with benzene. After washing with water, the benzene concentrate was poured through a column of Fisher alumina. The benzene was removed from the eluate by distillation and the crude solid residue had $[\alpha]_D^{25}$ −200° (chloroform; c, 0.369). The pure 2,4-dinitrophenylhydrazone[4] of 5-methylcyclohex-2-en-1-one has $[\alpha]_D^{25}$ −219° (chloroform; c, 0.06).

Dipole moments. The apparatus used for the dielectric constant measurements has been described.[28] The benzene and heptane solvents were purified by refluxing reagent grade solvents with sodium followed by distillation from sodium. The dioxane was purified according to Fieser.[29] The dielectric constant and density were measured with solutions of various mole fractions as indicated in Table IV. The calculations were made following the general procedure of Halverstadt and Kumler[30] as described earlier.[31] The molar refractivity was calculated from standard values[32] of atomic refractivities and had the value 65.929 c.c. Atomic polarization was neglected. Experimental error is about 0.02 D.

Acknowledgment. The authors would like to thank Dr. Max T. Rogers, Michigan State University, for kindly making available to them his apparatus for the measurement of dipole moments, and Miss P. Burcar for the spectral measurements. This work was supported in part by a grant from the Sloan Foundation and in part by the National Cancer Institute (grant CY-2919) of the National Institutes of Health, U.S. Public Health Service.

DETROIT, MICH.

(27) C. Djerassi, E. W. Foltz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955); C. Djerassi "Optical Rotatory Dispersion: Applications to Organic Chemistry," New York, McGraw-Hill, Chapter 3.

(28) M. T. Rogers, *J. Am. Chem. Soc.*, **77**, 3681 (1955).

(29) L. F. Fieser "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 368.

(30) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(31) N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957).

(32) J. A. Leermakers and A. Weissberger, in H. Gilman "Organic Chemistry", Vol. II, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1751.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE WESTVACO CHLOR-ALKALI DIVISION AND THE CENTRAL RESEARCH LABORATORY OF THE FOOD MACHINERY AND CHEMICAL CORP.]

α-Oximino Ketones. IV. The "Normal" and "Abnormal" Beckmann Rearrangements[1]

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The Beckmann rearrangement of α-oximino ketones possessing the *anti* configuration, whether brought about by acid chlorides like phosphorus pentachloride or thionyl chloride, by strong acids like sulfuric or trifluoroacetic, or by acylating agent and base, has been shown to proceed "abnormally", that is by cleavage to a nitrile and a carboxylic acid. If an amide product is obtained, it is always that which arises from hydrolysis of the nitrile initially formed. It is proposed that the term "second order" be retained to describe this type of Beckmann rearrangement, which is characterized by shift of an electron pair only.

It was observed a long time ago that α-oximino ketones possessing the *anti* or α-configuration behaved differently from simple ketoximes when treated with an acylating agent and base, in that they were cleaved to a carboxylic acid and a nitrile instead of giving the normal amide product of the Beckmann rearrangement.[2-4] This cleavage reaction has been called a Beckmann rearrangement of the second order[2,4] or an "abnormal" rearrangement. In contrast, it is generally stated or implied that rearrangement of α-oximino ketones with acids or acid chlorides such as phosphorus pentachloride proceeds "normally," that is, through an amide intermediate.[3,5,6] It was postulated originally that the rearrangement of α-oximino ketones in polyphosphoric acid proceeded *via* the "normal" route,[7] but more recent studies have shown that actually the "abnormal" or second order route is

(1) A preliminary account of this work has been presented in *J. Org. Chem.*, **24**, 580 (1959).

(2) A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904).

(3) A. H. Blatt, *Chem. Revs.*, **12**, 215 (1933).

(4) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).

(5) N. V. Sidgwick, *The Organic Chemistry of Nitrogen*, (revised and rewritten by T. W. J. Taylor and W. Baker), Oxford University Press, 1942, p. 182.

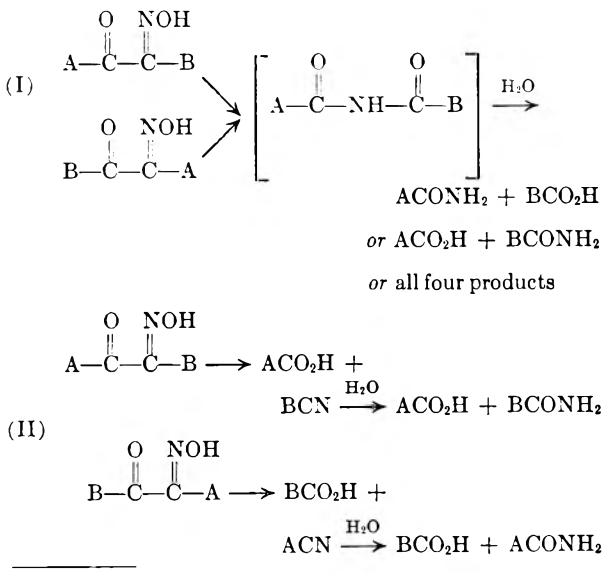
(6) V. Migrdichian, *Org. Syntheses*, Vol. 1, 376 (1957).

(7) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

followed, the nitrile originally formed frequently being hydrolyzed to the amide if the reaction is carried out at an elevated temperature.[8,9]

In this laboratory suspicion that the "normal" course of acid-catalyzed Beckmann rearrangements had not been correctly interpreted was aroused in the course of a study aimed at finding the best method for obtaining high yields in the rearrangement ("normal" or "abnormal") of α-oximino ketones. Because of the ease with which it is prepared and purified, 3-oximino-2-heptanone was used as a model compound. Treatment with a variety of acylating agents and base gave *n*-valeronitrile in 70–80% yield; sulfuric acid gave valeric acid (79%) when reaction conditions were vigorous and valeramide (59%) when they were milder; and polyphosphoric acid gave a mixture of valeric acid (28%) and valeramide (24%). In addition to these expected results, it was found most unexpectedly that phosphorus pentachloride, the classic reagent for carrying out the "normal" rearrangement, gave valeronitrile in 70% yield.

This discovery led to an investigation of both the supposedly "normal" and "abnormal" reactions, using a variety of unsymmetrical α-oximino ketones. In particular, two pairs of α-oximino ketones were chosen so that if an amide intermediate were involved in the so-called "normal" reaction the same one would be formed from both starting materials, and hence the same final products should be obtained, the nature of these being dependent only on the direction of hydrolysis of the intermediate secondary amide (route I). On the other hand, if the reaction were first a cleavage to nitrile and acid and then hydrolysis of the nitrile, different products would be formed (route II). This experimental concept is shown in generalized schematic form below:



The two pairs of α-oximino ketones chosen to test this concept were 2-oximino-1-phenyl-1-propanone and 1-oximino-1-phenyl-2-propanone, both of which should have given *N*-acetylbenzamide or the same hydrolysis products therefrom in the "normal" rearrangement, and 1,3-diphenyl-2-oximino-1-propanone and 1,3-diphenyl-1-oximino-2-propanone, both of which should have given *N*-benzoylphenylacetamide or the same hydrolysis products.

In these experiments 85% sulfuric acid at about 120° was used to bring about the "normal" reaction, and benzenesulfonyl chloride and aqueous sodium hydroxide at about 25° were used for the "abnormal" reaction. No attempt was made to isolate two carbon fragments (acetonitrile, acetamide, or acetic acid). Table I summarizes the results obtained with the two pairs of α-oximino ketones mentioned above, and with several other unsymmetrical α-oximino ketones for which pairing was inconvenient from a preparative standpoint. Although yields in some cases were lowered by isolation difficulties, evidence was obtained for the alternative products to be expected from route I in only two cases, and in both of these the relative yields made it seem almost certain that the carboxylic acid not predicted by route II was obtained by partial hydrolysis of the amide which was the major product. All solid products were identified by melting points and mixed melting points with authentic samples, and by infrared spectra identical with those of authentic samples. All liquid products were identified by boiling points and indices of refraction, and by infrared spectra identical with those of authentic samples.

The results obtained in the second order or "abnormal" reaction were those expected from the work of previous investigators of this reaction,[4,10–12] that is, in all cases the nitrile product contained the radical originally attached to the carbon bearing the oxime group, and the carboxylic acid product contained the radical originally attached to the carbonyl group. In contrast to what would have been predicted from the conventional view of the "normal" rearrangement, precisely the same relationship was noted in the products of the acid-catalyzed reaction. The amide products all contained the radical originally attached to the carbon bearing the oxime group, and the carboxylic acids all contained that originally attached to the carbonyl group. The conclusion seems inescapable that both the "normal" and "abnormal" reactions actually proceeded by the same route (II, above), and that the only difference between them was that the nitrile originally formed in the acid-

(8) C. T. Elston, doctoral dissertation, University of Illinois (1954), quoted by F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 372 (1958).

(9) R. T. Conley and F. A. Mikulski, *J. Org. Chem.*, **24**, 97 (1959).

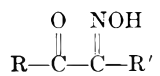
(10) J. Meisenheimer, P. Zimmermann, and U. v. Kummer, *Ann.*, **446**, 205 (1926).

(11) G. Darzens and R. Mentzer, *Compt. rend.*, **213**, 268 (1941).

(12) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

TABLE I

BECKMANN REARRANGEMENTS OF α-OXIMINO KETONES

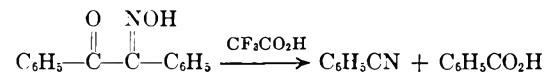


α-Oximino Ketone		Products and Yields from	
R	R′	85% H_2SO_4	$C_6H_5SO_2Cl$ + NaOH
C_6H_5	CH_3	$C_6H_5CO_2H$ (84%)	$C_6H_5CO_2H$ (91%)
CH_3	C_6H_5	$C_6H_5CONH_2$ (92%)	C_6H_5CN (87%)
C_6H_5	$CH_2C_6H_5$	$C_6H_5CH_2CONH_2$ (47%)	$C_6H_5CH_2CN$ (68%)[a]
		$C_6H_5CO_2H$ (86%)	$C_6H_5CO_2H$ (74%)
$C_6H_5CH_2$	C_6H_5	$C_6H_5CONH_2$ (61%)[b]	C_6H_5CN (77%)
		$C_6H_5CH_2CO_2H$ (68%)	$C_6H_5CH_2CO_2H$ (74%)
CH_3	$CH_3(CH_2)_3$	$CH_3(CH_2)_3CONH_2$ (59%)	$CH_3(CH_2)_3CN$ (70%)
CH_3	$CH_2C_6H_5$	$C_6H_5CH_2CONH_2$ (83%)[c]	$C_6H_5CH_2CN$ (87%)
$CH_3(CH_2)_2$	CH_3CH_2	$CH_3CH_2CONH_2$ (19%)	CH_3CH_2CN (45%)
		$CH_3(CH_2)_3CO_2H$ (78%)	$CH_3(CH_2)_2CO_2H$ (84%)

[a] A very small amount of 2-benzoyloximino-1,3-diphenyl-1-propanone was obtained also (see text). [b] An 8% yield of benzoic acid was obtained also. [c] A 12% yield of phenylacetic acid was obtained also.

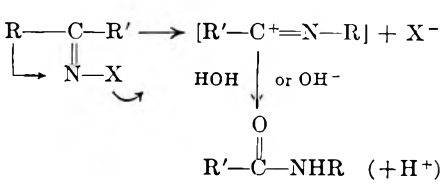
catalyzed reaction was hydrolyzed to the amide and sometimes in part to the carboxylic acid by the hot aqueous sulfuric acid.

The rearrangement in 85% sulfuric acid is not initiated below about 100°, and 100% sulfuric acid tends to char most of the α-oximino ketones used in this study. It thus appeared useless to attempt to isolate the nitrile products from the sulfuric acid reaction. Nitrile products were obtained, however, with a number of other typical catalysts for the "normal" reaction. The use of phosphorus pentachloride to obtain *n*-valeronitrile from 3-oximino-2-heptanone has been mentioned; this reagent also gave an 86% yield of phenylacetonitrile from 2-oximino-1-phenyl-3-butanone. Similarly, thionyl chloride gave an 88% yield of benzonitrile from 1-oximino-1-phenyl-2-propanone, and phosphorus oxychloride gave a 37% yield in the same reaction. Finally, trifluoroacetic acid, which has been shown recently to give normal amide products with a variety of ketoximes,[13-15] gave valeronitrile (58%) from 3-oximino-2-heptanone and benzonitrile (94%) and benzoic acid (88%) from α-benzil monoxime.



On the basis of all the evidence available on the Beckmann rearrangement of α-oximino ketones of the *anti* configuration, it seems reasonable to conclude that, however initiated, the reaction proceeds by only a single course, which results in cleavage of the molecule to a nitrile and a carboxylic acid. It is therefore suggested that the terms "normal" and "abnormal" as appiled to this reaction are superfluous and should be dropped. To do the least violence to accepted nomenclature it might be well to define two different types of Beckmann rearrangement; those of the *first order*, which are undergone by simple ketoximes and result in *N*-substituted amides as products, and those of the *second order*, which are undergone by *anti* α-oximino ketones or α-oximino alcohols[4] and result in cleavage to nitriles and carbonyl compounds, either carboxylic acids, aldehydes, or ketones. It should be noted also that some simple ketoximes rearrange by a "second order" path, giving a nitrile and another fragment whose exact nature depends on the structure of the oxime rearranged.[16] In some cases the rearrangement may follow a first or second order course depending on the nature of the reagent initiating it;[16b] in others the second order course appears to be followed regardless of the reagent.[16c] Such second order rearrangements of simple oximes have been called "abnormal,"[16c] and here the use of the term is logical. Because of the confusion in terminology which has existed in this area, it is suggested that such rearrangements be referred to as *abnormal Beckmann rearrangements of the second order*.

The two types of rearrangement also may be defined from a mechanistic point of view. It is commonly accepted[3,17,18] that the first order rearrangement of a simple ketoxime involves the con-



(13) M. L. Huber, U. S. Patent 2,721,199, Oct. 18, 1955.

(14) M. Hudlicky, *Chem. listy*, **51**, 470 (1957); *Collection Czechoslov. Chem. Communs.*, **23**, 462 (1958).

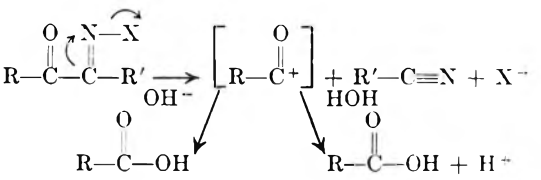
(15) W. D. Emmons, *J. Am. Chem. Soc.* **79**, 6522 (1957).

(16) (a) R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **18**, 1058 (1953). (b) R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955). (c) S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, **24**, 364 (1959). References to earlier work are given in these papers.

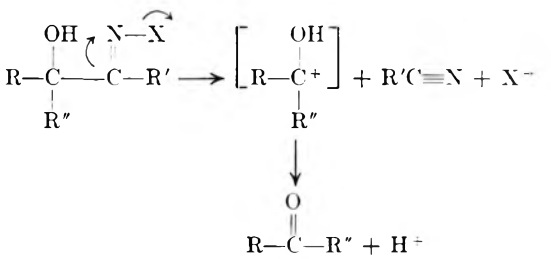
(17) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, p. 322.

(18) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1956, p. 321.

current departure of the hydroxyl or acylated hydroxyl, X, with its bonding pair of electrons and the 1,2-shift of the group, R, originally *trans* to X, with its bonding pair. The intermediate cation then completes the reaction by combining with an hydroxide anion, water, or some other suitable species. The second order reaction may be pictured very similarly, except that the departure of X is accompanied by the shift of *an electron pair only*,[19] forming the carbon-nitrogen triple bond and hence the nitrile. The cation which is left then combines

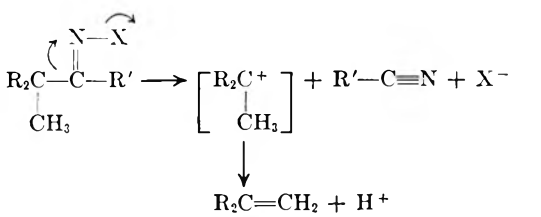


with an hydroxide anion, water, or other appropriate species. In the case of the α-oximino alcohols,[4] the intermediate cation expels a proton and forms an aldehyde or a ketone. Thus very

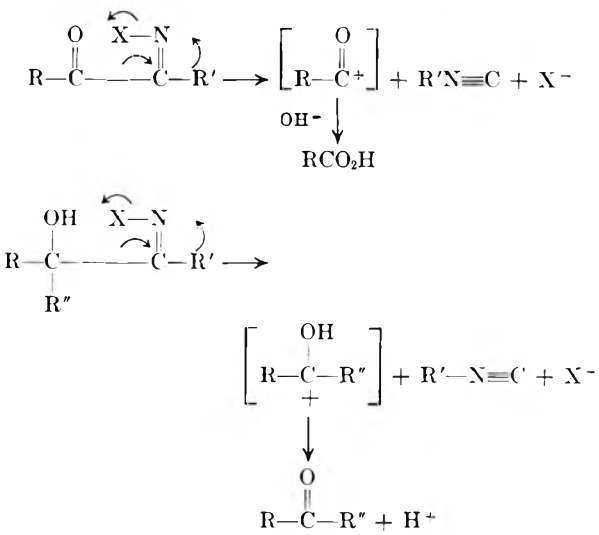


simple definitions result if the first order rearrangement is defined as one which involves shift of an organic group with its pair of electrons, and the second order rearrangement as one which involves shift of an electron pair only.

This mechanistic definition also applies to the abnormal second order rearrangement. In fact, mechanisms very similar to those presented above have been proposed[16] to explain the abnormal rearrangement. For example, the abnormal rearrangement of tertiary ketoximes may be pictured as involving departure of X and shift of the electron pair to give a nitrile and a tertiary carbonium ion. This ion then usually completes the reaction by expelling a proton and forming an olefin. The abnormal second order rearrangement of simple ketoximes is clearly related to the rearrangement of α-oximino ketones and alcohols, since in both cases the tendency of the *trans*-group to form a relatively stable cation is apparently what leads to shift of the electron pair only.



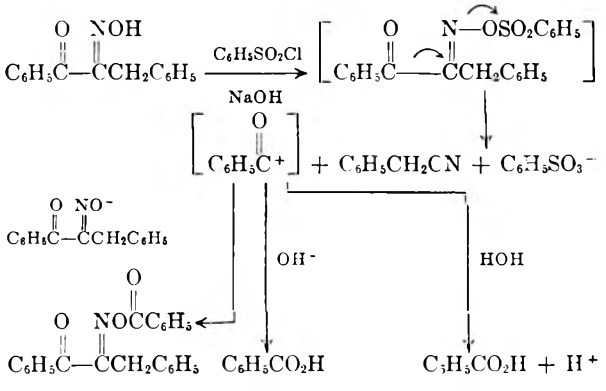
The considerations just presented suggest that possibly a "third order" Beckmann rearrangement also should be defined. Blatt and Barnes[4] found that α-oximino ketones or alcohols in the *syn* or β-configuration gave isonitriles and carbonyl compounds when treated with an acylating agent and base. These products can be accounted for by mechanisms analogous to those discussed, but wherein shifts of *both* an organic group with its electron pair and another electron pair take place.



A by-product obtained when 1,3-diphenyl-2-oximino-1-propanone was dissolved in base and treated with benzenesulfonyl chloride sheds some light on the mechanism of the second order reaction. As noted in Table I, the principal products of the reaction were phenylacetonitrile and benzoic acid, but there was obtained also a small amount of white solid which separated from the basic reaction medium as the reaction proceeded. Elemental analysis and infrared spectrum suggested that this was 2-benzoyloximino-1,3-diphenyl-1-propanone, and this was confirmed by synthesis of the compound from the α-oximino ketone and benzoyl chloride in the presence of pyridine. Although puzzling at first, the formation of this compound can be explained readily on the basis of the mechanism just discussed. Thus the first step in the rearrangement was almost certainly the formation of the benzenesulfonate of the oxime, and it may be hypothesized that this was followed by departure of the benzenesulfonate anion and shift of the electron pair as shown below to form phenylacetonitrile

(19) In referring to the Beckmann rearrangement it is very common to speak of the "shift" of a group to the nitrogen atom. This convention has been used in this paper to correlate the discussion with most previous discussions of the reaction. However, the reaction may be regarded as the attack of the electron-deficient nitrogen atom on the electron pair of the *trans*-group. See P. T. Scott, D. E. Pearson, and L. J. Bircher, *J. Org. Chem.*, 19, 1817 (1954); Footnote 4. It should be kept in mind that this is the probable course of the "shifts" discussed in this and other papers.

and the benzoyl oxocarbonium ion. Three principal modes of reaction were available to this carbonium ion: combination with water, with a hydroxide ion,



or with the anion of 1,3-diphenyl-2-oximino-1-propanone. Either of the first two possibilities would give benzoic acid, the observed major product; the third would give 2-benzoyloximino-1,3-diphenyl-1-propanone, the observed minor product. Since this minor product is an acylated α-oximino ketone it would be expected that normally it would be cleaved in the presence of excess base just as shown for the benzenesulfonate, and indeed, no such by-product was found with any other α-oximino ketone studied. In this case, however, it appears that the extreme insolubility of the benzoyl derivative preserved enough of it from destruction so that it was found among the products.

EXPERIMENTAL[20]

α-Oximino ketones. 2-Oximino-1-phenyl-1-propanone was purchased from Distillation Products Industries, Rochester, N. Y. All the other α-oximino ketones were prepared by the method previously described.[21] Their properties are listed in Table II.

TABLE II

α-OXIMINO KETONES

RCOCR'NOH R	R'	Yield, %	Melting Point, °C. Found	Lit.
CH_3	C_6H_5	86	162–163	164–165[a]
C_6H_5	$CH_2C_6H_5$	64	126–127.5	125–126[b]
$C_6H_5CH_2$	C_6H_5	57	114–114.5	——[c]
CH_3	$CH_3(CH_2)_2$	78	59–60	59–60[d]
CH_3	$CH_2C_6H_5$	75	80–81	80–81[e]
$CH_3(CH_2)_2$	CH_3CH_2	63	Liquid	——[f]

[a] H. Rheinboldt and O. Schmitz-Dumont, *Ann.*, 444, 113 (1925). [b] W. Schneidewind, *Ber.*, 21, 1323 (1888). [c] *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.29; H, 5.48; N, 5.85. Found: C, 75.46; H, 5.43; N, 5.81. [d] Ref. 21. [e] G. Ponzio, *Gazz. chim. ital.*, 35, 394 (1905). [f] B.p. 62–63° (0.45 mm.), n_D^{25} 1.4548. *Anal.* Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.97; H, 9.30; N, 9.51.

(20) All melting points and boiling points are uncorrected.

(21) A. F. Ferris, *J. Org. Chem.*, 24, 1726 (1959).

Rearrangements. Details of typical experiments reported in Table I and in the text are given. Those rearrangements not described in detail were carried out exactly as reported for the particular rearranging reagent in the examples presented below. Isolation of products was accomplished by conventional methods which were identical or similar to the techniques described in the examples.

Action of phosphorus pentachloride on 3-oximino-2-heptanone. To a suspension of 68.8 g. (0.33 mol.) of phosphorus pentachloride in 300 ml. of ether was added a solution of 43.0 g. (0.30 mol.) of 3-oximino-2-heptanone in 250 ml. of ether. The temperature rose rapidly to 37° and was held there by refluxing ether. The addition required 18 min., and the solution was maintained at reflux for another 30 min. by the application of heat. The ether solution was then poured into 1 l. of ice water, the layers were mixed thoroughly, and the ether solution was separated. The aqueous solution was extracted with two 100-ml. portions of ether, then the combined ether solution was washed with three 100-ml. portions of 5% sodium bicarbonate solution. The ether solution was dried and the solvent evaporated. The residue was distilled under reduced pressure to give 17.5 g. (70%) of *n*-valeronitrile, b.p. 67–70° (60 mm.), n_D^{25} 1.3897.

Action of 85% sulfuric acid on 1,3-diphenyl-2-oximino-1-propanone. To 75 ml. of 85% sulfuric acid preheated to 115° was added during 15 min. 18.0 g. (0.075 mol.) of 1,3-diphenyl-2-oximino-1-propanone. Reaction temperature was maintained at 107–117° during the addition by heat of reaction. The mixture cooled to 30° over 90 min., then was poured with stirring into 500 ml. of ice water. The precipitate was recovered by filtration, and the aqueous filtrate was treated with solid sodium bicarbonate. Additional precipitate was recovered by filtration. After drying, the total solid recovered amounted to 14.7 g. This material was stirred with a solution of 16.8 g. (0.20 mol.) of sodium bicarbonate in 200 ml. of water for several hours. Part of the solid went into solution. The material which failed to dissolve was recovered by suction filtration, washed with a little water, and dried. There was thus obtained 4.8 g. (47%) of phenylacetamide, m.p. 152–155°. After recrystallization from benzene the material melted at 156–158°; mixed melting point with authentic phenylacetamide, 155–158°. The aqueous filtrate from the bicarbonate neutralization was acidified with concentrated hydrochloric acid, and a white precipitate formed. After recovery, washing with water and drying this amounted to 7.9 g. (86%) of benzoic acid, m.p. 116–121°. After recrystallization from water this melted at 121–122.5°; mixed m.p. with authentic benzoic acid, 121–123°.

Action of benzenesulfonyl chloride and base on 1,3-diphenyl-2-oximino-1-propanone. A sample, 18.0 g. (0.075 mol.), of 1,3-diphenyl-2-oximino-1-propanone was dissolved in a solution of 16.0 g. (0.40 mol.) of sodium hydroxide in 100 ml. of water. Benzenesulfonyl chloride, 17.7 g. (0.10 mol.), was added during 17 min., the temperature being held below 40° by external cooling. A white solid began to separate almost as soon as addition was begun. When addition was complete, the mixture was allowed to stand several hours, then was extracted with three 100-ml. portions of ether. The solid dissolved in the ether. The ether solution was dried over anhydrous magnesium sulfate. The aqueous solution was acidified with concentrated hydrochloric acid, and the heavy white precipitate was recovered, washed with water and dried. Benzoic acid 6.8 g. (74% yield), m.p. 120–122°, was recovered. After recrystallization from water this material melted at 121–122.5°; mixed m.p. with authentic benzoic acid, 120–122.5°.

Evaporation of the ether solution left 10.1 g. of a mixture of liquid and solid. This was treated with 35 ml. of ethanol, the solid failing to dissolve. The solid was recovered by filtration, washed with a little ether, and dried. It amounted to 1.7 g., m.p. 117–118.5°. The ethanol was evaporated from the filtrate, leaving 8.2 g. of yellow liquid. Distillation under reduced pressure gave 6.0 g. (68%) of phenylaceto-

nitrile, b.p. 52–53° (0.15 mm.), n_D^{25} 1.5208. Authentic phenylacetonitrile gave n_D^{25} 1.5210.

The solid from the ether extract was recrystallized from 95% ethanol to give material of m.p. 117–119°. The analysis of the material (below) and its infrared spectrum indicated that it was probably 2-benzoyloximino-1,3-diphenyl-1-propanone, and this was confirmed by independent synthesis (next experiment).

Anal. Calcd. for $C_{22}H_{17}O_3N$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.20; H, 4.95; N, 4.22.

2-Benzoyloximino-1,3-diphenyl-1-propanone. To a solution of 2.8 g. (0.02 mol.) of benzoyl chloride and 1.2 g. (0.015 mol.) of pyridine in 10 ml. of benzene was added 1.0 g. (0.0042 mol.) of 1,3-diphenyl-2-oximino-1-propanone. The temperature rose from 25 to 32° and then began to fall. External heat was applied, and the temperature was held at 50–55° for 15 min. The mixture was cooled, and the solid which separated was removed by filtration. Solvent and excess benzoyl chloride were evaporated from the filtrate under reduced pressure. The residue crystallized on cooling and was recrystallized from 10 ml. of 95% ethanol. 2-Benzoyloximino-1,3-diphenyl-1-propanone, 0.4 g., m.p. 118–120°, was obtained. A mixture of this material and the minor product from the treatment of 1,3-diphenyl-2-oximino-1-propanone with benzenesulfonyl chloride and base melted at 117–119°. The infrared spectra of the two materials were identical.

Anal. Calcd. for $C_{22}H_{17}O_3N$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.91; H, 5.25; N, 4.26.

Action of 85% sulfuric acid on 1,3-diphenyl-1-oximino-2-propanone. To 75 ml. of 85% sulfuric acid preheated to 110° was added over 8 min. 15.5 g. (0.065 mol.) of 1,3-diphenyl-1-oximino-2-propanone. The temperature was maintained at 109–114° during the addition by heat of reaction. The reaction mixture was allowed to cool to 35° over 45 min. and was added to 500 ml. of ice water. Organic material separated. The aqueous mixture was neutralized with solid sodium carbonate, then was made just acid with 5*N* hydrochloric acid and was extracted with five 100-ml. portions of chloroform. The chloroform solution was extracted with three 100-ml. portions of 10% aqueous sodium carbonate, and the combined carbonate solution was made acid with concentrated hydrochloric acid. A white solid separated and was recovered by filtration and dried. The aqueous filtrate was extracted with three 100-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate. The precipitated solid amounted to 2.2 g., m.p. 73–76°, and was shown to be phenylacetic acid by the fact that its infrared spectrum was identical with that of an authentic sample of phenylacetic acid, and by the fact that a mixture of the material and authentic phenylacetic acid melted at 73–77°. Evaporation of the ether solution gave another 3.8 g. of less pure phenylacetic acid, identified by infrared spectrum. The total yield of phenylacetic acid was thus 6.0 g. (68%).

The original chloroform solution was next extracted with three 50-ml. portions of 10% aqueous sodium hydroxide. The chloroform solution was then dried over anhydrous magnesium sulfate. The basic solution was acidified with concentrated hydrochloric acid, and the solid which separated was recovered, washed and dried. Benzoic acid, 0.6 g. (8%), m.p. 119–121°, was obtained. A mixture of this material and authentic benzoic acid melted at 120–122°.

Evaporation of the chloroform solution left 4.8 g. (61%) of benzamide, m.p. (after washing with ether) 124.5–127°. A mixture of this material and authentic benzamide melted at 124.5–127.5°.

Action of benzenesulfonyl chloride and base on 1,3-diphenyl-1-oximino-2-propanone. 1,3-Diphenyl-1-oximino-2-propanone, 23.9 g. (0.10 mol.), was dissolved in a solution of 16.0 g. (0.40 mol.) of sodium hydroxide in 100 ml. of water. To the resulting solution, was added during 17 min., 21.2 g. (0.12 mol.) of benzenesulfonyl chloride. The temperature was held below 36° by external cooling. After all the chloride had been added, the reaction mixture was stirred for 45 min., then extracted with four 75-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate. The aqueous solution was acidified with concentrated hydrochloric acid, and the solid which separated was recovered by filtration, washed with cold water, and dried. The aqueous solution remaining was extracted with two 100-ml. portions of ether, and the ether solution was dried The total recovery of crude phenylacetic acid amounted to 14.1 g., 10.3 g. of precipitated solid and 3.8 g. from the ether extraction. The combined crude acid was recrystallized from 200 ml. of petroleum solvent (b.p. 65°) to give 10.1 g. (74%) of pure phenylacetic acid, m.p. 74.5–76.5°, mixed m.p. with authentic phenylacetic acid, 74.5–78°.

The ether solution from the original basic extraction was evaporated to leave 10.1 g. of brown oil. Distillation under reduced pressure gave 7.9 g. (77%) of benzonitrile, b.p. 67° (10 mm.), n_D^{35} 1.5207; authentic benzonitrile, n_D^{35} 1.5210.

Action of thionyl chloride on 1-oximino-1-phenyl-2-propanone. Thionyl chloride, 26.2 g. (0.22 mol.), was added during 15 min. to a suspension of 32.6 g. (0.20 mol.) of 1-oximino-1-phenyl-2-propanone in 150 ml. of ether. The temperature was maintained at 35–36° by refluxing ether, and vigorous evolution of hydrogen chloride took place. The reaction mixture was allowed to stand for several hours then was poured into 100 ml. of ice water. The layers were mixed thoroughly, then the ether layer was separated and the aqueous layer was extracted with 100 ml. of ether. The combined ether layer was washed with three 50-ml. portions of 5% sodium bicarbonate solution and dried. The ether was evaporated and the residue was distilled under reduced pressure to give 18.1 g. (88%) of benzonitrile, b.p. 68–70° (10 mm.), n_D^{35} 1.5210; authentic benzonitrile, n_D^{35} 1.5210.

Action of benzoyl chloride and base on 3-oximino-2-heptanone. 3-Oximino-2-heptanone, 35.8 g. (0.25 mol.), was dissolved in a solution of 40.0 g. (1.00 mol.) of sodium hydroxide in 250 ml. of water. Benzoyl chloride, 49.2 g. (0.35 mol.), was added during 25 min., the temperature being held at 30–35° by external cooling. The reaction mixture was extracted with three 100-ml. portions of ether and the solution was dried. The solvent was evaporated, and the residue was distilled under reduced pressure to give 17.1 g. (82%) of *n*-valeronitrile, b.p. 67–69° (60 mm.), n_D^{35} 1.3900; authentic *n*-valeronitrile, n_D^{35} 1.3901.

Action of polyphosphoric acid on 3-oximino-2-heptanone. To 125 ml. of polyphosphoric acid, preheated to 120°, was added 35.8 g. (0.25 mol.), 3-oximino-2-heptanone, during 18 min. Heat of reaction held the temperature at 120–135°. The mixture was allowed to cool to 54° over 25 min., then was poured into 750 ml. of ice water. The resulting mixture was extracted with three 100-ml. portions of ether. The aqueous solution was brought to *p*H 6 by the addition of solid sodium bicarbonate, and extracted with six 100-ml. portions of ether. Both ether solutions were dried over anhydrous magnesium sulfate. The ether was evaporated from the first extract to leave 16.1 g. of brown oil. Distillation under reduced pressure gave 7.1 g. (28%) of *n*-valeric acid, b.p. 80–84° (8 mm.), n_D^{35} 1.4027; authentic *n*-valeric acid, n_D^{35} 1.4024. The residue from this distillation was added to the second ether extract, and cautious evaporation of part of the ether led to the crystallization of 6.1 g. (24%) of *n*-valeramide, m.p. 102–104°. A mixture of this material and authentic *n*-valeramide melted at 102.5–105°.

Action of trifluoroacetic acid on α-benzil monoxime. To 150 g. of trifluoroacetic acid was added 45.1 g. (0.20 mol.) of α-benzil monoxime during 30 min. The temperature rose from 26 to 67° during the addition, then dropped to 30° during the next 30 min. To the clear solution was added 100 ml. of water at 15–30°, and a white solid separated. A solution of 65 g. of sodium hydroxide in 150 ml. of water was added, with cooling to hold the temperature below 25°. The solid dissolved, and an organic liquid separated. The liquid was extracted with four 100-ml. portions of ether. The ether

solution was dried, the solvent was evaporated, and the residue was distilled under reduced pressure to give 19.4 g. (94%) of benzonitrile, b.p. 70–71° (10 mm.), n_D^{35} 1.5206. The aqueous solution was made strongly acid with concentrated hydrochloric acid, and the solid which separated was recovered by filtration, washed with water and dried. There was obtained 33.3 g. of solid, much more than the 24.4 g. of benzoic acid required by theory. It appeared that sodium trifluoroacetate or sodium chloride had coprecipitated with the benzoic acid. This was removed by treating the solid with 300 ml. of ether, filtering to remove undissolved solid, washing with two 50-ml. portions of water to remove any dissolved sodium trifluoroacetate, and drying. Evaporation of the ether left 21.4 g. (88%) of benzoic acid, m.p. 120.5–122°. A mixture of this material and authentic benzoic acid melted at 120.5–122°.

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

Correlation of Polarographic Data with Structure. Use of the Hammett-Taft Relation

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The success which the Hammett polar substituent relation has had in correlating the polarographic half-wave potential data of certain series of organic compounds with their structure, prompted an examination of the applicability of the Taft elaboration on the Hammett relation for the same purpose. The Taft-Hammett equation very satisfactorily correlates data in the electrochemical reduction of a variety of functional groups in both aliphatic and aromatic compounds. In the case of aliphatic compounds, the equation is apparently not applicable for substituents larger than ethyl groups.

Considerable attention has been given in the polarographic literature to the search for consistent relationships between the half-wave potential, $E_{1/2}$, and the structural characteristics of electroreducible and electrooxidizable organic substances.[1] Generally, none of the various relationships developed has been widely applied. However, specific areas of good agreement between the observed behavior of a series of related compounds and a particular correlating equation are well known, especially in connection with the Hammett equation,[2]

$$\log (k/k_0) \text{ or } \log (K/K_0) = \sigma\rho \qquad (1)$$

where k is a rate constant, K an equilibrium constant, σ a polar substituent constant based on the structure of the reacting molecule, and ρ a reaction constant which measures the susceptibility of a given reaction series to polar substituents; the zero subscript refers to some member of a reaction series arbitrarily chosen as standard; k or K *sans* subscript refers to any other member of the same series.

Successful correlation of polarographic half-wave potentials with structure has been achieved through use of Equation 1 by assuming that $E_{1/2}$ is proportional to log K, the unknown proportionality constant being absorbed in the ρ factor, *e.g.*,

$$E_{1/2} - (E_{1/2})_0 = \sigma\rho \qquad (2)$$

As in the case of rates and equilibrium constants, this correlation fails for *ortho* benzene derivatives and aliphatic compounds.[3]

Taft[4] developed an equation analogous to that of Hammett but applicable to *ortho* derivatives and aliphatic compounds, and a further equation of great generality

$$P_\sigma = \sigma^*\rho^* \qquad (3)$$

where P_σ is any parameter proportional to energy and dependent upon the polar effect of substituent groups, *e.g.*, dipole moments, vibration frequencies and bond energies; dimensional consistency is maintained by assigning the proper dimensions to the empirical constant, ρ^*.

Taft[4] has applied his generalized form of the Hammett equation to predict successfully the outcome of the experimental determination of $E_{1/2}$ of an aliphatic compound studied by the

(1) *E.g.*, R. L. Bent, J. C. Dessloch, F. C. Duennebier, D. W. Fassett, D. B. Glass, T. H. James, D. B. Julian, W. R. Ruby, J. M. Snell, J. H. Sterner, J. R. Thirtle, P. W. Vittum, and A. Weissberger, *J. Am. Chem. Soc.*, **73**, 3100 (1951); P. Zuman, *Chem. Listy*, **48**, 94 (1954).

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

(3) E. C. Bennett, Ph.D. Thesis, University of Michigan, 1954.

(4) (a) R. W. Taft, *J. Am. Chem. Soc.*, **74**, 2729 (1952); (b) *J. Am. Chem. Soc.*, **74**, 3120 (1952); (c) *J. Am. Chem. Soc.*, **75**, 4231 (1953).

authors.[5,6] Consequently, the study of the applicability of the Taft relationship to the correlation of the ease of polarographic reduction with structure in other series of organic compounds was undertaken. The greater applicability of the Taft equation as compared to the Hammett equation would be especially advantageous in polarography.

Application of the Hammett-Taft equation. The success of the Taft-Hammett equation in correlating $E_{1/2}$ with structure is illustrated by Table I, which summarizes data for the polarographic reduction of eight series of compounds (other series, which do not follow Taft's correlation, are discussed later). The correlation is used in the form

$$E_{1/2} = \sigma^*\rho^* + (E_{1/2})_0 \qquad (4)$$

in which $(E_{1/2})_0$ corresponds to $E_{1/2}$ for reduction of that member of a series of related compounds for which σ^* is zero. Taft's σ^* parameters[4c] are referred in all cases to the methyl group, *e.g.*, in compound series 1 of Table I where the general formula is $R_1R_2C(Br)COOH$, $(E_{1/2})_0$ is the half-wave potential of 2-bromo-2-methylpropanoic acid. The fit of Equation 4 to the data was performed by the method of least squares; the standard deviation, δ, is given.

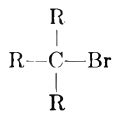
TABLE I

CORRELATION OF POLAROGRAPHIC HALF-WAVE POTENTIALS BY THE TAFT-HAMMETT EQUATION

Reaction Series[a]	Equation Applicable	δ	Ref.
1. 2-Bromoalkanoic acids $R_1R_2C(Br)COOH$	$-0.41\ \sigma^*-0.030$	0.02	6
2. Ethyl-2-bromoalkanoates $R_1R_2C(Br)COOC_2H_5$	$-0.28\ \sigma^*-2.71$	0.02	6
3. Substituted phenones C_6H_5COR			
*p*H 5	$0.33\ \sigma^*-1.27$	0.01	7
*p*H 9	$0.36\ \sigma^*-1.44$	0.01	
4. Substituted ethylenes $R_1R_2C=CR_3R_4$	$0.72\ \sigma^*-3.77$	0.05	8
5. Ethyl trichloroacetate (three waves)	$0.81\ \sigma^*-2.37$	0.03	9
6. Alkyl bromides $R_1R_2R_3CBr$	$0.63\ \sigma^*-2.71$	0.12	10
7. Bromomethane derivatives $BrCH_2R$	$1.04\ \sigma^*-2.11$	0.03	10, 11
8. Iodobenzoic acids (*o*, *m*, and *p*)	$-0.44\ \sigma^*-1.32$	0.01	12

[a] Substituents corresponding to the above reaction series are given below, e.g., the pairs of substituents used in the first series of the 2-bromoalkanoic acids were H and H, H and CH_3, CH_3 and CH_3, CH_3 and C_2H_5, etc. (numbers are those of the tabulated values of the substituent constants in Taft's paper[4c]; the constants used here are the following: 1. Cl_3C, 2.65; 3. Cl_2H, 1.940: 4, CH_3CO, 1.65; 6. $ClCH_2$, 1.050; 7. CH_2Br, 1.030; 11. C_6H_5. 0.600; 14. H, 0.490; 23. CH_3, 0.000; 25. C_2H_5, −0.100; 26. *n*-C_3H_7, −0.115; 28. *n*-C_4H_9, −0.130; 30. *i*-C_3H_7, −0.210):
1. 14, 14; 14, 23; 23, 23; 23, 25; 14, 25; 25, 25; 25, 28.
2. 23, 25; 14, 25; 23, 23; 25, 25.
3. 11; 14; 25; 26; 30.
4. 11, 14, 14, 14; 11, 14, 14, 23; 11, 14, 14, 11; 11, 11, 14, 14; 11, 11, 14, 11; 11, 11, 11, 11.
5. 1; 3; 6.
6. 14, 14, 14; 14, 14, 23; 14, 14, 26; 14, 14, 27; 14, 23, 25; 7, 14, 14;
7. 4; 14; 23; 26.

The disparate nature of the kinds of compounds which can be successfully correlated by this method is evident. However, anomalies occur, some of which are instructive in themselves. For example, in the 2-bromoalkanoic acids (series 1), the equation fails to predict $E_{1/2}$ correctly for 2-bromo-2-ethylhexanoic acid, or, indeed, for any of the straight chain acids larger than 2-bromobutanoic acid; $E_{1/2}$ is more positive than the equation predicts, indicating the action of structure-sensitive factors other than pure polar effects. Much the same kind of anomaly occurs with the alkyl bromides (series 6), in which the *n*-butyl and isobutyl bromides lie off the mean straight line of the equation by a distance exceeding the standard deviation for the remaining members of the series, whereas *sec*-butyl bromide lies precisely on the line. The consistency of these facts with those for series 1 may be seen by considering the structure upon which the correlation for the alkyl bromides is based:



(5)

In *n*-butyl bromide one of the substituents, R, is normal propyl and in isobutyl bromide one of them is isopropyl; however, in *sec*-butyl bromide the largest substituent is ethyl. Thus, in both the 2-bromoalkanoic acids and in the alkyl bromides the Taft-Hammett relationship, when applied to half-wave potentials, breaks down for substituents larger than ethyl groups.

In the monobromomethane derivatives (series 7), the compounds included are bromoacetone, ethyl bromide, bromoform and *n*-butyl bromide; $E_{1/2}$ data are not available for methyl bromoacetate, which is structurally a member of this series, and Taft gives no σ^* value for ethyl bromoacetate, for which polarographic data are available. An attempt to correlate $E_{1/2}$ data for chloroacetone,

(5) R. W. Taft, personal communication.

(6) P. J. Elving, J. M. Markowitz, and I. Rosenthal, *J. Electrochem. Soc.*, **101**, 195 (1954).

(7) P. J. Elving and J. T. Leone, *J. Am. Chem. Soc.*, **80**, 1021 (1958).

(8) H. A. Laitinen and S. Wawzonek, *J. Am. Chem. Soc.*, **64**, 1765 (1942).

(9) P. J. Elving and C.-S. Tang, *J. Am. Chem. Soc.*, **76**, 1412 (1954).

(10) M. von Stackelberg and W. Stracke, *Z. Elektrochem.*, **53**, 118 (1949).

(11) R. E. Van Atta, Ph.D. Thesis, The Pennsylvania State University, 1952.

(12) P. J. Elving and C. L. Hilton, *J. Am. Chem. Soc.*, **74**, 3368 (1952).

chloroform, and methyl chloroacetate was unsuccessful, suggesting that carboalkoxy groups, unlike the ketone group, cannot be successfully correlated by the present scheme (although more data would be necessary for verification). Therefore, any attempt to extend Taft's list of σ^* values to include the carboethoxy group by use of the polarographic data of series 7 would likely lead to an erroneous assignment.

In general, attempts to extend the list of σ^* values by using polarographic data did not lead to consistent results, especially for the case of halomethyl substituents. For example, Taft[4c] lists σ^* values for $-CH_2Cl$ and $-CH_2Br$, but not for $-CH_2I$. A precise value for the substituent constant of the latter group is readily obtained by plotting the data for the three monohaloacetones. However, use of this value to correlate $E_{1/2}$ for the three haloforms does not give a straight line. As a second example, the success of the correlation for the three polarographic waves of ethyl trichloroacetate (series 5, which is equivalent to the series of the three ethyl esters of the chloroacetic acids), encouraged the belief that the data for ethyl bromoacetate might fall on the same line; it does not.

Actually, in series 5 the Taft substituent constants are being used somewhat improperly, since they are intended to measure the effect of substituents on a *nearby* reaction center. In the reduction of the haloacetates, the halogen is being attacked, leading to carbon-halogen bond fission, *i.e.*, the entity being used as a substituent is itself at the reaction center. Whether the success of the Taft-Hammett equation in the face of this misuse is only fortuitous or whether it indicates a greater generality for this equation than has been suspected, cannot now be decided.

It should be noted that in addition to predicting the effect of substituents on carbon-halogen bond fission, the Taft-Hammett equation is successful in predicting their effect upon the reduction of both carbonyl and carbon-carbon double bonds (series 3 and 4). Furthermore, the success of correlation is somewhat independent of solution environment, a good fit being achieved at each of two different *p*H values (series 3).

The Taft-Hammett equation was unsuccessful when applied to the nitroalkanes and hydroxynitroalkanes; values based on the Taft substituent values for the structure $R_1R_2R_3CNO_2$ were completely scattered, regardless of the bulk of the R groups.

Conclusions. Like the Hammett equation, the Taft-Hammett equation appears to be generally useful in discussing the ease of electrochemical reduction (and presumably of oxidation) of certain series of structurally related compounds. It is likely that those series or those members of a series which follow the equation are subject to polar effects only, as far as the structural effect on $E_{1/2}$ is concerned, or that the energetic magnitude of polar effects overshadows the energetic contributions of other effects such as adsorption. Thus, the Taft-Hammett relation may have possibilities for serving as a type of screen for pure polar effects in examining the electrode mechanisms of organic compounds, with deviations from the predicted behavior indicating the influence of factors in the electrochemical process other than polar effects due to structure.

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Tetrabutylammonium Iodotetrachloride as a Chlorinating Agent

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Tetrabutylammonium iodotetrachloride has been used successfully as a source of chlorine for addition on a small scale to the double bonds of *cis*- and *trans*-stilbene, tetraphenylethylene, cyclohexene, and styrene, and to the triple bond of diphenylacetylene. A successful substitution was carried out on the α-carbon atom of acetophenone, and some chlorination of phenol to trichlorophenol was observed. Of particular interest was the fact that with *cis*- or *trans*-stilbene stereospecific *trans* addition was observed. When molecular chlorine reacted with *cis*- or *trans*-stilbene in the dark, the addition was not stereospecific even when antimony pentachloride or tetrabutylammonium chloride was present.

The observation[1] that tetrabutylammonium iodotetrachloride (tetrabutylammonium tetrachloroiodate [III]) chlorinated itself when illuminated to yield the (1-chlorobutyl)tributylammonium ion has led to the consideration of this salt as a source of chlorine for small scale chlorinations. In the present investigation tetrabutylammonium iodotetrachloride has been tried for

(1) R. E. Buckles and J. F. Mills, *J. Am. Chem. Soc.*, **76**, 3716 (1954).

TABLE I

CHLORINATION REACTIONS OF TETRABUTYLAMMONIUM IODOTETRACHLORIDE IN ETHYLENE CHLORIDE

Compound Chlorinated		$(C_4H_9)_4NICl_4$	Reaction	Light (L)[a] or	Products				
Name	Wt. G.	Wt. G.	time, days	Dark (D)	Identity	Crystn. Solvent	M.P.[b]	Wt. G.	Yield, %
trans-Stilbene	2.0	5.7	3	D	*meso*-Dichloride	C_2H_5OH	191–192	1.4	50
cis-Stilbene	2.0	5.7	3	D	DL-Dichloride	C_2H_5OH	91–92	1.4	50
cis-Stilbene	5.0	14.2	3–14	D	DL-Dichloride[c]	C_2H_5OH	91–92	3.0	43
					meso-Dichloride[c]	C_2H_5OH	191–193	0.5	7
Tetraphenylethylene	2.0	3.1	21	D	Dichloride	CCl_4[d]	183–184	0.8	33
Diphenylacetylene	2.0	5.7	5	D	*trans*-Dichloride	C_2H_5OH	138–139	1.3	47
Cyclohexene	5.0	31.2	3	D	Dichloride[e]	—	—	4.5	48
Styrene	10.0	49.1	4	D	Dichloride[f]	—	—	12.4	74
Tetraanisylethylene	4.0	4.6	7–35	D	Starting material	$(CH_3)_2C{=}O$	183–184	1.5	38
Cinnamic acid	2.0	6.9	3–5	D	Mixture	C_6H_{14}	130–160	0.6	—
Crotonic acid	2.0	11.9	5	D	Oily mixture	$(C_2H_5)_2O$	—	—	—
Acetophenone	2.0	8.5	5	L	Phenacyl chloride	CH_3OH	57–58	1.4	54
Triphenylmethane	2.0	4.2	5	L[g]	Starting material	C_6H_{14}	85–86	1.4	70
Bibenzyl	2.0	11.2[h]	5	L[i]	Starting material	C_2H_5OH	50–51	1.5	75
Toluene	5.0	27.8	3	L	Mixture[j]	—	—	—	—
Phenol	2.0	32.7[j]	5	D	2,4,6-Trichlorophenol	—	51–58	0.5	12
Acetic acid[k]	2.0	17.0	5	L	Liquid mixture	—	—	0.2	—

[a] Unless otherwise noted the light was diffuse daylight. [b] All melting points were corrected. [c] This type of result was obtained in several experiments. The most *meso*-isomer was obtained from reaction mixtures which were allowed to become too warm during the initial reaction. [d] This solvent was used to wash the finely ground product. [e] The boiling point was 180–185° (745 mm.). [f] The boiling point was 95–97° (7.0 mm.). The crude product was shown by gas chromatography to be mostly dichloride contaminated by a little styrene. [g] The illumination was carried out in a silica flask with a quartz mercury arc. [h] Two moles of $(C_4H_9)_4NICl_4$ were used for one of bibenzyl. [i] B.p. 120–130°. [j] Three moles of $(C_4H_9)_4NICl_4$ were used for one of phenol. [k] Two drops of phosphorus trichloride were added.

both addition reactions and substitution reactions. The results are summarized in Table I.

In general the salt did not appear to be as reactive as molecular chlorine, but the reactions that were successful were more easily controlled. This controlled addition was especially important in the addition of chlorine to *cis*- and *trans*-stilbenes. When tetrabutylammonium iodotetrachloride was used in the dark, *cis*-stilbene consistently yielded mostly *dl*-α,α'-dichlorobibenzyl while *trans*-stilbene gave the *meso* isomer. Such stereospecific *trans* additions of molecular chlorine to double bonds would be expected[2] for simple alkenes—especially in the presence of antimony pentachloride,[2a] but such results have not been observed for the *cis* and *trans*-stilbenes. In fact the chlorination of *trans*-stilbene by molecular chlorine under ultraviolet radiation[3] and by sulfuryl chloride in the presence of a peroxide[4] has been reported to give mixtures of *meso*- and *dl*-α,α'-dichlorobibenzyl often with the low melting point (91–92°) *dl*-isomer[5] as the predominant product.[3a] With molecular chlorine in the present investigation both *cis*- and *trans*-stilbene yielded mixtures of *dl*- and *meso*-dichloride which were difficult to separate in the small scale experiments carried out. The *meso* form which is the less soluble diastereomer was isolated

TABLE II

CHLORINATION OF *cis*- AND *trans*-STILBENE BY CHLORINE IN ETHYLENE CHLORIDE IN THE DARK TO GIVE α,α'-DICHLOROBIBENZYL

Isomer	Added Reagent	Product Yield, %	Product *meso* %	Product DL %
cis	None	47	92	8
cis	$(C_4H_9)_4NCl$	40	91	9
cis	$SbCl_5$	48	97	3
cis[a]	None	43	99	1
trans	None	86	35[b]	65[b]
trans	$(C_4H_9)_4NCl$	68	32[b]	68[b]
trans	$SbCl_5$	93	96	4

[a] In this experiment the reaction mixture was left in diffuse daylight for three days. [b] These percentages were estimated from the infrared spectra of the mixtures in carbon disulfide.

(2) (a) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Am. Chem. Soc.*, **73**, 3329 (1951); (b) H. J. Lucas and C. W. Gould, Jr., *J. Am. Chem. Soc.*, **63**, 2546 (1941).

(3) (a) R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *J. Am. Chem. Soc.*, **72**, 2496 (1950); (b) P. Pfeiffer, *Ber.*, **45**, 1810 (1912); (c) T. Zincke, *Ber.*, **10**, 999 (1877); *Ann.*, **198**, 115 (1879).

(4) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 3432 (1939).

(5) A. Weissberger and H. Bach, *Ber.*, **64**, 1095 (1931).

in much larger amounts than the more soluble *dl* form. These nonstereospecific additions are summarized in Table II. The addition in the presence of antimony pentachloride was expected to be stereospecific and *trans* on the basis of the results reported[2a] with various alkenes, but it was not when applied to the stilbenes.

In the case of tetrabutylammonium iodotetrachloride reacting with stilbene, conditions must be satisfactory for a controlled, polar *trans*-addition of chlorine to the double bond possibly with the aid of the iodotetrachloride ion or the iododichloride ion which is present. Under other conditions with chlorine and stilbene addition by way of an intermediate allowing relatively free rotation about the central carbon-carbon bond must modify the stereochemical results expected from a polar addition by way of a chloronium ion[2] or its molecular equivalent.

With *trans*-cinnamic acid and with *trans*-crotonic acid tetrabutylammonium iodotetrachloride appeared to react incompletely so that the products were mixtures from which no dichloride could be isolated. From *trans*-cinnamic acid with chlorine both stereoisomeric dichlorides have been reported[6]—the one with low melting point (84–86°) in the dark or in subdued light and the one of high melting point (167–168°) under strong illumination. In the present investigation chlorine yielded the high melting isomer in very subdued light. With either *cis*- or *trans*-crotonic acid, on the other hand, chlorine has been reported to yield only the isomer of low melting point (63°) whether the reaction mixture was illuminated or not.[7] The problems of stereochemistry in these cases of chlorine addition were not resolved by the use of tetrabutylammonium iodotetrachloride.

Further evidence of the control possible in the use of tetrabutylammonium iodotetrachloride for the addition of chlorine is given in the reaction with diphenylacetylene. In this case a 47% yield of *trans*-α,α'-dichlorostilbene was obtained. The reaction of diphenylacetylene with chlorine in the cold has been reported[8] to yield $\alpha,\alpha,\alpha',\alpha'$-tetrachlorobibenzyl rather than the dichlorostilbene, but in one instance the isolation of an unspecified yield of α,α'-dichlorostilbene (m.p. 143, presumably *trans*) was reported.[9]

The reaction of tetrabutylammonium iodotetrachloride with tetraphenylethylene yielded only one 1,2-dichloro-1,1,2,2-tetraphenylethylene, m.p. 183–184°. No second isomer melting at 175° as reported[10] for the chlorination of tetraphenylethylene by chlorine was obtained. In the course of the isolation of the product by fractional crystallization samples of melting point lower than 184° were obtained, but in each case x-ray powder diagrams showed the presence of two crystalline phases and carbon-hydrogen analysis showed that the sample was not pure dichloride. In some of the lower melting fractions, the dichloride appeared to be contaminated by tetraphenylethylene as shown by powder diagrams and analyses.

From the reaction of tetraanisylethylene (tetrakis-(*p*-methoxyphenyl)-ethylene) with tetrabutylammonium iodotetrachloride only starting ethylene was obtained. With chlorine, however, 1,2-dichloro-1,1,2,2-tetrakis(3,5-dichloro-4-methoxyphenyl)-ethane was isolated. This decachloride was dehalogenated with zinc to tetrakis(3,5-dichloro-4-methoxyphenyl)ethylene.

The only substitution reaction of tetrabutylammonium iodotetrachloride which gave a satisfactory yield of pure product on a small scale was that with acetophenone to give phenacyl chloride. Phenol gave a low yield of impure 2,4,6-trichlorophenol. Bibenzyl, triphenylmethane, toluene, and acetic acid (in the presence of a catalytic amount of phosphorus trichloride) gave only impure starting material from the reaction with tetrabutylammonium iodotetrachloride under illumination in each case. Bibenzyl with chlorine has never been reported to give chlorination of the side chain but stilbene has been reported[11] as a product, so that dihalides or higher substitution products would be expected[3a] with excess chlorine under illumination. With chromyl chloride, bibenzyl has been reported[12] to give a low yield of α,α'-dichlorobibenzyl. Triphenylmethane has also not been reported as chlorinated directly, but with sulfuryl chloride in the presence of lauryl peroxide[13] or of α,α'-azodiisobutyronitrile[14] good yields of triphenylmethyl chloride have been reported.

EXPERIMENTAL

Tetrabutylammonium iodide. A solution of 156 g. (0.84 mol.) of tributylamine and 159 g. (0.87 mol.) of butyl iodide in 400 ml. of anhydrous ethyl acetate was boiled under reflux for 4 days. This solution yielded crystalline product which was dissolved in 200 ml. of 95% ethanol. This solution was extracted with 20% aqueous sodium hydroxide. The alcohol layer was separated and evaporated nearly to dryness on a steam bath. The crystalline product was dried to constant weight (263 g.). This crude product was crystallized twice from anhydrous benzene–ethyl acetate (300 ml. of each) to give 256 g. (82%), m.p. 144–145°. This

(6) A. Michael and H. D. Smith, *Am. Chem. J.*, **39**, 16 (1908).

(7) A. Michael and O. D. E. Bunge, *Ber.*, **41**, 2907 (1908).

(8) W. Redsko, *Zhur. Russ. Fiz.-Khim. Obshchestva* **21**, 421 (1889); *Chem. Zentr.*, **1880** I, 533.

(9) C. Liebermann and J. Homeyer, *Ber.*, **12**, 1971 (1879).

(10) H. Bassett, N. Thorne, and C. L. Young, *J. Chem. Soc.*, 85 (1949).

(11) R. Kade, *J. prakt. Chem.*, [2] **19**, 461 (1879).

(12) M. Weiler, *Ber.*, **32**, 1050 (1899).

(13) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939).

(14) M. C. Ford and W. A. Waters, *J. Chem. Soc.*, 1851 (1951).

method is a modification of one in which no solvent was used for the reaction mixture.[15] Another such method,[16] which was run at considerably higher temperatures over longer periods of time, gave a solid product which yielded no quaternary ammonium salt when crystallization from benzene–ethyl acetate was attempted.

Tetrabutylammonium iodotetrachloride (tetrabutylammonium tetrachloroiodate (III)). This salt of m.p. 137–139° (dec.) was prepared in 99% yield as described.[17] It was found that the point at which the solution became orange and product began to precipitate, was also the point at which the temperature of the reaction mixture reached a maximum (about 37°).

When tetrabutylammonium iodotetrachloride was used as a chlorinating agent it was possible to isolate the crude tetrabutylammonium iododichloride,[1] the unchanged iodotetrachloride, or a mixture of the two as a by-product. This crude salt was accumulated and chlorinated in a relatively large batch. A solution of 67.5 g. of the crude salt, which was accumulated from reactions using a total of 74.5 g. of tetrabutylammonium iodotetrachloride, in 500 ml. of chloroform was clarified by filtration and then treated with dry chlorine until solid product no longer precipitated. The reaction mixture was heated on a steam bath in a hood for 10 min. Cooling yielded 64.0 g. of tetrabutylammonium iodotetrachloride of m.p. 138–139° (dec.). This yield represents a recovery of 86% from the tetrachloroiodide originally used in the chlorination reactions.

All samples of tetrabutylammonium iodotetrachloride were kept in the dark because of tendency of the compound to photochlorinate itself even in the solid state.[1]

Other reagents. Most of the other reagents and materials used were available commercially or were synthesized by methods given in the *Organic Syntheses* series. Tetraanisylethylene was kindly supplied by Mr. Ronald E. Erickson of this laboratory.

Chlorination reactions of tetrabutylammonium iodotetrachloride. In each case, 0.005 mol. to 0.06 mol. of the compound to be chlorinated was mixed with an equimolar amount of tetrabutylammonium iodotetrachloride in 25 ml. of ethylene chloride. The mixture was allowed to stand either in the dark or under illumination for the desired length of time. The reaction mixture was then evaporated to dryness and the residue was extracted with ether. The ether-insoluble solid was the tetrabutylammonium salt mixture which was saved for rechlorination. The ether solution was evaporated and the residue was crystallized or distilled. The results are summarized in Table I.

When tetraphenylethylene was used in this reaction a 33% yield of dichloride, m.p. 183–184°, was obtained. This product checks reasonably well with the isomer melting at 188.5°.[10] This pure product was found by means of x-ray powder diagrams to have the same crystalline phase present as other samples which were crystallized from chloroform, methylene chloride, or ethylene chloride.

Anal. Calcd. for $C_{26}H_{20}Cl_2$: C, 77.4; H, 4.96. Found: C, 77.4; H, 4.75.

In some experiments of this type a fraction melting around 172–175° was isolated as well as the fraction of higher melting point already described. This lower melting compound checks for the isomer reported[10] to have m.p. 175°. By analyses and x-ray powder diagrams, however, these samples appeared to be mixtures of the dichloride of m.p. 184° with tetraphenylethylene or an unidentified substance. Particular trouble with some of the samples was encountered when ethyl alcohol was used as a solvent for crystallization. There appeared to be a solvolysis reaction and badly contaminated products were obtained.

Chlorination of tetrakis(p-methoxyphenyl)ethylene. A solution of 2.0 g. (0.0044 mol.) of tetrakis(*p*-methoxyphenyl)-ethylene in 25 ml. of ethylene chloride was mixed with a saturated solution of chlorine in ethylene chloride. The reaction mixture turned purple and became warm. It was allowed to stand in the dark for 10 days. At the end of this time the solution was orange and 1.7 g. of a solid, m.p. 220–221° (dec.), was obtained by filtration. Evaporation of the mother liquor yielded 0.4 g. more of product of m.p. 205–210° (dec.). Crystallization of the total crude product from hexane–carbon tetrachloride yielded 1.7 g. (74%) of 1,2-dichloro-1,1,2,2-tetrakis(3,5-dichloro-4-methoxyphenyl)-ethane of variable melting point depending on how fast the sample in the capillary was heated. Even with a bath preheated to 215° the melting point varied from 217–218° to 220–221° (dec.). This decomposition of the solid during the melting point determination may explain the low melting point (195–196°) reported[10] for this compound.

Anal. Calcd. for $C_{30}H_{20}Cl_{10}O_4$: C, 45.1; H, 2.52. Found: C, 44.8; H, 2.69.

The decachloride reacted only very slowly with a hot solution of sodium iodide in acetone to give a cloudy brown solution characteristic of vicinal dihalides. With hot alcoholic silver nitrate a very slow precipitation of silver chloride was observed.

Tetrakis(3,5-dichloro-4-methoxyphenyl)ethylene. A mixture of 0.32 g. (4.0×10^{-4} mol.) of the decachloride described above and excess (0.30 g.) zinc dust in 20 ml. of glacial acetic acid was boiled for 15 min. The solution was filtered and poured into 100 ml. of water. The crystalline product was washed thoroughly with water and then with acetone. The crude product was crystallized from hexane–carbon tetrachloride to give 0.16 g. (55%) of tetrakis(3,5-dichloro-4-methoxyphenyl)ethylene, m.p. 242–244°.

Anal. Calcd. for $C_{30}H_{20}Cl_8O_4$: C, 49.5; H, 2.77. Found: C, 48.8; H, 2.71.

The ultraviolet absorption spectrum of the octachloride in carbon tetrachloride ($9.2 \times 10^{-5}M$) show a peak at 325 mμ ($\epsilon = 12.1 \times 10^4$) which is characteristic of the stilbene chromophore of the tetraarylethylenes.[18] The decachloride on the other hand showed no absorption peak down to 260 mμ.

Reactions of the stilbenes with chlorine. A two-gram (0.011 mol.) sample of *cis*- or *trans*-stilbene in 25 ml. of ethylene chloride was mixed with 25 ml. of ethylene chloride saturated with chlorine. The mixture was then allowed to stand in the dark for 3 days. In some experiments 0.011 mol. of either antimony pentachloride or tetrabutylammonium chloride[19] were added. The reaction mixtures were filtered if necessary and evaporated to dryness. The residues were crystallized from 95% ethanol to give *meso*-α,α′-dichlorobibenzyl, m.p. around 190°. From the mother liquors small amounts of DL-α,α′-dichlorobenzyl m.p. around 90° were obtained. The results are summarized in Table II.

The reaction of cinnamic acid with chlorine. A solution of 2.0 g. (0.014 mol.) of *trans*-cinnamic acid in 25 ml. of ethylene chloride was treated with dry chlorine for 1 hr. in subdued light. Evaporation gave a residue which was crystallized from heptane to give 1.5 g. (51%) of 2,3-dichloro-3-phenylpropionic acid, m.p. 165–167°. This checks well for the isomer of high m.p. (167–168°) reported[6] for the reaction under strong illumination.

Gas chromatography. Some of the volatile compounds involved in this investigation were analyzed by gas chromatography. Measurements were carried out on a Perkin-Elmer Vapor Fractometer, Model 154B, with a 2-meter column (4 mm. ID) filled with silicone oil on Celite. Helium

(15) H. A. Laitinen and S. Wawzonek, *J. Am. Chem. Soc.*, **64**, 1765 (1942).

(16) G. I. Mikhailov, *Zhur. priklad. khim.*, **27**, 217 (1954); *Chem. Abstr.*, **49**, 3785 (1955).

(17) A. I. Popov and R. E. Buckles, *Inorg. Syntheses*, **5**, 176 (1957).

(18) R. E. Buckles and W. D. Womer, *J. Am. Chem. Soc.*, **80**, 5055 (1958).

(19) R. E. Buckles and J. F. Mills, *J. Am. Chem. Soc.*, **76**, 4845 (1954).

was used as a carrier gas at 25 p.s.i. The flow rate was 1.30 ml. per sec. at 225° and 0.86 ml. per sec. at 150°. The elution times are summarized in Table III. The samples of *cis*-stilbene were often contaminated with quinoline and isoquinoline. A commercial mixture of these compounds was used as a solvent in the synthesis[20] of *cis*-stilbene. A maximum of 5% of the *trans*-isomer was detected as an impurity in the *cis*-stilbene. It was often considerably less, but there was always some present.

TABLE III

ANALYSIS BY GAS CHROMATOGRAPHY WITH A COLUMN CONTAINING SILICONE OIL ON CELITE

Compound	Temp., °C.	Elution Time, Min.
cis-Stilbene	225	6.6
trans-Stilbene	225	11.5
Quinoline	225	3.0
Isoquinoline	225	3.5
Diphenylacetylene	226	9.9
Styrene	150	2.6
Styrene dichloride	150	14.3

(20) R. E. Buckles and N. G. Wheeler, *Org. Syntheses*, **33**, 88 (1953).

X-ray powder diagrams. These measurements were carried out by Dr. Norman C. Baenziger of this laboratory. A Straumanis-type camera of 114 mm. diameter was used. The powdered sample was placed in a 0.5-mm. capillary and irradiated with either the copper K_α or the iron K_α radiation.

Spectra. Infrared spectra were measured in the sodium chloride region with a Perkin-Elmer, Model 21, Spectrophotometer.[21] This type of data was used in the identification and analysis of samples of α,α'-dichlorobibenzyl dissolved in carbon disulfide. The DL-isomer had two characteristic bands at 645 and 675 cm.$^{-1}$ which were sufficiently different from the absorption of the *meso*-isomer at those frequencies that an estimate of the composition of mixtures could be made.

Ultraviolet absorption spectra were carried out on a Cary Recording Spectrophotometer, Model 11.

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

Addition Reactions of Mixtures of Bromine and Chlorine

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Mixtures of bromine and chlorine have been used as sources of bromine chloride for the synthesis of bromochlorides from cyclohexene, styrene, ethylene, *trans*-cinnamic acid, *cis*- and *trans*-stilbene, and diphenylacetylene. With styrene and cinnamic acid the products isolated were those expected from the addition of positive bromine and negative chlorine to the unsymmetrically substituted double bonds. With *cis*- and *trans*-stilbene stereospecific *trans* addition was observed.

In an earlier report[1] the addition to a double bond of the elements of bromine chloride arising from *N*-bromoacetamide and hydrochloric acid was found to give the products expected of polar, stereospecific *trans* additions. In the present investigation mixtures of bromine and chlorine—presumably in equilibrium with bromine chloride—were used as reagents for addition reactions. The results are given in Table I. Bromochlorides predominated as products in most of the experiments although often in disappointing yields. The bromochloride products obtained are those expected of polar, *trans* addition of bromine chloride to the double bonds just as was found in the investigation[1] involving mixtures of *N*-bromoacetamide and hydrochloric acid.

The predominance of bromochlorides as products is consistent with results reported for the addition reactions of mixtures of bromine and chlorine with compounds containing double bonds[2] and triple bonds.[3] Of the compounds listed in Table I only ethylene[4] and cinnamic acid[5] have been previously reported as reacting with mixtures of bromine and chlorine to give the bromochloride products.

The results with styrene and cinnamic acid show the expected polar addition of bromine chloride to unsymmetrically substituted double bonds in that cinnamic acid yielded 2-bromo-3-chloro-3-phenylpropionic acid and styrene yielded 2-bromo-1-chloro-1-phenylethane. Such a mode of addition has been reported in the case of mixtures of bromine

(1) R. E. Buckles and J. W. Long, *J. Am. Chem. Soc.*, **73**, 998 (1951).

(2) (a) P. B. D. de la Mare and S. Gandauer, *J. Chem. Soc.*, **36**, (1958); (b) A. Michael, *J. prakt. Chem.*, [2] **60**, 448 (1899); (c) P. Walden, *Ber.*, **30**, 2883 (1897).

(3) N. W. Hansen and T. C. James, *J. Chem. Soc.*, 2979 (1928).

(4) M. Simpson, *Bull. soc. chim. France*, [2] **31**, 409 (1879); J. W. James, *J. Chem. Soc.*, **43**, 37 (1883); M. Delepine and L. Ville, *Bull. soc. chim. France*, [4] **27**, 673 (1920).

(5) (a) N. W. Hanson and T. C. James, *J. Chem. Soc.*, 1955 (1928); (b) E. Erlenmeyer, *Ann.*, **289**, 259 (1896).

TABLE I

REPRESENTATIVE EXAMPLES OF ADDITION REACTIONS OF MIXTURES OF BROMINE AND CHLORINE

Unsaturated Compound			Products		
Name	Mole	Solvent	Yield, %	M.P.	Identity[a]
Ethylene[b]	—	CH_2Cl_2	39	106–109[c]	BrCl
Ethylene[b,d]	—	CH_2Cl_2	34	104–106[c]	BrCl
Cyclohexene	0.56[e]	$CHCl_3$	56	84–94[f]	BrCl
Styrene	1.0	$CHCl_3$	67	26–27	BrCl[g]
trans-Stilbene	0.10	$CHCl_3$	52	220–221	*erythro*-BrCl
			14	193–196	*meso*-di-Cl
cis-Stilbene	0.055	$CHCl_3$	68	99–100	*threo*-BrCl
			5.5	222–223	*erythro*-BrCl
cis-Stilbene[h]	0.11	$CHCl_3$	18	80–81	*threo*-BrCl
			2	222–223	*erythro*-BrCl
			5	121–122	*trans*-Stilbene
Diphenylacetylene	0.11	CH_2Cl_2	20	173–175	*trans*-BrCl
			1	159–160	*tetra*-Cl
Diphenylacetylene	0.11	$CHCl_3$	12	159–160	*tetra*-Cl[i]
trans-Cinnamic acid[j]	1.0	$CHCl_3$	31	187–188	BrCl
trans-Cinnamic acid[k]	0.068	CH_2Cl_2	73	164–167	di-Cl[i]

[a] The identity of products is represented as BrCl for a bromochloride, di-Cl for a dichloride, and tetra-Cl for a tetrachloride. [b] The halogen mixture used consisted of 80 g. (0.50 mol.) of bromine and 35.5 g. (0.50 mol.) of chlorine. [c] This was the boiling point at 745 mm. [d] The mixture of bromine and chlorine was not illuminated in this experiment. [e] An 80% excess of the bromine-chlorine mixture was used. [f] This is the boiling point at 15–17 mm. The distilled product also had the properties: d_4^{20} 1.497, n_D^{27} 1.5240. These properties are consistent with those reported[15] for *trans*-1-bromo-2-chlorocyclohexane, which was synthesized by methods other than the addition of bromine chloride to cyclohexene. The success of this experiment depended on the distillation of the product from anhydrous potassium carbonate. A number of experiments in which this was not done gave little or no bromochloride product. [g] This product had the physical and chemical properties reported[1] for 2-bromo-1-chloro-1-phenylethane as well as the melting point given in the table. [h] Several experiments like this one were carried out with *cis*-stilbene which was contaminated by quinoline and isoquinoline. The *threo*-bromochloride (m.p. 99–101°[1]) could not be isolated in a satisfactory manner from the reaction mixtures in these cases. [i] No reason was apparent for the formation of the chloride rather than the bromochloride as predominant products in this experiment. The experiments were carried out in essentially the same way in all cases. [j] Similar results could be obtained in methylene chloride. [k] Similar results could be obtained in chloroform even with a 13% excess of bromine over chlorine.

and chlorine with cinnamic acid[5] and with phenylpropiolic acid.[3] In the case of propylene with bromine chloride in water both isomeric bromochlorides as well as both bromohydrins were reported[2a] but the results were shown to be consistent with a polar mechanism involving positive bromine and negative chlorine.

No clear-cut case of stereospecific *trans*-addition of bromine chloride from mixtures of bromine and chlorine has been reported previously. In the present investigation such a stereospecific addition was observed. *cis*-Stilbene yielded *threo*-α-bromo-α′-chlorobibenzyl[1] and *trans*-stilbene gave the *erythro* isomer[1] as predominant products as summarized in Table I. Only one product was reported to be obtained from the reaction of maleic anhydride with mixtures of bromine and chlorine, but no comparison was made with additions to fumaric acid or its derivatives.[6] In other cases where two stereoisomers were possible both were reported[3,5a] from additions of bromine chloride.

Bromine chloride, concerning which some controversy has developed in the past as to whether its physical properties could be measured[7] or not,[8] has been shown[9] spectrophotometrically to exist in solution in equilibrium with bromine and chlorine. Its presence is not essential to the explanation of the addition of the elements of bromine chloride in the reaction of olefinic compounds with mixtures of bromine and chlorine, however. Either bromine or bromine chloride could act as a source of positive bromine, and chloride ion (or relatively negative chlorine) could be supplied by either bromine chloride or the bromodichloride ion expected[10] from bromide ion and chlorine.

EXPERIMENTAL

cis-Stilbene. It was observed[11] by means of gas chromatography that samples of *cis*-stilbene prepared[12] by the decarboxylation of α-phenylcinnamic acid often contained significant amounts of quinoline and isoquinoline, which came from the solvent used in the decarboxylation.

(6) P. Walden, *Ber.*, **30**, 2883 (1897).

(7) L. W. Andrews and H. A. Carlton, *J. Am. Chem. Soc.*, **29**, 688 (1907); H. Lux, *Ber.*, **63**, 1156 (1930).

(8) M. Berthelot, *Compt. rend.*, **94**, 1619 (1882); P. Lebeau, *Compt. rend.*, **143**, 589 (1906); B. J. Karsten, *Z. anorg. Chem.*, **53**, 365 (1907).

(9) See A. I. Popov and J. J. Mannion, *J. Am. Chem. Soc.*, **74**, 222 (1952) and the references cited there.

(10) A. I. Popov and R. E. Buckles, *Inorg. Syntheses*, **5**, 167 (1957).

(11) R. E. Buckles and D. F. Knaack, *J. Org. Chem.*, **25**, 20 (1960).

(12) R. E. Buckles and N. G. Wheeler, *Org. Syntheses*, **33**, 88 (1953).

Such impure samples of *cis*-stilbene were dissolved in hexane (20 g. in 200 ml.) and washed with four 50 ml. portions of 10% hydrochloric acid. The solution was then washed with 50 ml. of 10% sodium carbonate, and finally with 50 ml. of water. The resulting solution was dried over anhydrous sodium sulfate, cooled to 0°, and filtered to remove the drying agent and most of the *trans*-stilbene present as a contaminent. Fractional distillation yielded *cis*-stilbene, b.p. 135–136° (10 mm.), which appeared to be relatively pure on the basis of the ultraviolet absorption spectrum[13] and gas chromatography.

A modification of the synthetic procedure[12] for *cis*-stilbene was also carried out. A mixture of 46.0 g. (0.205 mol.) of α-phenylcinnamic acid, 280 ml. of quinoline, and 4 g. of copper chromite was heated at 210–220° for 1.25 hr. The mixture was then filtered and distilled at 10 mm. as quickly as possible. The fraction distilling around 104° was recovered quinoline. The crude product, b.p. 125–140° was dissolved in 200 ml. of hexane and then was washed and purified as described above. A yield of 21 g. (59%) of *cis*-stilbene, b.p. 135–136° (10 mm.), was obtained.

Other materials. The compounds used in the reactions with bromine chloride were either commercially available or were synthesized by methods given in the Organic Syntheses series. Cyclohexene was purified by fractional distillation, b.p. 81.0–81.5° (739 mm.). Chloroform, and methylene chloride were reagent grade. They were used without further purification.

Addition reactions of bromine-chloride. The addition reactions were carried out in a 1 l., three necked flask fitted by means of spherical joints with: (1) a combination dropping funnel, and gas delivery tube extending close to the bottom of the flask, (2) a stirrer, and (3) a cold-finger condenser which was kept filled during the runs with Dry Ice in a mixture of chloroform and carbon tetrachloride. The reaction flask was kept in an ice-water bath. In each run the desired amount of chlorine was liquefied in a trap cooled in a Dry Ice bath and then weighed. The liquid chlorine was then allowed to distill slowly from the trap by way of the delivery tube into the reaction flask containing the solvent (500 ml. per 35.5 g. of chlorine). An amount of liquid bromine equivalent to the amount of chlorine was then added by way of the dropping funnel and washed in with additional solvent. The bromine-chlorine mixture was illuminated with an ultraviolet lamp because the equilibrium between bromine, chlorine, and bromine chloride is set up more rapidly under these conditions.[14] Actually on the basis of the results with ethylene in Table I this illumination may not be strictly necessary. In the dark an equivalent amount of the unsaturated compound was added in solution or as a gas in the case of ethylene. The reaction mixture was allowed to stand in the dark overnight. The solvent was distilled at 30 to 40 mm. pressure. The residue was then crystallized from a suitable solvent or distilled. For most crystallizations ethanol, carbon tetrachloride, or hexane was used. The results of the experiments are summarized in Table I. The identity of most of the bromochlorides was established by comparison with samples obtained in the earlier investigation[1] by the addition of the elements of bromine chloride from *N*-bromoacetamide and hydrochloric acid. The properties of the bromochloride of cyclohexene compared satisfactorily with those reported[15] for *trans*-1-bromo-2-chlorocyclohexane. The bromochloride of diphenylacetylene checked with the α-bromo-α′-chlorostilbene, m.p. 173–174°, reported by Sudborough.[16] The chloride products listed in Table I were identified by comparison with samples obtained in another investigation.[11]

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(13) R. E. Buckles, *J. Am. Chem. Soc.*, **77**, 1040 (1955).

(14) H. G. Vesper and G. K. Rollefson, *J. Am. Chem. Soc.*, **56**, 620 (1934).

(15) M. Mousseron, R. Granger, and J. Valette, *Bull. soc. chim. France*, 244 (1946); M. Mousseron, F. Winternitz, and R. Jacquier, *Bull. soc. chim. France*, 81 (1947).

(16) J. J. Sudborough, *J. Chem. Soc.*, **71**, 218 (1897).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Preparation of Homobenzyl and Homoallyl Alcohols by the Hydroboration Method[1,2]

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H. C. Brown's elegant hydroboration-oxidation method for hydrating olefins provides a convenient route to homoallyl and homobenzyl alcohols. Δ^3-Cyclopentenol may be prepared from cyclopentadiene, while the pure diastereomeric *threo*- and *erythro*-3-*p*-anisyl-2-butanols arise in good yield from the *cis*- and *trans*-2-*p*-anisyl-2-butenes, respectively. The stereochemistry of the overall hydration is clearly *cis*.

The elegant method of H. C. Brown and his coworkers[3,4] for accomplishing the hydration of olefins by successive hydroboration and oxidation appeared to offer a convenient route to certain homobenzyl[5] and homoallyl[6] alcohols of interest in various studies in these laboratories. The alcohols desired were Δ^3-cyclopentenol (II) and the diastereomeric *threo*- and *erythro*-3-*p*-anisyl-2-butanols (XII and XIII). Therefore, hydration by means of hy-

(1) Research supported in part by the National Science Foundation.

(2) This research was supported in part by a grant from The Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

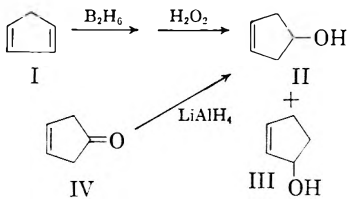
(3) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

(4) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(5) *e.g.*, (a) S. Winstein, M. Brown, K. C. Schreiber, and A. H. Schlesinger, *J. Am. Chem. Soc.*, **74**, 1140 (1952); (b) S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.*, **80**, 169 (1958).

(6) *e.g.*, (a) S. Winstein, H. M. Walborsky, and K. Schreiber, *J. Am. Chem. Soc.*, **72**, 5795 (1950); (b) S. Winstein, M. Shatavsky, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955); (c) S. Winstein and M. Shatavsky, *J. Am. Chem. Soc.*, **78**, 592 (1956).

droboration and subsequent oxidation was studied with cyclopentadiene (I) and the *cis*- and *trans*-2-anisyl-2-butenes (IX and XI). For comparison with the latter, anethole was also investigated. The results are presented in the present manuscript.

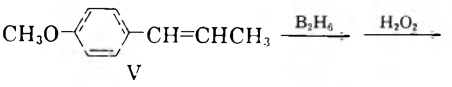


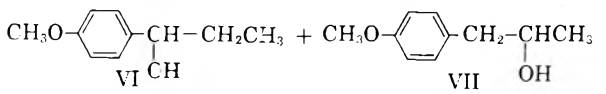
Cyclopentadiene. Hydroboration of cyclopentadiene was carried out by the general method of Brown and Zweifel[3] using a considerable excess of cyclopentadiene in order to minimize glycol formation. Under the conditions employed, the consumption of diborane was incomplete and some dicyclopentadiene was formed from the monomer. A 30% yield of Δ^3-cyclopentenol (II) was obtained, no systematic effort being made to maximize the yield of alcohol. The infrared spectrum of the alcohol product was identical with that of an authentic sample of Δ^3-cyclopentenol (II), and phenylurethane and toluenesulfonate derivatives of the product of hydroboration and oxidation agreed in melting point and mixed melting point with derivatives prepared from authentic alcohol II.

A sample of authentic homoallylic alcohol II was prepared by lithium aluminum hydride reduction of the corresponding ketone IV, which in turn was prepared in poor yield by the method of Alder and Flock[7] from pyrolysis of dicyclopentadienol-3.

The alcohol product from hydroboration of cyclopentadiene proved to be 94% pure by vapor phase chromatographic analysis. While the alcohol contained less than 1% of allylic alcohol III, there was present 3–4% of a material which had the same vapor phase chromatographic behavior as cyclopentanol and which may possibly have arisen from reduction of cyclopentenyl alcohol by diborane. Further, vapor phase chromatographic analysis indicated contamination by 1–2% of an unidentified component. Even on the basis of a 30% yield of 94% pure homoallylic alcohol II, the hydroboration-oxidation method is in our opinion the method of choice for the preparation of a sizable quantity of this homoallylic alcohol.

Anethole. Conversion of anethole (V) to alcohol product by the procedure of Brown and Zweifel[3] gave rise to a 66% yield of alcohol which was separated from unreacted olefin by chromatography. Infrared analysis of the alcohol product indicated it was a mixture of 75% of the benzylic alcohol VI and 25% of the homobenzyl alcohol VII. The low yield of 1-*p*-anisyl-2-propanol(VII) was further substantiated by the low yield (*ca.* 18%) of 1-*p*-anisyl-2-propyl *p*-toluenesulfonate obtained from reaction of the alcohol mixture with *p*-toluenesulfonyl chloride in pyridine under the usual conditions.[5a]





The 2-p-anisylbutenes. A mixture of isomeric 2-*p*-anisylbutenes was produced by the acetic anhydride dehydration of 2-*p*-anisyl-2-butanol (VIII). On the basis of gas phase chromatography, the mixture of olefins contained three components roughly in the ratio 74:14:12. By careful fractionation and refractionation using an efficient fractionating column, it was possible to obtain pure samples of the low and high boiling components and an essentially pure sample of a product with an intermediate boiling point (Table I). With a trace of *p*-toluenesulfonic acid added to the olefin mixture, only the pure low boiling olefin is obtained from slow distillation of the continually equilibrating mixture.

As indicated in Table I, the *trans*-2-anisyl-2-butene designation XI is assigned to the lowest boiling isomer and the *cis*-2-anisyl-2-butene designation IX to the highest boiling isomer. These assignments may be made on the basis of the physical properties of the isomers, especially the ultraviolet absorption spectra, the situation here being completely analogous with that in the case of the isomeric 2-phenyl-2-butenes.[8] The gross structure of the olefins is confirmed by the hydroboration to 3-anisyl-2-butanols described below. Although the structure of the intermediate boiling isomer (Table I) was not proved as definitely as that of the other two, it is almost certainly 2-*p*-anisyl-1-butene (X) on the basis of its ultraviolet absorption spectrum, refractive index and boiling point, and analogy with the isomeric 2-phenylbutenes.[8]

TABLE I

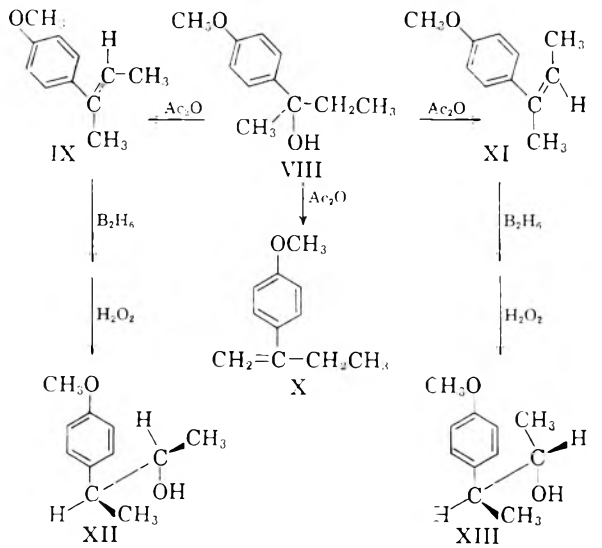
SUMMARY OF THE PROPERTIES OF THE 2-*p*-ANISYLBUTENES

Olefin	B.P., °C. (10 mm.)	n_D^{25}	λ_{max} mμ	ε	Configuration of Derived Alcohol
cis-2-*p*-anisyl-2-butene (IX)	117.5	1.5495	252	14,540	*threo*
2-*p*-anisyl-1-butene (X)	107	1.5400	252	13,780	
trans-2-*p*-anisyl-2-butene (XI)	103	1.5316	243	10,890	*erythro*

(7) K. Alder and F. H. Flock, *Ber.*, **89**, 1732 (1956).

(8) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949); **74**, 2137 (1952).

Hydration of the *trans*-olefin XI by the hydroboration method of Brown and Zweifel[3] and chromatographic separation of the alcohol products from residual olefin gave a 72% yield of solid alcohol. After one recrystallization this was pure *erythro*-3-*p*-anisyl-2-butanol (XIII). A similar stereospecific result was obtained from the *cis*-olefin IX. Reaction of the crude alcohol product with phthalic anhydride in pyridine resulted in a 77% yield of crude acid phthalate. One recrystallization of the latter gave rise to pure *threo*-3-*p*-anisyl-2-butyl acid phthalate. A comparison of the infrared spectra of the crude alcohol products from the *cis*- and *trans*-2-*p*-anisyl-2-butenes (IX and XI) with the spectrum of authentic 2-*p*-anisyl-2-butanol (VIII) indicated that the formation of the latter is essentially negligible for both olefins.



The present method is certainly convenient for preparation of the pure diastereomeric 3-*p*-anisyl-2-butanols (XII and XIII), especially for the *threo*-isomer XII. This is a distinct improvement over the conventional method formerly employed.[5b]

Stereochemistry and orientation. As regards the stereochemistry of the over-all hydration of the double bond by hydroboration-oxidation, the present results with the *cis*- and *trans*-2-anisyl-2-butenes (IX and XI) illustrate further the stereospecific *cis*-addition already demonstrated with 1-methylcyclohexene, 1-methylcyclopentene, 1,2-dimethylcyclohexene, and 1,2-dimethylcyclopentene,[3] as well as cholesterol.[9]

As regards orientation in the over-all hydration of the double bond, that observed in the case of cyclopentadiene with very predominant formation of the homoallylic alcohol II is what we anticipated on the basis of the reported results with unsymmetrical olefins[3] and styrene.[4] This orientation makes the hydroboration-oxidation method applied to conjugated dienes a promising one for preparation of homoallylic alcohols.[10] The orientation observed in the over-all hydration of the *cis*- and *trans*-2-*p*-anisyl-2-butenes (IX and XI) was also the one anticipated on the basis of the results reported with unsymmetrical olefin[3]. How important the 1-methyl group is in promoting this orientation for the 2-*p*-anisyl-2-butenes (IX and XI) is obvious from the contrasting results obtained with anethole.[5] In this case, the benzylic alcohol VI predominates over the homobenzyl alcohol VII by a factor of *ca.* 3. More extended discussion of this point is probably best deferred until information is available on the orientation of the over-all hydration in more cases.

(9) W. J. Wechter, *Chem. & Ind.* (*London*), 294 (1959).

EXPERIMENTAL

Δ^3-*Cyclopentenol.* The 0.067 mol. of diborane from 3.8 g. (0.1 mol) of sodium borohydride in 100 ml. of diglyme (diethyleneglycol dimethyl ether) and 21 g. (0.15 mol.) of boron trifluoride etherate in 35 ml. diglyme was passed into 45 g. (0.68 mol.) of freshly distilled cyclopentadiene in 150 ml. of anhydrous ether at 0° over a period of 30 min., while a slow stream of nitrogen was maintained. A precipitate frequently formed which clogged the fritted glass bubbler and made the complete addition of diborane impossible. Similar results were obtained in tetrahydrofuran.

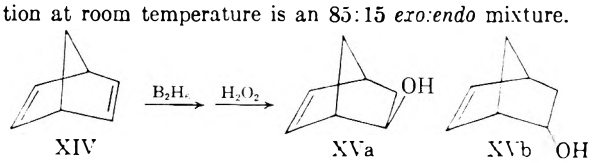
After the reaction mixture stood at room temperature for 30 min., the excess cyclopentadiene and solvent were removed under vacuum, a viscous oil remaining (65% calculated as tri-Δ^3-cyclopentenyl boron). The oil was hydrolyzed in ether with 3*M* sodium hydroxide, followed by the slow addition of 30% hydrogen peroxide (exothermic reaction). Similar results were obtained by adding small pieces of ice to the original reaction mixture and then hydrolyzing as above.

The organic layer was separated and the aqueous solution continuously extracted with ether. After the ether extract was dried over magnesium sulfate, the ether was removed, and an alcohol fraction boiling in the range 60–70° (36 mm.) was collected. A higher boiling residue remained. The cyclopentenol fraction was freed from dicyclopentadiene, the major impurity, by chromatography on alumina. Distillation through a Podbielniak column gave rise to material, b.p. 67–68° (36 mm.), n_D^{25} 1.4673, in 30% yield. The infrared spectrum of this material was identical with that of an authentic specimen of Δ^3-cyclopentenol described below. The alcohol product also gave a phenylurethan, m.p. 140.4–140.8°, mixed m.p. with authentic material 140.4–141.0°, and a toluenesulfonate (80% yield), m.p. 53.4–54.2°, mixed m.p. with authentic material 53.2–54.2°.

Vapor phase chromatography on carbowax indicated 94% purity of the Δ^3-cyclopentenol, with 3–4% of cyclopentanol and 1–2% of an unidentified component. Vapor phase chromatography on didecyl phthalate indicated a maximum of 1% Δ^2-cyclopentenol and no trace of bis-Δ^2-cyclopentenyl ether.

Authentic Δ^3-cyclopentenol was prepared in 84% yield

(10) The homoallylic alcohol XV from the unconjugated diene, bicycloheptadiene (XIV), may be prepared by the hydroboration-oxidation method (E. Vogelfanger, unpublished work). The 5-norbornenol XV obtained from the reaction at room temperature is an 85:15 *exo*:*endo* mixture.



by lithium aluminum hydride reduction of Δ^3-cyclopentenone, the latter ketone being obtained in poor yield by pyrolysis of dicyclopentadienol-3 according to the method of Alder and Flock.[7] The Δ^3-cyclopentenol product displayed b.p. 69–70° (40 mm.) and n_D^{25} 1.4688.

Anal. Calcd. for C_5H_8O: C, 71.39; H, 9.57. Found: C, 71.18; H, 9.58.

The Δ^3-cyclopentenol gave rise to a phenylurethan, m.p. 141.6–142.1°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.81; H, 6.41; N, 6.71.

Hydrogenation of the alcohol over platinum oxide in ethanol gave rise to cyclopentanol, whose *N*-phenylcarbamate, m.p. 135.5–136.0°, showed no melting point depression on admixture with authentic material, m.p. 136.4–136.5°.

The Δ^3-cyclopentenol gave rise to a *p*-toluenesulfonate, m.p. 53.4–54.6°, in 90% yield by the usual preparative method from alcohol and toluenesulfonyl chloride in pyridine.

Anal. Calcd. for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.14. Found: C, 60.63; H, 5.79; S, 12.86.

Δ^2-Cyclopentenol. This material was prepared by addition of hydrogen chloride to cyclopentadiene and hydrolysis of the 1-chloro-2-cyclopentene with aqueous sodium bicarbonate.[7] The alcohol yielded a phenylurethan, m.p. 128.5–129.5°, m.p. depressed by addition of the phenylurethan of Δ^3-cyclopentenol.

1-p-Anisyl-2-propanol. This material was prepared as described previously[5a]; b.p. 119.5° (4 mm.), n_D^{25} 1.5262.

1-p-Anisyl-1-propanol. To the Grignard reagent prepared from 75 g. (0.4 mol.) of *p*-bromoanisole and 9.6 g. (0.4 gram atom) of magnesium in 250 ml. of ether was added, as rapidly as possible, 23.3 g. (0.4 mol.) of freshly distilled propanal in 200 ml. of ether. After an additional stirring time of 30 min., the reaction mixture was decomposed with a saturated ammonium chloride solution. Fractionation of the crude product yielded 52 g. (78%) of 1-*p*-anisyl-1-propanol, b.p. 120.5–121° (4 mm.), n_D^{25} 1.5257.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.50. Found: C, 72.03; H, 8.44.

Hydroboration of anethole. A 14.8 g. (0.1 mol.) sample of freshly distilled anethole was reacted with diborane and the organoborane converted to alcohol according to the procedure of Brown and Zweifel.[3,11] From this reaction was recovered 16 g. of an alcohol-olefin mixture which on chromatographic separation (alumina) yielded 11.0 g. (66%) of alcohol and 3.4 g. of anethole. The alcohol fraction was distilled; b.p. 119.5–121° (4 mm.), n_D^{25} 1.5262.

Infrared analysis[12] of the alcohol product, using characteristic bands at 900 and 752 cm.$^{-1}$, showed a mixture of 75 ± 2% 1-*p*-anisyl-1-propanol and 25 ± 2% 1-*p*-anisyl-2-propanol, the figures being average values from two separate hydroboration reactions. A known mixture of 78.8% 1-*p*-anisyl-1-propanol and 21.2% 1-*p*-anisyl-2-propanol analyzed 78% and 22%, respectively. This latter spectrum was essentially superimposable with the spectrum of the alcohol product from the above described hydroboration.

A 5.0-g. sample of the hydroboration alcohol product in 10 ml. of pyridine was allowed to react with 5.8 g. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine allowing the reaction mixture to stand overnight at 0°. From this reaction was obtained 1.8 g. (18%) of 1-*p*-anisyl-2-propyl-*p*-toluenesulfonate, m.p. 79–80° after one recrystallization from ether and pentane, mixed m.p. 79–80° with an authentic sample (m.p. 80°). An 80% yield from pure 1-*p*-anisyl-2-propanol has been reported.[5a]

2-p-Anisyl-2-butanol. The Grignard reagent from 364.1 g. (2 mol.) of *p*-bromoanisole and 48.6 g. (2 gram atoms) of magnesium, prepared in *ca.* 800 ml. of ether, was reacted in the usual manner with 144.2 g. (2 mol.) of 2-butanone dissolved in 400 ml. of ether. The reaction complex was decomposed with saturated ammonium chloride solution. On distillation, the crude product yielded 250 g. (70%) of 2-*p*-anisyl-2-butanol, b.p. 98.5–99° (0.5 mm.), n_D^{25} 1.5260.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 9.07.

Cis and trans-2-p-anisyl-2-butenes. A solution of 187 g. (1.04 mol.) of 2-*p*-anisyl-2-butanol in 450 ml. of freshly distilled acetic anhydride was heated under reflux (b.p. 136–124°) for a period of 4 hr. Following this, the acetic acid and acetic anhydride were removed by distillation and the concentrate distilled through a Vigreux column; weight 150 g. (88%), b.p. 105–118° (10 mm.). Analysis of this material by vapor phase chromatography (Perkin-Elmer Corp. Vapor Fractometer, Model 154-B, fitted with a 2-m. Perkin-Elmer Column C) indicated the presence of three components in the ratio 74:14:12. This material was submitted to fractionation on a center rod column (75 theoretical plates at the highest operating efficiency) at 10 mm. of pressure. Two large fractions were collected: (1) 36.6 g., b.p. 109–116°; (2) 112.3 g., b.p. 116–117.5°. Fraction (2) was refractionated to give 16.9 g. of material, b.p. 108–115° (10 mm.); 23.3 g. of material, b.p. 115–117.5° (10 mm.); and 71.0 g. of pure *cis*-isomer, b.p. 117.5° (10 mm.) (Table I).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found for the *cis*-olefin: C, 81.24; H, 8.81.

All of the fractions boiling below 116° were again refractionated to give 6.1 g. of pure *trans*-isomer, b.p. 103° (10 mm.) (Table I), and 8.5 g. of another olefin, b.p. 107° (10 mm.) (Table I), presumably 2-*p*-anisyl-1-butene.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found for the *trans*-olefin: C, 81.26; H, 8.62.

A combined fraction (32 g.) with b.p. 116.5–117.5° (10 mm.) was mixed with 0.10 g. of *p*-toluenesulfonic acid and the mixture submitted to slow fractionation at 10 mm. to produce 26.4 g. of pure *trans*-isomer, b.p. 103° (10 mm.), n_D^{25} 1.5325.

Hydroboration of trans-2-p-anisyl-2-butene. A 16.2 g. (0.1 mol.) sample of pure *trans*-2-*p*-anisyl-2-butene was hydroborated and converted to alcohol exactly as described for anethole. From this reaction was recovered 17.5 g. of an alcohol-olefin mixture which on chromatographic separation (alumina) gave 13.0 g. (72%) of a solid alcohol fraction and 4.2 g. of *trans*-olefin (unchanged from starting material according to the infrared spectrum). One recrystallization from pentane gave 10.6 g. of pure *erythro*-3-*p*-anisyl-2-butanol, m.p. 58.5–59.5°, mixed m.p. 59.5–60° with an authentic sample (m.p. 60°).[5b]

A comparison of the infrared spectrum of the crude alcohol product (after chromatography) with the spectrum of pure 2-*p*-anisyl-2-butanol indicated that no more than a very small amount of the latter could have been formed.

Hydroboration of cis-2-p-anisyl-2-butene. A pure sample of *cis*-2-*p*-anisyl-2-butene (28.0 g., 0.17 mol.) was reacted with diborane and converted to the alcohol as described for anethole. A 29.0-g. sample of alcohol (with very little olefin according to the infrared spectrum) was recovered and reacted with 26.2 g. of phthalic anhydride in 85 ml. of dry pyridine for 2 hr. at 75° to yield 40.3 g. (77%) of crude acid phthalate, m.p. 113.5–121.5°. One recrystallization from benzene gave 34.3 g. of pure *threo*-3-*p*-anisyl-2-butyl acid phthalate, m.p. 122–123.5°, mixed m.p. 123–124° with an authentic sample (m.p. 123–124°).[5b] Recrystallization of the residue from the first crystallization gave an additional 5.3 g. of acid phthalate, m.p. 121.5–123.5°.

The infrared spectrum of the crude alcohol product was essentially identical with the spectrum of pure *threo*-alcohol[5b] and showed no detectable amount of 2-*p*-anisyl-2-butanol.

LOS ANGELES 24, CALIF.

(11) Considerably higher yields were obtained by adding the diborane to the olefin at room temperature and then allowing the reaction mixture to stand several hours before oxidation.

(12) A Perkin-Elmer Model 21 Infrared Spectrophotometer with sodium chloride optics was used for analysis.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY OF THE ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY]

Labeled Substrates. I. The Synthesis of DL-2-Deuteriolactic Acid[1]

HENRY D. HOBERMAN AND AMEDEO F. D'ADAMO, JR.

Received June 8, 1959

DL-2-Deuteriolactic acid has been prepared with incorporation of deuterium in approximately 75 atom per cent excess by concurrent hydrolysis and decarboxylation of bromomethylmalonic acid in refluxing deuterium oxide or by prior decarboxylation of the deuterium exchanged solid bromo di-acid to 2-deuterio-2-bromopropionic acid followed by hydrolysis with zinc carbonate.

In studies on the coupling of the oxidation of substrates to reductive biosynthesis, DL-2-deuteriolactic acid was utilized to give deuterium labeled phospho-pyridine nucleotides in the intact rat, and the utilization of the labeled nucleotides in glycogen and lipid synthesis has been reported.[2a,b] The present report describes the synthesis of DL-2-deuteriolactic acid.

Deuterated lactic acid has been prepared from optically active lactic acid by exchange with deuterium oxide in the presence of a platinum catalyst at 120–130° for 45 hr.[3] Incorporation occurs to the extent of 6% in both the α and β positions and the optical data show that the exchange proceeds with inversion of configuration.

For purposes of investigating reductive biosynthesis, since one would expect that any isotope in the methyl group would be incorporated into glycogen and lipids by the normal glycolytic reactions of lactic acid, it is necessary that the isotope be preponderantly in the 2-position. This has been accomplished by the preparation of DL-2-deuteriolactic acid with incorporation of deuterium up to 75 atom per cent by concurrent hydrolysis and decarboxylation of bromomethylmalonic acid in boiling deuterium oxide. The deuteriolactic acid was isolated as the zinc salt, with the labile deuterium removed by successive treatments with water and concentration to dryness.

An alternative procedure employed was the replacement of the acidic hydrogens of the bromomethylmalonic acid with deuterium by several exchanges with deuterium oxide, reisolation of the solid bromo di-acid and decarboxylation by heating to 2-deuterio-2-bromopropionic acid. Reaction of the bromopropionic acid, which contained over 70 atom per cent of deuterium, with zinc carbonate served to give the lactic acid as the zinc salt without loss of deuterium.

In these transformations, impure samples of bromomethylmalonic acid were used since it was not found possible to isolate the pure bromo di-acid even after repeated recrystallizations from various solvents. Analysis of the zinc salt for lactic acid by the method of Barker and Sommerson[4] indicated that the synthetic preparations had a lactic acid content of 50% or less than the expected value. That these low results are due to an isotope effect in the analytical method was shown by running two concurrent reactions with bromomethylmalonic acid: one in deuterium oxide and the other in water. The synthetic, unlabeled zinc lactate prepared in this fashion gave lactic acid values of 105% of the standard. The analytical method is based on color formation between *p*-hydroxydiphenyl and acetaldehyde, formed by reaction of concentrated sulfuric acid and lactic acid in a given time interval. If the formation of acetaldehyde occurs by removal of the α-hydrogen from lactic acid followed by decarboxylation and this hydrogen abstraction is the rate-determining step, then the observed isotope effect is easily understood.

The purity of the lactic acid was verified by analysis for zinc and water of hydration of the zinc hydrate and by the titration of the effluent on passing an aqueous solution of the zinc salt through an ion exchange resin. In all cases values near theoretical were obtained. Further proof of the identity of the deuterated compound was obtained from qualitative paper chromatography on filter paper. In the system, phenol, water, and formic acid, the lactic acid standard had an R_f of 88.4 and the synthetic deuterated lactic acid had an R_f of 88.2.

The position of the isotope was established both enzymatically[5] and chemically. At least 90% of the deuterium in the labeled lactic acid is present in the 2-position. This was shown by observing

(1) This investigation was supported in part by research funds from the U. S. Public Health Service and the Sugar Research Foundation.

(2) (a) H. D. Hoberman, *J. Biol. Chem.*, **232**, 9 (1958). (b) H. D. Hoberman, *J. Biol. Chem.*, **233**, 1045 (1958).

(3) J. Bell, T. Hill, K. A. MacDonald, R. I. Reed, and A. MacDonald, *J. Chem. Soc.*, 3454 (1953).

(4) S. B. Barker and W. H. Sommerson, *J. Biol. Chem.*, **138**, 535 (1941).

(5) Unpublished observations carried out in collaboration with Dr. Harold Strecker. The value of 90% of the theoretical amount of deuterium is probably the limit of accuracy of the experiment. It involves the colorimetric determination of glutamic acid, dilution with carrier glutamic acid, and two deuterium analyses. Furthermore, since the determination involves two enzymatic equilibria, any difference in the isotope effect of the enzymes involved would be reflected in the deuterium content of the glutamic acid.

that oxidation of the deuteriolactate by crystalline lactic dehydrogenase in the presence of α-ketoglutaric acid, ammonia, diphospho-pyridine nucleotide and highly purified glutamic dehydrogenase yields glutamic acid containing deuterium in a concentration equivalent to 90% of the calculated value.

The amount of deuterium in the methyl group was determined by oxidation of lithium lactate with a sulfuric acid–sodium dichromate mixture and isolation of the resulting acetic acid as the benzyl isothiuronium salt. Correction for washout of the isotope during the reaction by oxidation of unlabelled lithium lactate in a deuterated sulfuric acid–sodium dichromate mixture shows that the β- position contains less than 0.5% of the total isotope in the molecule.

EXPERIMENTAL[6]

Bromomethylmalonic acid[7] was obtained by reaction of methylmalonic acid in ether with bromine until no further uptake of the halogen was observed. In the several preparations made, less than the expected equimolar quantity of bromine was absorbed. The crystalline solid obtained in each case represented less than 50% of the theoretical amount. In each preparation the solid obtained sublimed at about 135°; however the m.p. (actually a decomposition point with carbon dioxide evolution) varied from preparation to preparation. The various m.p. obtained are: 176–190°, 176–184°, 185–195°, 163–172°, and 142–145°. Repeated recrystallization from various organic solvents did not effect much change in the melting points so the impure solid was used in the subsequent reactions.

Lactic acid from bromomethylmalonic acid. A. *DL-2-deuteriolactic acid.* Bromomethylmalonic acid (4.5 g.) was dissolved in 5 ml. of deuterium oxide by heating to 50°. The solvent was removed *in vacuo* and the semicrystalline solid obtained refluxed in 5 ml. of deuterium oxide for 30 hr. At the end of this time 50 ml. of water and excess zinc carbonate were added to the reaction mixture and refluxing continued for 6 hr. The solution was filtered hot to remove the unreacted zinc carbonate, and the filtrate concentrated to dryness. The solid obtained was redissolved in water and concentrated to dryness several times to remove labile deuterium. To remove zinc bromide, it was then extracted with hot absolute ethanol until the extract gave a negative halide test. The residue was dissolved in the minimum amount of hot water and the zinc DL-2-deuteriolactate trihydrate precipitated by addition of absolute ethanol. Filtration, washing successively with ethanol, then with ether, and air drying overnight gave 2.45 g. of the zinc salt. Analysis of the zinc hydrate for lactic acid gave values of 30–50% of the standard.

B. *Unlabelled lactic acid* was obtained as the zinc hydrate by following the above procedure exactly with the substitution of hydrogen oxide for deuterium oxide. The solid obtained weighed 2.70 g. Analysis of the zinc hydrate for lactic acid gave values of 105% of the standard.

Analysis of zinc-DL-2-deuteriolactate trihydrate. 298.3 mg. were eluted through Amberlite IR-120H until eluate was no longer acidic. Calcd. meq. of base: 2.00 meq.; found: 1.96 meq. 297 mg. were dried to constant weight. Calcd. H_2O: 18.1; found: 17.5. Zinc analysis: Calcd.: 22.0; found: 22.6.

Paper strip chromatography performed with the system described by Stark *et al.*[8] using Whatman Filter paper #40 and developing with bromcresol green gave an R_f of 88.4 for standard lactic acid and an R_f of 88.2 for the synthetic DL-2-deuteriolactic acid.

The anhydrous zinc salt contained 44.2 atom per cent excess of deuterium.

2-Deuterio-2-bromopropionic acid. Bromomethylmalonic acid (72.1 g., 0.37 mol.) was treated with deuterium oxide (20 ml., 1.0 mol.) and the mixture warmed on a steam bath. The solvent was then removed in vacuo at 40–50°. After the process was repeated two more times, the sludge obtained was dried over phosphorus pentoxide for several days. The light brown, crystalline solid obtained was heated in an oil bath at 170°, at which temperature decarboxylation proceeded rapidly. After heating for 7 hr. the evolution of carbon dioxide virtually ceased. The liquid obtained was distilled *in vacuo* and a fraction boiling between 70–80° at 15 mm. of Hg was collected. This was carefully refractionated and a fraction boiling at 101–103° at 20 mm. of Hg was collected. It weighed 26.8 g., representing a yield of 45.2%. Mass spectrographic analysis showed that the compound had 70.8 atom per cent excess of deuterium.

DL-2-deuteriolactic acid from 2-deuterio-2-bromopropionic acid. To 25.8 g. (0.167 mol.) of DL-2-deuterio-2-bromopropionic acid in 150 ml. of water was added excess zinc carbonate and the mixture refluxed for 6 hr. The mixture was filtered to remove the unreacted zinc carbonate and the filtrate concentrated to dryness *in vacuo*. Extraction of the solid with absolute ethanol until the extract gave a negative halide test removed the zinc bromide. The residue was dissolved in water and concentrated to a small volume; crystallization was effected by the addition of ethanol. The crystals were filtered off, washed first with ethanol, then with ether, and air-dried overnight. A yield of 20.8 g. (87.5%) of the zinc hydrate containing 71.1 atom per cent excess of deuterium was obtained.

Degradation of DL-2-deuteriolactic acid. A. *Chemical oxidation.* To 500 mg. of labelled lithium lactate (containing 77.0 atom per cent D) was added 1.5 ml. of conc. sulphuric acid in 3.75 ml. of water and 1.78 g. of $Na_2Cr_2O_7$ in 3 ml. of water and the solution heated for 19 hr. on a steam bath. At the end of this time 200 ml. of water were added and the solution distilled until 125 ml. of distillate were collected. This was neutralized with standard sodium hydroxide. Reaction with *S*-benzylisothiuronium chloride gave the desired derivative, m.p. 144°. Admixture with authentic *S*-benzylisothiuronium acetate gave no depression of the melting point. Deuterium analysis gave 0.046 atom per cent excess for the salt or 0.21 atom per cent excess in the methyl group.

Acknowledgment. The authors are indebted to Mr. B. Lopez for his technical assistance.

BRONX 61, N. Y.

(6) Deuterium analyses were performed by a modification of the method of J. Graff and D. Rittenberg, *Anal. Chem.*, 24, 878 (1952). The mass spectrometer used for these analyses (Consolidated Electrodynamics Inc., model 21-401) was purchased with funds made available by a grant from the National Heart Institute (No. AH-950), National Institutes of Health, Public Health Service.

(7) The literature values for this compound vary from 118–119° reported by H. Byk, *J. prakt. chem.*, (2) 1, 19 (1870) to 165–170° by R. Meyer and P. Bock, *Ann.*, 347, 105 (1906).

(8) S. B. Stark, A. E. Goodban, and H. S. Owens, *Anal. Chem.*, 23, 413 (1951).

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

Preparation and Reactions of Some 2-Acylhalo-1,8-naphthalic Anhydrides

DOROTHY V. NIGHTINGALE AND WILLIAM S. WAGNER[1]

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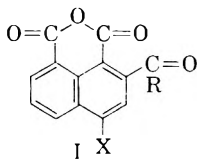
The oxidation of a series of acylhaloacenaphthenes with sodium dichromate in glacial acetic acid gave the corresponding acylhalo-1,8-naphthalic anhydrides in nearly quantitative yields.

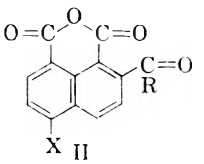
4-Bromo-1,8-naphthalic anhydride and 2-ethyl-4-bromo-1,8-naphthalic anhydride each reacted with phenylmagnesium bromide to form a mixture of isomeric keto acids.

In connection with our study of the reactions of some polynuclear aroyl acid chlorides and anhydrides with organometallic compounds,[2] we have prepared a series of acylhalo-1,8-naphthalic anhydrides of types I and II. In view of the recent publication in this area by Richter and Stocker,[3] it seems advisable to record at this time our data relative to these anhydrides.



I

Ia. R = C_6H_5; X = Br
Ib. R = C_6H_5; X = Cl
Ic. R = CH_3; X = Br
Id. R = CH_3; X = Cl



II

IIa. R = C_6H_5; X = Br
IIb. R = C_6H_5; X = Cl

The acylhalonaphthalic anhydrides in Series I and the anhydrides IIa and IIb were readily obtained in nearly quantitative yields by the oxidation of the corresponding acylhaloacenaphthenes with sodium dichromate in glacial acetic acid. No isolatable product was obtained from the oxidation of 3-acetyl-6-chloro- and 3-acetyl-6-bromoacenaphthene.

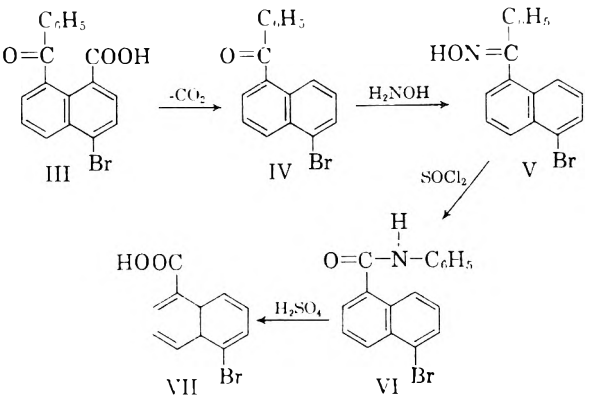
There were noticeable differences in the ease with which the anhydrides were formed. 3-Acetyl-5-bromo- and 3-acetyl-5-chloroacenaphthene were the most readily oxidized and formed the corresponding anhydrides in theoretical yields, even when the reaction time was only ten minutes. The oxidation of the four benzoylhaloacenaphthenes required a reaction time of forty-five minutes to obtain a theoretical yield of anhydride, while 3-ethyl-5-chloro- and 3-ethyl-5-bromoacenaphthene required one hour.

For comparison, 5-bromoacenaphthene and acenaphthene were oxidized under the same conditions. The former required a reaction time of one hour to obtain 4-bromo-1,8-naphthalic anhydride in 93% yield while the latter gave only a 63% yield of 1,8-naphthalic anhydride after a reaction time of an hour and a half and the yield was not increased by longer heating.

The 2-ethyl-4-haloacenaphthenes were prepared by the Clemmensen reduction of the corresponding ketones. The Wolff-Kishner reduction of the ketones gave a tar from which no product was isolated.

As might be expected, the reaction of phenylmagnesium bromide with 4-bromo-1,8-naphthalic anhydride gave a mixture of isomeric keto acids in 93% yield. One isomer, 8-benzoyl-4-bromo-1-naphthoic acid III was isolated in 25% yield by crystallization of the mixture from toluene.

Compound III was not described in the literature and its structure was determined by the reactions illustrated.



When III was decarboxylated, the product IV was found to melt at 95–96°. This value is close to the reported values of 98° and 100.5° for the 1-benzoylbromonaphthalene which Elbs and Steinike[4] and Rospendowski[5] obtained from the bromination of 1-benzoylnaphthalene. The procedure of Rospendowski[5] for this bromination was repeated and the product was shown by a mixed melting point to be identical with IV.

When the oxime V was treated with thionyl chloride, a rearrangement product VI was obtained which melted at 218–218.5°. This value agreed closely with the value 216–217° reported by Ruggli and Preuss[6] for the anilide of authentic

(1) Abstract of a portion of the Ph.D. dissertation of William S. Wagner, 1952.

(2) D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Am. Chem. Soc.*, **75**, 4701 (1953).

(3) H. J. Richter and F. B. Stocker, *J. Org. Chem.*, **24**, 214 (1959).

(4) K. Elbs and G. Steinike, *Ber.*, **19**, 1965 (1886).

(5) M. Rospendowski, *Compt. rend.*, **102**, 872 (1886).

(6) P. Ruggli and R. Preuss, *Helv. Chim. Acta*, **24**, 1345 (1941).

TABLE I

SUBSTITUTED 1,8-NAPHTHALIC ANHYDRIDES

1,8-Naphthalic Anhydrides	M.P., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H
2-Acetyl-4-chloro	283.5–284	$C_{14}H_7ClO_4$	61.22	2.57	61.44	2.69
2-Acetyl-4-bromo	275–275.5	$C_{14}H_7BrO_4$	52.69	2.21	52.50	2.47
2-Benzoyl-4-chloro	257.5–258.5	$C_{19}H_9ClO_4$	67.78	2.69	67.99	2.99
2-Benzoyl-5-chloro	215–216	$C_{19}H_9ClO_4$	67.78	2.69	67.40	2.96
2-Benzoyl-4-bromo[a]	250–251	$C_{19}H_9BrO_4$	59.86	2.38	59.65	2.62
2-Benzoyl-5-bromo[a]	250–251	$C_{19}H_9BrO_4$	59.86	2.38	59.62	2.68
2-Ethyl-4-chloro	209–210	$C_{14}H_9ClO_3$	64.48	3.48	64.25	3.52
2-Ethyl-4-bromo	212–213	$C_{14}H_9BrO_3$	55.10	2.97	55.10	3.17

[a] A mixture of these two anhydrides melted at 232°.

5-bromo-1-naphthoic acid. Hydrolysis of VI gave 5-bromo-1-naphthoic acid, m.p. 245–247°. Ekstrand[7] reported a melting point of 246° for this acid. This further established the structure of IV and III.

The reaction of phenylmagnesium bromide with 2-ethyl-4-bromo-1,8-naphthalic anhydride gave a mixture of keto acids from which one isomer was isolated in 21% yield.

EXPERIMENTAL[8]

2-Acetyl-4-chloro-1,8-naphthalic anhydride. The preparation of this anhydride is typical of the preparation of the substituted naphthalic anhydrides and is described in detail. It is essentially the method of Graebe and Hass.[9] The acylhaloacenaphthenes were prepared by the procedure of Nightingale and Brooker.[10]

3-Acetyl-5-chloroacenaphthene (10 g., 0.048 mol.) was dissolved in 120 ml. of glacial acetic acid and to this solution was added 50 g. (0.19 mol.) of sodium dichromate. After the spontaneous reaction had subsided, the solution was refluxed for 10 min. and then poured into 400 ml. of hot water. The precipitated anhydride was separated by filtration and washed with water. The yield of anhydride was practically quantitative. After recrystallization from benzene or ethyl acetate, the compound melted at 283.5–284° with decomposition and sublimation.

The melting points and analyses of the anhydrides are summarized in Table I.

Reaction of phenylmagnesium bromide with 4-bromo-1,8-naphthalic anhydride. The Grignard reagent prepared in the usual manner from 30 g. (0.19 mol.) of bromobenzene in 100 ml. of ether was added rapidly to a well stirred suspension of 48 g. (0.17 mol.) of 4-bromonaphthalic anhydride in 525 ml. of dry toluene. The solution was refluxed for 30 min., then the ether was removed by distillation and the complex was hydrolyzed by the addition of 75 ml. of concd. hydrochloric acid. The solution was filtered to remove a small amount of unchanged anhydride and the acid layer separated and discarded. When the toluene solution was cooled in an ice bath, 16 g. (26%) of crude 8-benzoyl-4-bromo-1-naphthoic acid III, m.p. 184–187°, separated. After recrystallization from toluene, the melting point was 194.5–195.5°.

Anal. Calcd. for $C_{18}H_{11}BrO_3$: C, 60.87; H, 3.12; neut. equiv., 355.2. Found: C, 60.92; H, 3.19; neut. equiv., 353.4.

The toluene filtrate was extracted with sodium carbonate solution. When the aqueous extract was acidified, a total of 41 g. (67%) of crude keto acid m.p. 140–146°, was obtained. After recrystallization from toluene, the melting point of this material was 140–141°, and the neutral equivalent was 352.4. A series of mixture melting points of this product with pure 8-benzoyl-4-bromo-1-naphthoic acid indicated that it may be a eutectic mixture of the two isomeric acids possible from this reaction.

Decarboxylation of III. A mixture of 4 g. of III and 4 g. of copper oxide was heated in a distilling flask at 200–250° until gas was no longer evolved. Distillation of the reaction mixture yielded 1 g. of ketone IV, m.p. 95–96°.

Authentic IV was synthesized by the bromination of 1-naphthyl phenyl ketone by the procedure of Rospendowski.[5] It melted at 95–96°, the recorded value, and did not depress the melting point of ketone IV obtained from the decarboxylation of III.

Preparation and rearrangement of the oxime (V) *of* IV. The ketone (6.5 g., 0.021 mol.) was dissolved in 125 ml. of ethanol with 8 g. (0.12 mol.) of hydroxylamine by heating on a steam bath. To the refluxing solution was added 10 g. (0.25 mol.) of sodium acetate at such a rate that the reaction did not become violent. The solution was refluxed an additional 1.5 hr. and poured into water. The oxime separated as a pasty solid which could not be recrystallized from ethanol. The solvent-free product was rearranged to the acylated amine without further purification.

The procedure was an adaptation of the method of Huntress and Walter[11] for the rearrangement of phenyl 2-pyridyl ketoxime with thionyl chloride.

To a solution of crude V from 6.5 g. of IV in 50 ml. of chloroform was added slowly 3.3 g. (0.028 mol.) of thionyl chloride. The chloroform was removed by distillation on a steam bath and the residue recrystallized from ethanol. The white crystals of 1-benzoylamino-5-bromonaphthalene VI melted at 218–218.5°, the literature value.[6] This sample of VI did not depress the melting of authentic VI. A mixture melting point of VI with an authentic sample of the isomeric 1-benzoylamino-4-bromonaphthalene (m.p. 237.5–238°) was 180–210°.

Authentic 1-benzoylamino-4-bromonaphthalene (m.p. 237.5–238°) was prepared by benzoylation of 4-bromo-1-naphthylamine.[12]

Anal. Calcd. for $C_{17}H_{12}BrNO$: C, 62.60; H, 3.71. Found: C, 62.51; H, 3.96.

Hydrolysis of VI by means of 60% sulfuric acid yielded 5-bromo-1-naphthoic acid, m.p. 245–247°, literature value[7] 246°.

(7) A. Ekstrand, *J. prakt. Chem.*, (2), 38, 155 (1910).

(8) The carbon and hydrogen analyses were performed by Mr. P. D. Strickler, Mr. D. W. Rosenburg, and Mr. Y. C. Lee. All melting points and boiling points are uncorrected.

(9) C. Graebe and P. Hass, *Ann.*, **237**, 91 (1903).

(10) D. V. Nightingale and R. M. Brooker, *J. Am. Chem. Soc.*, **72**, 5539 (1950).

(11) E. Huntress and H. Walter, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(12) L. F. Fieser and V. Desreux, *J. Am. Chem. Soc.*, **60**, 2255 (1938).

3-Ethyl-5-chloroacenaphthene. To 16 g. of amalgamated mossy zinc was added a solution of 7 g. of 3-acetyl-5-chloroacenaphthene in 225 ml. of glacial acetic acid and 40 ml. of concd. hydrochloric acid. After the solution had refluxed for 1 hr., an additional 40 ml. of concd. hydrochloric acid was added and refluxing continued for an additional 9 hr. The reduction product was isolated in the usual manner and was obtained in white needles m.p. 43.5–44.5°. The yield was 4.5 g. (68%).

Anal. Calcd. for $C_{14}H_{13}Cl$: C, 77.59; H, 6.05. Found: C, 77.38; H, 6.14.

3-Ethyl-5-bromoacenaphthene. 3-Acetyl-5-bromoacenaphthene was reduced in the same way. The product, m.p. 46.5–47°, was obtained in 63% yield.

Anal. Calcd. for $C_{14}H_{13}Br$: C, 64.37; H, 5.02. Found: C, 64.55; H, 5.28.

Reaction of 2-ethyl-4-bromo-1,8-naphthalic anhydride with phenylmagnesium bromide. A solution of phenylmagnesium bromide in 100 ml. of ether was added to a well stirred suspension of 30 g. (0.098 mol.) of 2-ethyl-4-bromonaphthalic anhydride. The reaction mixture became blood red in color, and was heated with stirring while the ether was removed by distillation. The complex was decomposed with 50 ml. of concd. hydrochloric acid and the solution heated to boiling. The solution was filtered and the aqueous layer separated and discarded. The toluene layer was cooled in the ice box and the solid which separated was collected on a filter. Recrystallization of this crude product (11.5 g. m.p. 155–158°) from toluene raised the melting point to 182.5–183°.

Anal. Calcd. for $C_{20}H_{15}BrO_3$: C, 62.68; H, 3.95; neut. equiv., 383.2. Found: C, 62.88; H, 4.21; neut. equiv., 380.8.

The melting point of this compound varied with the rate of heating. The reported melting point was obtained by heating the block at a rate of about two degrees per minute.

After standing for several days, another 22 g. of solid, m.p. 140–146° neut. equiv. 381.1, separated from the toluene mother liquor. This material, apparently a mixture of the isomeric keto acids, could not be further purified by recrystallization.

2-Benzoyl-4-bromo-N-phenyl-1,8-naphthalimide. 4-Bromo-1,8-naphthalic anhydride (4 g.) and 6 ml. of aniline were heated over a free flame for 30 min. The solid which formed on cooling was washed with 5% hydrochloric acid and warmed briefly with 10% sodium carbonate solution. The crude product (4.4 g., 87% yield) was recrystallized once from glacial acetic acid and then from ethanol to give white crystals, m.p. 230–230.5° with sublimation.

Anal. Calcd. for $C_{18}H_{10}BrNO_2$: C, 61.39; H, 2.96. Found: C, 61.50; H, 3.06.

COLUMBIA, MO.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY AND THE NATIONAL RESEARCH CENTRE, DOKKI, CAIRO]

Action of Grignard Reagents. XV.[1] Action of Phenylmagnesium Bromide on Substituted 1-Phenyl-4-methylene-3,5-pyrazolidinediones

AHMED MUSTAFA, MOHAMED KIRA, AND (MISS) MAKAREM EL-ESSAWI

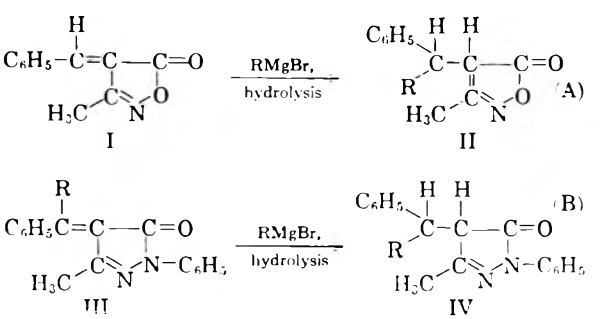
Received July 20, 1959

Phenylmagnesium bromide adds to the exocyclic double bond of the highly colored 1-phenyl-4-benzilidene- and 1-phenyl-4-benzhydrylidene-3,5-pyrazolidinediones (Va–b) to give, after hydrolysis, colorless products believed to have structure VI. Similarly, VIII is obtained by the action of the same reagent on benzylidenemalonic anilide (VII). Syntheses for VIb and VIII are reported.

In extension of the work of one of us[2] on the action of Grignard reagents on heterocyclic compounds, the action of phenylmagnesium bromide on 1-phenyl-4-benzylidene-3,5-pyrazolidinedione (Va) now has been investigated.

The wide spectrum of pharmacological action of 3,5-pyrazolidinedione derivatives,[3] has made this class of compounds among the most widely investigated in this field. In view of these activities, a series of new derivatives of 4-methyl-1-phenyl-3,5-pyrazolidinedione (VI) was synthesized.[4]

The addition of organomagnesium compounds to the conjugation created by attachment of an exocyclic double bond in the 4-position of a heterocyclic nitrogen ring having a carbonyl function has been reported in the case of 3-methyl-4-benzylideneisoxazolone (I)[5] and its nitrogen analog, namely,



(1) For part XIV *cf.* A. Mustafa, W. Asker, A. F. A. Shalaby, S. A. Khattab, and Z. E. Selim, *J. Am. Chem. Soc.*, in press.

(2) *Cf.* (a) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby and A. E. Hassan, *J. Am. Chem. Soc.*, **77**, 1612 (1955); (b) A. Mustafa, W. Asker, and O. H. Hishmat, *J. Am. Chem. Soc.*, **77**, 5127 (1955); (c) A. Mustafa, W. Asker, A. F. A. Shalaby and M. E. Sobhy, *J. Org. Chem.*, **23**, 1992 (1958); (d) A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, **21**, 575 (1956).

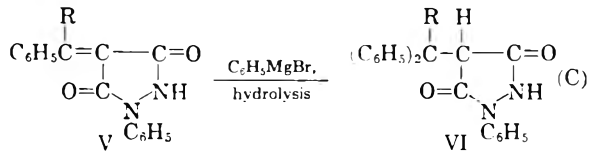
(3) *Cf.* L. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The MacMillan Co., New York, 1953, pp. 322–323; Drill (ed.); R. C. Elderfield, *Heterocyclic Compounds*, Vol. 5, John Wiley & Sons, Inc., 1957, pp. 148–149; J. Buchi, J. Ammann, R. Lieberherr, and E. Eichenberger, *Helv. Chim. Acta*, **36**, 75 (1953).

(4) The pharmacological results will be published elsewhere.

(5) L. Panizzi, *Gazz. chim. ital.*, **76**, 44 (1926).

1 - phenyl - 3 - methyl - 4 - benzylidene - 5 - pyrazolone (III) to yield II and IV respectively (*cf.* Scheme A and B).

When the colored Va is treated with excess of phenylmagnesium bromide, followed by hydrolysis, a colorless product, believed to be 1-phenyl-4-diphenylmethyl-3,5-pyrazolidinedione (VIa), is obtained (*cf.* Scheme C). Similarly, treatment of 1-

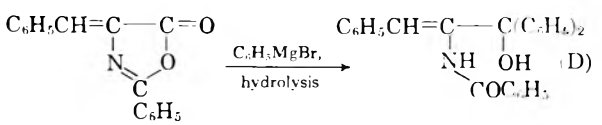


a, R = H; b, R = C_6H_5

phenyl-4-diphenylmethylene-3,5 - pyrazolidinedione (Vb) with phenylmagnesium bromide, followed by hydrolysis, resulted in the formation of 1-phenyl-4-triphenymethyl-3,5-pyrazolidenedione (VIb).

The assigned structure for the Grignard products VIa-b, is inferred from the fact that they are colorless. The melting point and the infrared spectra of VIa are identical with those of the product obtained by the catalytic reduction of Vb. Moreover, the identity of the reaction product obtained by the action of triphenylchloromethane on 1-phenyl-3,5-pyrazolidinedione, an inner hydrazide of malonic acid, in the presence of metallic sodium with VIb is in favor of the given structure.

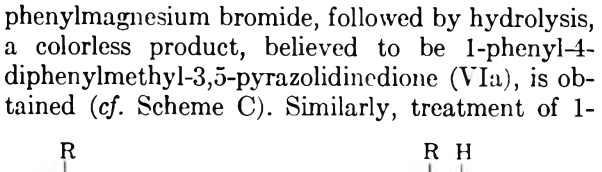
Va-b have the added feature of an α,β-unsaturated carbonyl system and the activity of the exocyclic double bond in position 4 in Va may be compared with the activity of the double bond in I and III. Moreover, the stability of the 5-membered heterocyclic ring in V is in contrast to the ready opening of the oxazolone ring in 2-phenyl-4-benzylidene-2-oxazoline-5-one[2d] (*cf.* Scheme D). We would not like to overlook the



possibility of the tautomeric structures[6] for VI; VIa gives a color reaction with ferric chloride solution.

The action of phenylmagnesium bromide on benzylidenemalondianilide (VII), the open-chain analog of 1,2-diphenyl-4-benzylidene-3,5-pyrazolidinedione (*cf.* Va, N—Ph instead of —NH), now has been investigated. 1,4-Addition[7] of the Grignard reagent takes place and VIII is obtained in good yield (*cf.* Scheme E).

The assigned structure for VIII is inferred from the fact that it is proved to be identical with the product, obtained by the action of aniline on ethyl benzylidenemalonate which was prepared by the condensation of diphenylbromomethane with ethyl malonate in the presence of metallic sodium.



EXPERIMENTAL

1-Phenyl-4-diphenylmethylene-3,5-pyrazolidinedione (Vb). A mixture of 3 g. of 1-phenyl-3,5-pyrazolidinedione[8] and 10 g. of benzophenone was heated at 170° (bath temperature) for 6 hr. The cooled reaction mixture was triturated with ether and the solid so obtained was filtered off and crystallized from ethyl alcohol (*ca.* 1.5 g.). Vb forms deep red crystals and melts at 204° (dec.).

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: N, 8.23. Found: N, 8.49.

Action of Grignard reagents on Va-b. The following illustrates the general procedure; to an ethereal solution of phenylmagnesium bromide (prepared from 0.9 g. of magnesium, 8 g. of bromobenzene, and 40 ml. of dry ether) was added a suspension of Va[8] in 30 ml. of dry ether. The red color of Va readily disappeared. The reaction mixture was refluxed (steam bath) for 8 hr., set aside at room temperature overnight, and then treated with a cold saturated aqueous ammonium chloride solution and extracted with an ether-benzene mixture. The ethereal benzene layer was extracted with a cold aqueous sodium hydroxide solution (100 ml.; 5%). The aqueous alkaline solution was acidified with cold dilute hydrochloric acid and the solid that separated was extracted with cold chloroform (*ca.* 50 ml.) and was dried over anhydrous sodium sulfate. The chloroform extract, on evaporation deposited pale yellow crystals. 1-Phenyl-4-diphenylmethyl-3,5-pyrazolidinedione (VIa) was obtained as colorless crystals (0.8 g.) from ethyl alcohol; m.p. 200° (dec.).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.71; H, 5.35; N, 8.47.

An alcoholic solution of Va gives a red color upon treatment with an alcoholic solution of ferric chloride.

1-Phenyl-4-triphenylmethyl-3,5-pyrazolidinedione (VIb) was obtained by the action of phenylmagnesium bromide on 1 g. of Vb, as described above, as colorless crystals from a chloroform ethyl alcohol mixture (*ca.* 0.78 g.), m.p. 234° (dec.).

Anal. Calcd. for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.81; H, 5.53; N, 6.69.

It gives a red color when its alcoholic solution is treated with an alcoholic solution of ferric chloride.

Catalytic hydrogenation of Vb. A mixture of 0.2 g. of 5% palladium on calcium carbonate[9] in 50 ml. of absolute ethyl alcohol was shaken in a hydrogen atmosphere for 15 min. to reduce the palladium hydroxide, then 1 g. of Vb in 50 ml. of absolute ethyl alcohol was added. The hydrogenation

(6) For the possibility of tautomerization of a number of substituted 3,5-pyrazolidinediones (*cf.* A. Michaelis, H. Rohmer, *Ber.*, **31**, 2907, 3003, 3193 (1898); S. Imanishi, *J. Chem. Phys.*, **18**, 1307 (1950); R. C. Elderfield, *Heterocyclic Compounds*, Vol. 5, John Wiley & Sons, 1957, p. 148).

(7) Similar 1,4-additions have been reported in the case of ethyl benzylidenemalonate (E. P. Kohler, *Am. Chem. J.*, **34**, 132 (1906); Reynolds, *Am. Chem. J.*, **44**, 305 (1910); M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 563) and in the case of *N,N*-disubstituted cinnamides (*cf.* E. P. Kohler, *Am. Chem. J.*, **33**, 21 (1905); N. Maxim and N. Ioanid, *Bull. soc. chim. Romania*, **10**, 29 (1928); *Chem. Abstr.*, **22**, 4114 (1928).

(8) A. Michaelis and R. Burmeiser, *Ber.*, **25**, 1502 (1892).

(9) R. Mozingo, *Org. Syntheses*, **III**, 685 (1955), John Wiley & Sons, Inc., New York.

was continued until the red color was completely discharged (*ca.* 20 min.). The alcoholic solution was separated by filtration and on concentration and cooling, it deposited colorless crystals (*ca.* 0.82 g.).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.04; H, 5.26; N, 8.46.

They were identified as 1-phenyl-4-diphenylmethyl-3,5-pyrazolidinedione (VIa). Determination of the melting point and mixed m.p. with a sample of VIa, obtained as above, gave no depression; similarly the infrared spectra of both samples were found to be identical.

Action of triphenylchloromethane on 1-phenyl-3,5-pyrazolidinedione. To a solution of 0.23 g. of metallic sodium in 10 ml. of absolute ethyl alcohol was added a solution of 1.78 g. of 1-phenyl-3,5-pyrazolidinedione[8] in 15 ml. of absolute ethyl alcohol. The stirred reaction mixture was treated, at room temperature, with a solution of 2.28 g. of triphenylchloromethane in 15 ml. of absolute ethyl alcohol. It was left overnight and then refluxed (steam bath) for 1 hr. to effect completion of the reaction. The cooled reaction mixture was poured into ice cold water and the solid that separated was filtered off, washed with water, and crystallized from a chloroform–ethyl alcohol mixture (*ca.* 1.9 g.), m.p. 234° (dec.).

Anal. Calcd. for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.32; H, 5.84; N, 7.24.

The reaction product proved to be identical with VIb; (melting point and mixed melting point determination with a sample of VIb obtained as above).

Action of phenylmagnesium bromide on VII. One gram of VII was treated with phenylmagnesium bromide as described in the case of V. The reaction product (VIII) was obtained from ethyl alcohol and/or from acetone in colorless crystals (*ca.* 0.78 g.), m.p. 285°.

Anal. Calcd. for $C_{28}H_{24}N_2O_2$: C, 79.97; H, 5.75. Found: C, 79.92; H, 5.93.

Action of aniline on ethyl diphenylmethylmalonate. Ethyl diphenylmethylmalonate was prepared after the procedure described for the preparation of ethyl *n*-butylmalonate,[10] and was obtained as colorless crystals from petroleum ether (b.p. 50–80°) (52% yield), m.p. 55°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.44; H, 6.15. Found: C, 73.53; H, 6.45.

A mixture of 2 g. of ethyl diphenylmethylmalonate and 6 g. of freshly distilled aniline was refluxed (oil bath) for 7 hr. The cooled reaction mixture was treated with ether and the separated solid was filtered off, washed with ether, and crystallized from ethyl alcohol. Colorless needles (*ca.* 1.9 g.), m.p. 285°.

Anal. Calcd. for $C_{28}H_{24}N_2O_2$: C, 79.97; H, 5.75. Found: C, 80.26; H, 5.58.

It proved to be identical with VIII (m.p. and mixed m.p. determinations).

GIZA, CAIRO
U. A. R.

(10) *Cf. Org. Syntheses*, I, 250 (1948).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF ABERDEEN]

Studies in the Juglone Series. IV. The Addition of Aniline and Toluene-*p*-thiol to 5-Substituted 1,4-Naphthoquinones

J. W. MACLEOD AND R. H. THOMSON

Received August 5, 1959

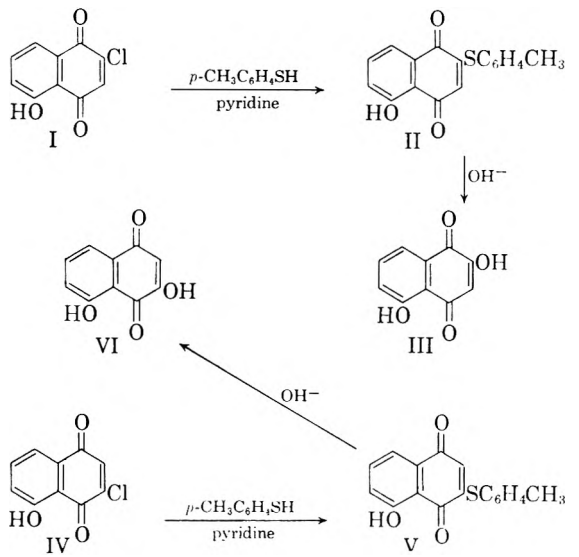
The structures previously assigned to the products of addition of toluene-*p*-thiol to juglone and juglone acetate have been confirmed. Addition of both aniline and toluene-*p*-thiol to 5-methoxy-, 5-methyl-, 5-acetamido- and 5-chloro-1,4-naphthoquinones takes place predominantly at position 3.

In Part III[1] of this series it was reported that addition of toluene-*p*-thiol and thioglycolic acid to juglone occurred predominantly at position 3, whereas addition to juglone acetate occurred mainly at position 2. The 3-substituted juglones were also prepared by reaction of 3-chlorojuglone with the appropriate thiol in the presence of pyridine; in addition 2-*p*-tolythiojuglone was obtained, in small yield [together with a second product, now identified as 2,3-di(*p*-tolythio)juglone] by reaction of 2-chlorojuglone with toluene-*p*-thiol in the presence of pyridine. These reactions were considered to establish the structures of the addition products. However, the thioglycolic acid reactions were recently reexamined by Rothman[2] who concluded that addition to juglone occurred predominantly at position 2, while addition to juglone acetate occurred mainly at position 3. These results are opposite to those found earlier by one of us,[1] and, at first sight appear to be very satisfactory insofar as they bring thioglycolic acid and, by implication, toluene-*p*-thiol, into line with other nucleophilic additions in the juglone series, and the radical addition mechanism proposed[1] becomes unnecessary. Unfortunately, Rothman's experimental evidence is not entirely convincing. His method of orientation consisted in catalytic reduction of each juglone-thioglycolic acid, followed by condensation of the carboxyl group with the neighboring quinol hydroxyl group. This gave two isomeric lactones (which can be regarded as substituted naphthalene-1,5- and 4,5- diols) which were distinguished by their relative abilities to increase the acidity of a boric acid solution. As one of the lactones was amorphous (and no analysis was reported) the results are in some doubt, and further verification is therefore desirable. We have confirmed (by comparison of their ethyl esters) that the compound obtained by addition of thioglycolic acid to juglone is identical with that formed by reaction

(1) R. H. Thomson, *J. Org. Chem.*, 16, 1082 (1951).
(2) F. G. Rothman, *J. Org. Chem.*, 23, 1049 (1958).

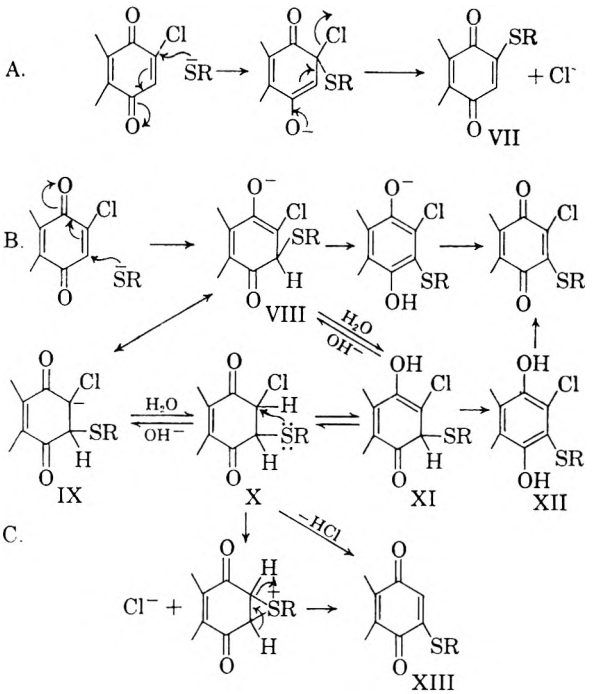
of 3-chlorojuglone with thioglycolic acid, but in view of Rothman's findings the structures of these juglone-thioglycolic acids may be regarded as an open question. We hope to obtain independent evidence establishing their structure in due course.

In this communication we are concerned with the addition of toluene-*p*-thiol to juglone and other 5-substituted-1,4-naphthoquinones. Rothman's results imply that the structures originally proposed[1] for the *p*-tolylthiojuglones are incorrect, and consequently that the method used to determine these structures is ambiguous. Attention is drawn to "the unreliability of assuming that in stoichiometric replacements of halogen in haloquinones the replacing substituent will occupy the same position as the halogen."[2] We have now confirmed the original structures by converting the tolylthio compounds into the corresponding hydroxyjuglones by alkaline hydrolysis.[3] The structures of 2-chlorojuglone I (obtained *via* chromic acid oxidation of 5 - acetoxy - 2,4 - dichloronaphthalene[4]) and 2-hydroxyjuglone III (prepared *via* condensation of *p*-nitrosodimethylaniline with 5-methoxytetralone-1[5]) cannot be doubted. Hence the conversion of I into III must either proceed as shown, or *via* the sequence, 2-chlorojuglone → 3-*p*-tolylthiojuglone → 2-hydroxyjuglone. The last step, in particular, seems highly improbable. 3-Chlorojuglone is made



by elimination of hydrochloric acid from juglone dichloride[6] and, by difference, must be the 3-isomer. The structure of 3-hydroxyjuglone is established independently through the alternative syntheses of droserone[5,7] (3-hydroxy-2-methyljuglone). Here again, we believe that the conversion of IV into VI proceeds *via* V, and not *via* its isomer. Admittedly, it may not be wise to extrapolate from these results to all halogenoquinones and all thiols, and thioglycolic acid, which is particularly reactive,[8] may be exceptional. The use of pyridine is a possible complicating factor, and in the replacement reactions described below, this has been avoided by converting the thiol into its anion by addition of aqueous sodium hydroxide, before reaction with the halogenoquinone.

We consider that the normal nucleophilic replacement reaction proceeds according to reaction Scheme *A*, and the normal addition reaction according to Scheme *B*. If an "abnormal" replacement reaction occurs (Scheme *C*), this must also proceed *via* the intermediate anion VIII (mesomeric with structure IX). Abstraction of a proton (*e.g.*, from a water molecule) will give rise to the



tautomers X and XI. Assuming that X is formed (*i.e.*, 1,2-addition of the thiol to the quinone), it is then possible that a neighboring group displacement reaction could lead to the formation of XIII, as indicated (and/or VII), but enolization of XI to form the aromatic tautomer XII would be energetically much more favorable. Alternatively, XIII might arise from structure X by direct dehydrochlorination, but this implies initial removal of the proton from position 3 whereas the proton at position 2 should be more readily detached (since chlorine has a much more powerful inductive

(3) The juglone-thioglycolic acids also hydrolyze under these conditions but working up invariably leads to tar formation.

(4) R. H. Thomson, *J. Org. Chem.*, **13**, 371 (1948).

(5) R. G. Cooke and W. Segal, *Australian J. Sci. Research*, **3A**, 628 (1950).

(6) R. H. Thomson, *J. Org. Chem.*, **13**, 377 (1948).

(7) R. H. Thomson, *J. Chem. Soc.*, 1277 (1949); M. Asano and J. Hase, *J. Pharm. Soc. Japan*, **63**, 90 (1943); M. Asano, Y. Miyashita, and J. Hase, *J. Pharm. Soc. Japan*, **63**, 109 (1943).

(8) A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 1138 (1953).

effect than the tolythio group). Thus elimination of halogen by direct replacement (*e.g.*, reaction of 5-acetamido-3-bromo-1,4-naphthoquinone with toluene-*p*-thiol), or addition without replacement (*e.g.*, reaction of 2,5-dichloro-1,4-naphthoquinone with toluene-*p*-thiol, in the cold), or both (*e.g.*, reaction of 2-chlorojuglone with toluene-*p*-thiol), seem more probable than the reactions depicted in Scheme *C*.

The addition of toluene-*p*-thiol to juglone acetate is peculiar. As reported some years ago,[1] it leads to the formation of 2-*p*-tolylthiojuglone acetate. This has been successfully repeated, but recently this reaction has given predominantly the 3-isomer on several occasions! The implication is that the expected nucleophilic addition is taking place at position 3 while radical addition[1] is occurring under different, but as yet undefined, conditions at position 2. The problem is under investigation. Our present purpose is to demonstrate that toluene-*p*-thiol usually undergoes addition to 5-substituted-1,4-naphthoquinones to give products having the same orientation as the corresponding aniline addition products, although this, of itself, does not prove that the toluene-*p*-thiol additions proceed by an ionic mechanism. In some cases the more reactive thiols attack both positions 2 and 3, and appreciable quantities of two isomers can be isolated. In the case of 6-substituted-1,4-naphthoquinones, it has been shown[9] that addition of aniline affords one isomer in good yield (*ca.* 80%) whereas toluene-*p*-thiol gives a mixture of approximately equal amounts of both isomers. As can be seen from Table I, in the corresponding reactions with 5-substituted-1,4-naphthoquinones,[10] both reagents give predominantly one isomer, nucleophilic additions taking place mainly at position 3,[11] in agreement with predictions.[1] It is also noteworthy that both aniline and toluene-*p*-thiol react with 2,5-dichloro-1,4-naphthoquinone, in the cold, by addition at position 3, and 2-chlorojuglone reacts with toluene-*p*-thiol in the hot, in the presence of pyridine, to give both 2-*p*-tolylthio- and 2,3-di(*p*-tolylthio)juglones.

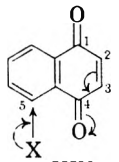
Two results call for comment: (a). It was considered[1] that an electron-releasing group situated at position 5 and hence conjugated with the carbonyl group at position 4, would diminish the electronic displacement from the C_2—C_3 double bond shown in XIV, leading to preferential nucleophilic attack at position 3. It is therefore surprising

TABLE I

ADDITION OF ANILINE AND TOLUENE-*p*-THIOL TO 5-SUBSTITUTED 1,4-NAPHTHOQUINONES

Quinone[a]	Orientation and Yields (%)[b] of Compound(s) produced by	
	Aniline	Toluene-*p*-thiol
5-Hydroxy-1,4-NQ[c]	—	3(90%)
5-Acetoxy-1,4-NQ[c]	3(66%)[d]	3 or 2[e] (75–80%)
5-Methoxy-1,4-NQ	3(86%)	3(73%)
5-Methyl-1,4-NQ	3(72%)	3(75%); 2(10%)
5-Acetamido-1,4-NQ	—	3(72%)
5-Chloro-1,4-NQ	3(86%)	3(49%); 2(12%)

[a] NQ-naphthoquinone. [b] The yields given are for the quinones obtained by oxidation of the initial adducts. [c] See ref. 1. [d] Given, in error, as 56% in ref. 1. [e] See Discussion, p. 38.



XIV

to find that a chlorine atom at position 5 has the same orientating influence as the other substituents listed in Table 1.[12] This may be due to the direct field effect of the chlorine atom on the neighboring carbonyl group, or possibly to a steric effect, the rather large chlorine atom tending to displace the 4-carbonyl group out of the plane of the rings. Both effects would hinder conjugative activation at position 2, and hence nucleophilic addition at position 3 would predominate.

(b). Juglones undergo nucleophilic attack at position 2, in a few instances; namely, the addition of dimethylamine to juglone,[1] and the reaction of various 2,3-dihalogenojuglones with aniline and *p*-toluidine.[6,13] In the first case the yield is poor. To account for these reactions it was suggested that a hydroxyl group at position 5 (in contrast to other electron-releasing groups) could assist the electronic displacement shown in XIV, by virtue of the intramolecular hydrogen bond which enhances the electronegativity of the carbonyl oxygen at position 4. If the addition of toluene-*p*-thiol to juglone at position 3 *is* a nucleophilic reaction (which has yet to be established) it is clear that the hydrogen bond has no significant effect in this case. It was hoped that the reactions of 5-acetamido-1,4-naphthoquinone (which also has an intramolecular hydrogen bond) would clarify the situation but unfortunately this quinone, like juglone, only gives black amorphous material, on reaction with aniline.

Orientation of the products. 5-Methoxy-1,4-naphthoquinone. Acid hydrolysis of the aniline deriva-

(9) J. M. Lyons and R. H. Thomson, *J. Chem. Soc.*, 2910 (1953).

(10) This work was done concurrently with that reported in ref. 9.

(11) R. G. Cooke, H. Dowd, and W. Segal, *Australian J. Chem.*, 6, 38 (1953), have shown that reaction of 5-methoxy-1,4-naphthoquinone with excess dimethylamine gives (in 42% yield) a mixture of two isomers. Similar treatment of 5-methyl-1,4-naphthoquinone gave mainly the 3-isomer, with indications of the presence of the other.

(12) In the corresponding 6-substituted naphthoquinones the orientating effect of a chlorine atom is opposite to that of electron-releasing groups.[9]

(13) R. H. Thomson, *J. Org. Chem.*, 13, 870 (1948).

tive, followed by demethylation, gave the known 3,5-dihydroxy-1,4-naphthoquinone. The intermediate 3-hydroxy-5-methoxy-1,4-naphthoquinone was also obtained by alkaline hydrolysis of the toluene-*p*-thiol addition product which is therefore also the 3-isomer.

5-Methyl-1,4-naphthoquinone. This compound is most conveniently prepared *via* Diels-Alder addition of piperylene to benzoquinone.[11] Herzenberg and Ruhemann[14] obtained a yellow quinone, $C_{11}H_8O_2$, m.p. 102–103°, by chromic acid oxidation of 1-methylnaphthalene, which they claimed was 5-methyl-1,4-naphthoquinone. On repeating this work we obtained a small yield of the same product which proved to be 2-methyl-1,4-naphthoquinone.[15] Evidently our sample of 1-methylnaphthalene, like theirs, contained some of the 2-isomer, and the alleged hemimellitic acid, m.p. 190°, which they obtained by permanganate oxidation of the quinone, must have been phthalic acid.

Addition of toluene-*p*-thiol to 5-methyl-1,4-naphthoquinone yielded two isomers. Alkaline hydrolysis of the major product afforded the known 3-hydroxy-5-methyl-1,4-naphthoquinone which was also obtained by acid hydrolysis of the anilino-5-methyl-1,4-naphthoquinone. 2-Hydroxy-5-methyl-1,4-naphthoquinone was prepared by acid hydrolysis of 5-methyl-1,4-naphthoquinone-2,3-epoxide.

5-Acetamido-1,4-naphthoquinone. Two monobromo derivatives were obtained from this quinone by addition of bromine followed by elimination of hydrogen bromide from the dibromide. One of these (the 2-isomer) was identical with that prepared by chromic acid oxidation of 5-acetamido-2,4-dibromo-1-naphthol. Reaction of the other product (5-acetamido-3-bromo-1,4-naphthoquinone) with sodium *p*-tolylthiolate gave the same quinone as that obtained by addition of toluene-*p*-thiol to the acetamidonaphthoquinone, *i.e.*, 5-acetamido-3-*p*-tolylthiol-1,4-naphthoquinone.

5-Chloro-1,4-naphthoquinone. Hydrolysis of the anilino derivative gave a hydroxyquinone different from that derived from 5-chloro-1,4-naphthoquinone-2,3-epoxide. The latter was shown to be the 2-isomer by (a) an unambiguous synthesis from 5-chloro-1-naphthol (*via* its 2,4-dinitro and diamino derivatives) and (b), reductive acetylation to give 1,2,4-triacetoxy-5-chloronaphthalene which was also obtained by Thiele acetylation of 5-chloro-1,2-naphthoquinone. Thus the addition of aniline to 5-chloro-1,4-naphthoquinone gives the 3-anilino derivative. Aniline also reacts with 2,5-dichloro-1,4-naphthoquinone at position 3: hydrolysis of the resulting anilinodichloroquinone gave a dichlorohydroxyquinone identical with that obtained by chlorination of 5-chloro-3-hydroxy-1,4-naphthoquinone. Reaction of 2,5-dichloro-1,4-naphthoquinone with toluene-*p*-thiol in the cold gave 2,5-dichloro-3-*p*-tolylthio-1,4-naphthoquinone, but when the sodium salt of the thiol was used in boiling alcohol, the reactive chlorine was replaced forming 5-chloro-2-*p*-tolylthio-1,4-naphthoquinone. This enabled the products obtained by addition of toluene-*p*-thiol to 5-chloro-1,4-naphthoquinone to be orientated.

(14) J. Herzenberg and S. Ruhemann, *Ber.*, **60**, 897 (1927).

(15) *Cf.* Elsevier's *Encyclopaedia of Organic Chemistry*, **12B**, 2837 (1952).

EXPERIMENTAL

Light petroleum refers to the fraction b.p. 100–120° unless otherwise stated.

2,5-Dihydroxy-1,4-naphthoquinone. A solution of 0.4 g. of 2-*p*-tolylthiojuglone (obtained by addition of toluene-*p*-thiol to juglone acetate and subsequent hydrolysis[1]) in 16 ml. of ethanol was shaken for 30 min. with 1.35 ml. of 2*N* sodium hydroxide. After addition of water (8 ml.), the mixture was refluxed for 15 min. The red solution was then cooled and poured onto ice containing 8 ml. of 4*N* sulfuric acid. The sticky precipitate formed was taken into ether, extracted with 2% aqueous sodium acetate, and acidified. The resulting orange precipitate was crystallized from a small volume of glacial acetic acid forming orange-brown needles, m.p. 216–219° (dec.) not depressed by an authentic sample of 2-hydroxyjuglone. (Mixed m.p. with 3-hydroxyjuglone, 190°). Yield 59%. It formed a diacetate which crystallized from light petroleum in yellow needles, m.p. and mixed m.p. 152°.

3,5-Dihydroxy-1,4-naphthoquinone. A mixture of 0.3 g. of 3-*p*-tolylthiojuglone (obtained by addition of toluene-*p*-thiol to juglone[1]), 24 ml. of ethanol, and 12 ml. of 2*N* sodium hydroxide was refluxed on the steam bath for 1 hr., diluted with water (30 ml.), cooled in ice, and acidified with 4*N* sulfuric acid. The resulting brown crystalline precipitate was recrystallized from a small volume of glacial acetic acid forming brown needles, m.p. 215° (blackening from 210°), not depressed by authentic 3-hydroxyjuglone. The diacetate crystallized from methanol in yellow needles, m.p. and mixed m.p. 137°.

2,3-Di(p-tolylthio)juglone. A solution of 80 mg. of toluene-*p*-thiol in 4 ml. of ethanol was added to a suspension of 80 mg. of 2,3-dichlorojuglone in 10 ml. of the same solvent. The mixture was heated to boiling, dark red crystals separating almost at once. Recrystallization from light petroleum yielded dark red needles, m.p. 188°, not depressed by material obtained by the reaction of 2-chlorojuglone with toluene-*p*-thiol.[1] Yield 87%.

Anal. Calcd. for $C_{24}H_{18}O_3S_2$: C, 68.9; H, 4.3; S, 15.3. Found: C, 69.0; H, 4.3; S, 15.3.

3-Anilino-5-methoxy-1,4-naphthoquinone. Aniline in excess (20 ml.) was added to a suspension of 2 g. of 5-methoxy-1,4-naphthoquinone in 40 ml. of cold ethanol. After 5 days the mixture was poured into dilute sulfuric acid. The precipitate which formed was crystallized from light petroleum in deep red needles, m.p. 152°. Yield 86.5%.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 73.35; H, 4.6; N, 4.7.

3-Hydroxy-5-methoxy-1,4-naphthoquinone. (*a*) A solution of 0.5 g. of the above anilinoquinone in 20 ml. of concentrated sulfuric acid was cautiously diluted with 40 ml. of water, and the suspension gently boiled under reflux for 5 min. After cooling and dilution with 60 ml. of water, the yellow hydroxyquinone was collected, washed, and dried. It crystallized from light petroleum in yellow plates, m.p. 211° (dec.). Yield 82%.

(*b*) A fine suspension of 0.3 g. of 5-methoxy-3-*p*-tolylthio-1,4-naphthoquinone in 12 ml. of ethanol was shaken for 10 min. with 2 ml. of cold 2*N* sodium hydroxide. The resulting dark red solution was poured onto a mixture of ice and excess 2*N* sulfuric acid. The precipitate obtained was crys-

tallized first from ethanol, and then from light petroleum (charcoal) in glistening yellow plates, m.p. 209–211° (dec.), identical with those obtained in (*a*). Yield 50%. [The m.p. taken in a Pyrex tube sharpened to 210.5–211° (dec.)]

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.65; H, 3.95. Found: C, 64.45; H, 4.1.

Demethylation was effected by refluxing a solution of the quinone (0.5 g.) in 50 ml. of benzene with 1.5 g. of anhydrous aluminium chloride for 35 min. The mixture was then cooled, poured onto ice and hydrochloric acid, and extracted with ether, from which the dihydroxyquinone was removed by shaking with 2% aqueous sodium acetate. After treatment with charcoal, the alkaline solution was acidified with 2*N* sulfuric and extracted with ether. Evaporation of the dried extract gave a residue which was sublimed *in vacuo* and then crystallized from light petroleum. It formed orange needles, m.p. 216° (dec.) not depressed by an authentic sample of 3,5-dihydroxy-1,4-naphthoquinone. The diacetate had m.p. and mixed m.p. 135–136°.

5-Methoxy-3-p-tolylthio-1,4-naphthoquinone. A solution of 0.34 g. of toluene-*p*-thiol in 4 ml. of ethanol was added to a cold suspension of 0.5 g. of 5-methoxy-1,4-naphthoquinone in 20 ml. of ethanol. Next day the mixture was warmed to complete solution, cooled, and then oxidized by pouring into a mixture of 0.6 g. of potassium dichromate, 0.3 ml. of concentrated sulfuric acid, and 3 ml. of ice water. Crystallization of the precipitate from ethanol gave 5-methoxy-3-*p*-tolylthio-1,4-naphthoquinone as long yellow needles, m.p. 162–162.5°. Yield 73%.

Anal. Calcd. for $C_{18}H_{14}O_3S$: C, 69.65; H, 4.55; S, 10.3. Found: C, 69.45; H, 4.45; S, 10.3.

3-Anilino-5-methyl-1,4-naphthoquinone. On addition of 8 ml. of aniline to a suspension of 1.5 g. of 5-methyl-1,4-naphthoquinone in 15 ml. of ethanol the quinone rapidly dissolved forming a red solution. The crystals which separated on keeping were collected after 3 days, and recrystallized from benzene forming fine scarlet needles, m.p. 179–180°. Yield 72%.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 5.0; N, 5.3. Found: C, 77.6; H, 5.2; N, 5.15.

3-Hydroxy-5-methyl-1,4-naphthoquinone. (*a*) 3-Anilino-5-methoxy-1,4-naphthoquinone (0.65 g.) was hydrolyzed, as above, by boiling for 5 min. with 75 ml. of 33% (v./v.) sulfuric acid. The hydroxyquinone, which separated on cooling, followed by dilution with 75 ml. of water, crystallized from light petroleum (b.p. 80–100°) in yellow plates, m.p. 176–177°. Yield 79.5%.

(*b*) A fine suspension of 0.5 g. of 5-methyl-3-*p*-tolylthio-1,4-naphthoquinone in 20 ml. of ethanol, was shaken with 4 ml. of 2*N* sodium hydroxide for 20 min. in the cold. The mixture was then brought to the boil, diluted with water until dissolution was complete, and refluxed for 5 min. After cooling, acidification with 4*N* sulfuric acid precipitated the hydroxyquinone. It was taken into ether and extracted with 2% aqueous sodium acetate. After treatment with charcoal the hydroxyquinone was reprecipitated, and then crystallized from methanol forming yellow plates, m.p. 175–176°, not depressed by material obtained in (*a*). (Lit.[11] 175–176°). Yield 50%. Reductive acetylation using zinc dust, acetic anhydride, and a drop of pyridine afforded 1,3,4-triacetoxy-5-methylnaphthalene which separated from light petroleum, (b.p. 80–100°) in colorless needles, m.p. 132–133.5°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.1. Found: C, 64.45; H, 5.3.

5-Methyl-1,4-naphthoquinone-2,3-epoxide.[16] A solution of 1 g. of 5-methyl-1,4-naphthoquinone in 10 ml. of hot ethanol was cooled to the crystallizing point when 0.2 g. of sodium carbonate, dissolved in 5 ml. of water containing 1 ml. of 30% hydrogen peroxide, was added with continued cooling. An initial deep purple coloration was followed by a copious precipitate. After dilution with water, this was collected, dried, and crystallized from light petroleum (b.p. 80–100°) forming long needles, m.p. 111°. Yield 31%.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.2; H, 4.3. Found: C, 70.2; H, 4.05.

2-Hydroxy-5-methyl-1,4-naphthoquinone. The above oxide (0.34 g.) was stirred with 1.5 ml. of concentrated sulfuric acid until it dissolved. After 10 min., 6 ml. of water were carefully added, with cooling. The resulting precipitate was dissolved in warm 2% aqueous sodium acetate, and filtered. Acidification of the red filtrate with 5*N* sulfuric acid yielded the hydroxyquinone which was crystallized from aqueous methanol in yellow needles, m.p. 146°. (Lit.[11] 145–146°). Yield 59%. Reductive acetylation afforded 1,2,4-triacetoxy-5-methylnaphthalene, which separated from ethanol in needles, m.p. 144°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.1. Found: C, 64.3; H. 5.2.

2-Bromo-5-methyl-1,4-naphthoquinone. A solution of bromine in glacial acetic acid (10 ml. of 5% v./v.) was added to a solution of 1.7 g. of 5-methyl-1,4-naphthoquinone in 10 ml. of the same solvent. After 10 min., the dibromide was precipitated with water. (Crystallized from light petroleum (b.p. 60–80°) it had m.p. 98–100°). To this (2.55 g.) in 10 ml. of glacial acetic acid, 0.8 g. of anhydrous sodium acetate was added, and the mixture was boiled for 3 min. Dilution with water afforded the bromoquinone which crystallized from light petroleum (b.p. 60–80°) in yellow needles, m.p. 90.5–92°. Yield 62.5% (from the dibromide).

Anal. Calcd. for $C_{11}H_7O_2Br$: C, 52.6; H, 2.8. Found: C, 52.65; H, 2.55.

5-Methyl-2- and 3-p-tolylthio-1,4-naphthoquinones. A solution of 0.72 g. of toluene-*p*-thiol in 10 ml. of ethanol was added to a suspension of 2 g. of 5-methyl-1,4-naphthoquinone in 20 ml. of the same solvent, and boiled for 2 min. Nearly pure 5-methyl-3-*p*-tolylthio-1,4-naphthoquinone separated on cooling. After recrystallization from ethanol it formed deep yellow diamond-shaped plates, m.p. 186°. Yield 75%.

Anal. Calcd. for $C_{18}H_{14}O_2S$: C, 73.45; H, 4.8; S, 10.9. Found: C, 73.4; H, 4.8; S, 10.8.

After keeping for 2 days the initial mother liquor deposited 5-methyl-2-*p*-tolylthio-1,4-naphthoquinone. It separated from light petroleum (b.p. 60–80°) in orange needles, m.p. 123°. Yield 10%.

Anal. Calcd. for $C_{18}H_{14}O_2S$: C, 73.45; H, 4.8; S, 10.9. Found: C, 73.45: H, 4.75; S, 10.75.

This compound was also obtained by mixing boiling solutions of 0.5 g. of 2-bromo-5-methyl-1,4-naphthoquinone in 10 ml. of ethanol, and 0.25 g. of toluene-*p*-thiol in a little ethanol containing 1 ml. of 2*N* sodium hydroxide. The product, obtained on cooling, formed orange needles, m.p. and mixed m.p. 122–123° (from light petroleum). Yield 76%.

5-Acetamido-1,4-naphthoquinone. A solution of 4 g. of 5-acetamido-1-naphthol in 200 ml. of methanol was oxidized[17] by addition of 12.7 g. of potassium nitrosodisulfonate dissolved in 700 ml. of water and 200 ml. of 0.16*M* potassium dihydrogen phosphate. Almost pure 5-acetamido-1,4-naphthoquinone separated on standing overnight. When recrystallized from acetone it formed orange needles, m.p. 173–174° (Pyrex). Yield 63%. The infrared spectrum (Nujol), showed bands at 1702 and 1695 (amide carbonyl), 1665 (free quinone carbonyl) and 1644 cm.$^{-1}$ (chelated quinone carbonyl). (*Cf.* 5-hydroxy-1,4-naphthoquinone[18] which also shows 2 quinonoid carbonyl frequencies at 1667 and 1643 cm.$^{-1}$) The chelated NH band appeared at 3219 cm.$^{-1}$ (KBr disk).

5-Acetamido-2,4-dibromo-1-naphthol. To a solution of 2 g. of 5-acetamido-1-naphthol in 20 ml. of glacial acetic

(16) Following the procedure of L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath & Co., 1941, p. 235.

(17) Oxidation by the method of H.-J. Teuber and N. Götz, *Ber.*, **87**, 1236 (1954).

(18) R. H. Thomson, *J. Chem. Soc.*, 1737 (1950).

acid, an equal volume of a 5% (v./v.) solution of bromine in the same solvent was added slowly, keeping the temperature at 18–20°. A precipitate soon appeared and was collected after 30 min. Crystallization from acetone afforded 5-acetamido-2,4-dibromo-1-naphthol in needles, m.p. 185°. Yield 42%.

Anal. Calcd. for $C_{12}H_9Br_2NO_2$: N, 3.9; Br, 44.5. Found: N, 3.9; Br, 44.0.

The acetone mother liquor yielded a small amount (0.35 g.) of a second compound,[19] m.p. 188–190° (mixed m.p. with the previous compound 177–180°).

5-Acetamido-2- and 3-bromo-1,4-naphthoquinone. A suspension of 2.5 g. of 5-acetamido-1,4-naphthoquinone in 12.5 ml. of glacial acetic acid was treated with 11.6 ml. of a 5% (v./v.) solution of bromine in the same solvent. After 15 min. the mixture was poured onto ice water forming a slightly sticky, yellow-orange precipitate of the dibromide. When dried (4.1 g.), this was refluxed for 2 min. in 25 ml. of glacial acetic acid containing 1.35 g. of anhydrous sodium acetate, and then poured onto ice. Crystallization of the product from glacial acetic acid gave 5-acetamido-3-bromo-1,4-naphthoquinone, m.p. 169–170°. After further crystallization from light petroleum it formed orange needles, m.p. 181°. (Yield, 9% from the dibromide).

Anal. Calcd. for $C_{12}H_8BrNO_3$: C, 49.0; H, 2.75; N, 4.75. Found: C, 48.9; H, 2.65; N, 4.8.

The acetic acid mother liquor was poured onto ice forming a precipitate which crystallized from methanol in orange-brown needles, m.p. 171–172.5°. (Yield, 26% from the dibromide.) The same compound, 5-acetamido-2-bromo-1,4-naphthoquinone, was obtained by treating a suspension of 0.5 g. of 5-acetamido-2,4-dibromo-1-naphthol in 2 ml. of glacial acetic acid with 0.5 g. of chromium trioxide dissolved in 1 ml. of water. The temperature rose spontaneously to 35° and was raised to 50° by warming. The bromoquinone separated on cooling, and recrystallized from methanol in dark red needles, m.p. 171–172.5°, not depressed by the material prepared above. Yield 54%.

Anal. Calcd. for $C_{12}H_8BrNO_3$: C, 49.0; H, 2.75; N, 4.75; Br, 27.2. Found: C, 49.05; H, 2.85; N, 4.65; Br, 27.0.

5-Acetamido-2-p-tolylthio-1,4-naphthoquinone. A solution of 85 mg. of toluene-*p*-thiol in 4 ml. of ethanol was neutralized with aqueous sodium hydroxide, brought to the boil, and added all at once to a boiling solution of 200 mg. of 5-acetamido-2-bromo-1,4-naphthoquinone in 12 ml. of ethanol. The tolylthioquinone separated on cooling, and was recrystallized from methanol in orange-red needles, m.p. 201°. Yield 57%.

Anal. Calcd. for $C_{19}H_{15}NO_3S$: C, 67.6; H, 4.5; S, 4.15. Found: C, 67.4; H, 4.45; N, 4.3.

5-Acetamido-3-p-tolylthio-1,4-naphthoquinone. (*a*) A suspension of 0.5 g. of 5-acetamido-1,4-naphthoquinone in 10 ml. of ethanol was treated with 0.15 g. of toluene-*p*-thiol dissolved in 2 ml. of ethanol, raised to the boil, and left to crystallize. The new quinone formed orange needles, m.p. 231° (from methanol). Yield 72%.

(*b*) Reaction of 5-acetamido-3-bromo-1,4-naphthoquinone (50 mg.) with neutralized toluene-*p*-thiol (20 mg.) in boiling ethanol, as above, gave the same product, m.p. and mixed m.p. 231°. Yield 52%.

Anal. Calcd. for $C_{19}H_{15}NO_3S$: C, 67.6; H, 4.5; N, 4.15; S, 9.5. Found: C, 67.65; H, 4.3; N, 4.0; S, 9.6.

3-Anilino-5-chloro-1,4-naphthoquinone. Five ml. of aniline were added to a suspension of 0.5 g. of 5-chloro-1,4-naphthoquinone in 60 ml. of ethanol. Dissolution occurred rapidly and the anilinoquinone began to crystallize almost at once. It recrystallized from benzene in dark red plates, with a bronze sheen, m.p. 221° (Lit.[20] m.p. 219°). Yield 86%. Similarly, the product Fries and Köhler[20] obtained by addition of aniline to 5-bromo-1,4-naphthoquinone must be 3-anilino-5-bromo-1,4-naphthoquinone.

5-Chloro-1,4-naphthoquinone-2,3-epoxide. This was prepared, as above, by treating 5-chloro-1,4-naphthoquinone (1 g.) in ethanol with alkaline hydrogen peroxide (1.78 ml., 30%). After 5 min. the oxide was precipitated by dilution with water. It crystallized from light petroleum in needles, m.p. 152–153°. Yield 74%.

Anal. Calcd. for $C_{10}H_5ClO_3$: C, 57.55; H, 2.4; Cl, 17.0. Found: C, 57.5; H, 2.7; Cl, 16.7.

5-Chloro-2-hydroxy-1,4-naphthoquinone. (*a*) The above oxide (0.8 g.) was warmed on a water bath with 3 ml. of concentrated sulfuric acid until it had all dissolved, the color changing from green to red. Ten minutes later the solution was cooled in ice and diluted cautiously with water (20 ml.). The hydroxyquinone which precipitated, crystallized from light petroleum in stout red needles, m.p. 199–200° (dec.). Yield 69%.

(*b*) The same compound was prepared from 5-chloro-1-naphthol following the method of Fieser and Brown[21] (which they used to obtain 7-chloro-2-hydroxy-1,4-naphthoquinone); intermediates were not purified. The product had m.p. 199–200°, not depressed by the above. Yield 25%.

Anal. Calcd. for $C_{10}H_5ClO_3$: C, 57.55; H, 2.4; Cl, 17.0. Found: C, 57.6; H, 2.1; Cl, 16.7.

5-Chloro-1,2-naphthoquinone. To an ice-cold solution of 3.3 g. of 5-chloro-1-naphthol and 1.27 g. of sodium nitrite in 31 ml. of 0.6*N* sodium hydroxide, 2.4 g. of concentrated sulfuric acid in 3.3 ml. of water, was added, dropwise. After stirring for 30 min., the nitroso compound was collected, washed, and dissolved in 9.5 ml. of 2*N* sodium hydroxide and 13 ml. of water. Fifteen ml. of 5*N* sodium hydroxide were then added, followed, at 35°, by 7.6 g. of sodium dithionite, in portions. On cooling, concentrated hydrochloric acid was added to precipitate the amine hydrochloride. This was recrystallized quickly from dilute hydrochloric acid (1:10), and then dissolved in 180 ml. of water containing 0.3 ml. of concentrated hydrochloric acid, at 35°, and oxidized by adding a solution of 4.3 g. of ferric chloride in 12 ml. of water and 1.3 ml. of concentrated hydrochloric acid. The crude quinone was collected, and repeatedly crystallized from ether (charcoal) in clusters of red needles, m.p. 150°. Yield 21%.

Anal. Calcd. for $C_{10}H_5ClO_2$: C, 62.35; H, 2.65. Found: C, 62.35; H, 2.7.

The *o*-quinone formed a quinoxaline with *o*-phenylene diamine, crystallizing from light petroleum in cream needles, m.p. 188°.

Anal. Calcd. for $C_{16}H_9ClN_2$: C, 72.6; H, 3.45. Found: C, 72.9; H, 3.6.

5-Chloro-3-hydroxy-1,4-naphthoquinone. The deep violet solution of 0.3 g. of 3-anilino-5-chloro-1,4-naphthoquinone in 7 ml. of concentrated sulfuric acid, was carefully diluted with 7 ml. of water, and refluxed for 10 min. After cooling and further dilution to complete precipitation of the hydroxyquinone, it was dissolved in ether (charcoal). The residue, after drying and evaporation, crystallized from light petroleum in long orange needles, m.p. 212–213°. Yield 86%.

Anal. Calcd. for $C_{10}H_5ClO_3$: C, 57.55; H, 2.4. Found: C, 57.4; H, 2.3.

Reductive acetylation afforded 1,3,4-triacetoxy-5-chloronaphthalene, crystallizing from light petroleum in needles, m.p. 137°.

Anal. Calcd. for $C_{16}H_{13}ClO_6$: C, 57.1; H, 3.9. Found: C, 57.3; H, 3.9%.

1,2,4-Triacetoxy-5-chloronaphthalene. (*a*) 5-Chloro-2-hydroxy-1,4-naphthoquinone was reduced with zinc dust, acetic anhydride, and a drop of triethylamine, in the usual

(19) This compound is 5-acetamido-2-bromo-1-naphthol: a small amount of 5-acetamido-2-bromo-1,4-naphthoquinone is also formed (K. M. Dargie and J. W. MacLeod, unpublished).

(20) K. Fries and E. Köhler, *Ber.*, **57**, 496 (1924).

(21) L. F. Fieser and R. H. Brown, *J. Am. Chem. Soc.*, 71, 3615 (1949).

way. The triacetate crystallized from light petroleum in needles, m.p. 152–153°.

(*b*) An ice-cooled suspension of 0.75 g. of 5-chloro-1,2-naphthoquinone in 1.5 ml. of acetic anhydride was treated with 2 drops of concentrated sulfuric acid. The quinone dissolved rapidly and the triacetate began to separate after 10 min. It formed needles, m.p. 153° (from light petroleum), identical with those obtained in (*a*).

Anal. Calcd. for $C_{16}H_{13}ClO_6$: C, 57.1; H, 3.9; Cl, 10.55. Found: C, 57.3; H, 4.05; Cl, 10.45.

2,5-Dichloro-1,4-naphthoquinone. Three grams of chlorine were passed into a suspension of 4 g. of 5-chloro-1,4-naphthoquinone in 80 ml. of glacial acetic acid. The quinone dissolved, the dichloride soon began to separate, and was collected after 1 hr. (5.1 g., m.p. 164–165°). This was refluxed for 10 min. in 100 ml. of glacial acetic acid containing 2.55 g. of anhydrous sodium acetate, and diluted with water. Crystallization of the precipitate from aqueous methanol afforded 2,5-dichloro-1,4-naphthoquinone in yellow plates, m.p. 98–100°. (Yield 70% from the dichloride.)

Anal. Calcd. for $C_{10}H_4Cl_2O_2$: C, 52.9; H, 1.8. Found: C, 53.0; H, 1.8. Reductive acetylation afforded 1,4-diacetoxy-2,5-dichloronaphthalene in needles, m.p. 160° (from ethanol).

Anal. Calcd. for $C_{14}H_{10}Cl_2O_4$: C, 53.7; H, 3.2. Found: C, 54.0; H, 3.2.

3-Anilino-2,5-dichloro-1,4-naphthoquinone. Aniline (1 ml.) was added to a suspension of 0.25 g. of 2,5-dichloro-1,4-naphthoquinone in 3.5 ml. of ethanol, and left overnight. The crystalline product was collected, and recrystallized from benzene in dark red needles, m.p. 220–221°. (Mixed m.p. with 3-anilino-5-chloro-1,4-naphthoquinone, 192–196°). Yield 57%.

Anal. Calcd. for $C_{16}H_9Cl_2NO_2$: C, 60.4; H, 2.85; N, 4.4. Found: C, 60.7; H, 2.29; N, 4.8.

2,5-Dichloro-3-hydroxy-1,4-naphthoquinone. (*a*) The above anilinodichloroquinone was hydrolyzed by boiling in 50% (v./v.) sulfuric acid for 10–15 min., as before. Crystallization from light petroleum, followed by sublimation *in vacuo* gave orange needles, m.p. 180–181°. Yield 33%.

(*b*) A solution of 0.18 g. of chlorine in 5 ml. of glacial acetic acid was added to 0.35 g. of finely powdered 5-chloro-3-hydroxy-1,4-naphthoquinone. The mixture was warmed for 3 hr. on the water bath and the product then isolated by pouring into water (50 ml.). Purification as above gave orange crystals, m.p. and mixed m.p. 180–181°. Yield 27%.

Anal. Calcd. for $C_{10}H_4Cl_2O_3$: C, 49.4; H, 1.65. Found: C, 49.6; H, 1.75.

5-Chloro-2 and 3-p-tolylthio-1,4-naphthoquinone. A solution of 0.33 g. of toluene-*p*-thiol in 2 ml. of methanol was added to a suspension of 0.5 g. of 5-chloro-1,4-naphthoquinone in 5 ml. of the same solvent. Next day the dark red solution was poured into an oxidizing solution of 0.6 g. of potassium dichromate, 0.3 ml. of concentrated sulfuric acid, and 5 ml. of ice water. The resulting precipitate was crystallized from methanol to give (*a*) orange-red needles and plates, m.p. 158° (49%), and (*b*) more soluble, pale orange needles, m.p. 175–176° (12%).

Anal. Calcd. for $C_{17}H_{11}ClO_2S$: C, 64.9; H, 3.5; Cl, 11.3; S, 10.2. Found: (a), C, 64.7; H, 3.25; Cl, 11.2; S, 9.7. (b), C, 64.6; H, 3.8; Cl, 10.85; S, 9.9.

Compound (*b*) was shown to be 5-chloro-2-*p*-tolylthio-1,4-naphthoquinone as follows: Solutions of 140 mg. of toluene-*p*-thiol in 1 ml. of ethanol, and 45 mg. of sodium hydroxide in 1 ml. of water, were mixed, brought to the boil, and added, all at once, to a boiling solution of 250 mg. of 2,5-dichloro-1,4-naphthoquinone in 4 ml. of ethanol, boiled for 1 min. and cooled. The product separated on cooling, and recrystallized from ethanol in pale orange needles, m.p. 175–176°, not depressed by admixture with material (*b*) obtained above. Yield 58%.

2,5-Dichloro-3-p-tolylthio-1,4-naphthoquinone. Solutions of 250 mg. of 2,5-dichloro-1,4-naphthoquinone in 4 ml. of ethanol, and 70 mg. of toluene-*p*-thiol in 1 ml. of ethanol, were mixed in the cold. After 4 hr. the red precipitate was collected and crystallized from light petroleum in lustrous, dark red needles, m.p. 148–149°. Yield 62%.

Anal. Calcd. for $C_{17}H_{10}Cl_2O_2S$: C, 58.45; H, 2.9. Found: C, 58.6; H, 3.1.

Acknowledgment. J.W.M. is indebted to Ross & Cromarty Education Committee for a Maintenance Allowance.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE PIONEERING RESEARCH LABORATORY, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Synthesis of Two Atom-Bridged Tetracyclic Ketones

H. K. HALL, JR.

August 31, 1959

Addition of acrylonitrile to bicycloheptadiene gave 6-cyano-tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonane, I, which was converted by standard reactions to tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonan-6-one, IV, and tetracyclo[3:3:1:$1^{3,9}$:$0^{2,4}$]decan-6-one, VII.

In connection with the synthesis of various atom-bridged lactams,[1] polycyclic ketones were required as intermediates. Dr. D. C. England of the Central Research Department[2] had found that acrylonitrile adds to bicycloheptadiene in a homoconjugate manner to give nitrile I (for analogous reactions see ref. 3 and 4). In the present work, this nitrile was converted to the interesting tetracyclo[3:2:1:$1^{3,3}$:$0^{2,4}$]nonan-6-one, IV, and tetracyclo[3:3:1:$1^{3,3}$:$0^{2,4}$]decane-6-one, VII, as shown in the reaction sequences diagram. Yields were mediocre, however, and no conversions to lactams were carried out.

(1) H. K. Hall, Jr., *J. Am. Chem. Soc.*, in press.
(2) Unpublished work.
(3) E. F. Ullman, *Chem. and Ind.*, 1173 (1958).
(4) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, 81, 667 (1959).

EXPERIMENTAL

6-Cyano-tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonane (I). A mixture of 500 g. (5.44 mol.) of bicycloheptadiene, 300 g. (5.66 mol.) of acrylonitrile, and 3 g. of cupric acetate was heated at 200° for 12 hr. The product was poured into 4 l. of hexane

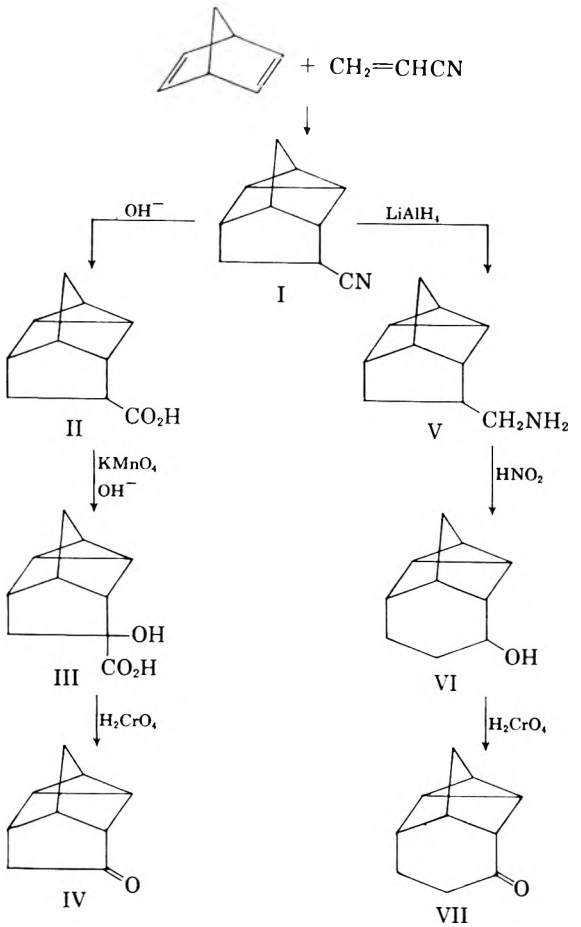


Fig. 1. Reaction sequence diagram

and filtered through Celite. The hexane was evaporated to leave 160 g. of crude product. This was dissolved in 300 ml. of acetone and to it was added, with stirring, a solution of 100 g. of potassium permanganate and 100 g. of anhydrous magnesium sulfate in 3.2 l. of water. A permanent purple color was reached, and the mixture was decolorized with sulfur dioxide. The salts were filtered and rinsed with hexane. The filtrate was extracted with hexane and the combined hexane extracts were dried and distilled to give 98.0 g. (12.4%) of I, b.p. 124–127° (17 mm.), n_D^{25} 1.5053.

Anal. Calcd. for $C_{10}H_{11}N$: N, 9.66. Found: N, 9.55.

Tetracyclo[3:2:1^{3,8}:0^{2,4}]nonane-6-carboxylic acid (II).[5] A solution of 95.0 g. (0.65 mol.) of nitrile II, 90.0 g. of sodium hydroxide, 100 ml. of ethanol, and 260 ml. of water was boiled for 50 hr. under reflux. The ethanol was distilled and the residue was cooled and extracted with two 100 ml. portions of ether, which were discarded. The aqueous layer was acidified with sulfuric acid and was again extracted twice with 100 ml. portions of ether. The ether extracts were dried and distilled to give 47 g. (43.6%) of II, b.p. 106–107° (0.25 mm.), n_D^{25} 1.4972.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.1; H, 7.4. Found: C, 72.6, 72.8; H, 7.33, 7.33.

The acid solidified on standing, m.p. 55–58°. Recrystallization from hexane raised the melting point to 61–62°.

6-Hydroxy-tetracyclo[3:2:1:1^{3,8}:0^{2,4}]nonane-6-carboxylic acid (III). Hydroxylation of acid II was carried out according to Kenyon and Symons.[6] To a solution of 41.0 g. (0.25 mol.) of II and 500 g. of potassium hydroxide in 625 ml. of water was added with stirring a solution of 78.7 g. of potassium permanganate and 250 g. of potassium hydroxide in 1.5 l. of water over 20 min. The temperature was not allowed to exceed 43°. Stirring was continued for an additional 45 min. The deep green solution was decolorized with excess sulfur dioxide. The mixture was filtered through Celite and the filtrate was extracted with 1 l. of ether. Drying and evaporation of this gave in two crops 11.11 g. of recovered acid II, m.p. 64–66°, undepressed when mixed with starting material.

Acidification of the aqueous layer with 1 l. of 6*M* sulfuric acid and extraction with three 70 ml. portions of ether led to an oil which crystallized on keeping for several hours. Recrystallization from hexane-benzene gave a first crop of 4.34 g. white crystals of III, m.p. 110–115° and a second crop of 1.23 g. (combined yield 16.9%), m.p. 102–110°.

Anal. Calcd. for $C_{10}H_{12}O_3$: O, 26.6. Found: O, 26.32.

Tetracyclo[3:2:1:1^{3,8}:0^{2,4}]nonanone-6 (IV). The two crops of hydroxyacid were added to a solution of 9.4 g. of potassium dichromate and 4.3 ml. of 96% sulfuric acid in 50 ml. of water.[7] The mixture was warmed on the steam bath for 30 min., at which time no more carbon dioxide was evolved. The mixture was cooled and extracted with 100 ml. of hexane. The hexane layer was washed with 5% sodium hydroxide, water, 5% hydrochloric acid, water, and was then dried and distilled in a small Claisen flask. There was obtained 1.37 g. (33.0%) of ketone IV, b.p. 104° (19 mm.), n_D^{25} 1.5225.

Anal. Calcd. for $C_9H_{10}O$: O, 11.9. Found: O, 11.97.

6-Aminomethyl-tetracyclo[3:2:1:1^{3,8}:0^{2,4}]nonane (V). To a stirred mixture of 15.5 g. of lithium aluminum hydride and 150 ml. of ether was added, over 30 min. with stirring and refluxing, a solution of 97.0 g. (0.670 mol.) of nitrile I in 150 ml. of ether. The mixture was stirred for 5 hr. and was then decomposed with 150 ml. of ice and water. A solution of 80 g. of sodium hydroxide in 250 ml. of water was added and the mixture was steam-distilled until 2 l. of distillate had been collected. The latter was extracted three times with 400 ml. portions of ether, which were dried over magnesium sulfate, evaporated and distilled through a spinning band column. This gave 27.5 g. (30.7%) of amine V, b.p. 109–112° (17 mm.), n_D^{25} 1.5110, an intermediate fraction weighing 5.5 g., and 9.9 g. of recovered nitrile, b.p. 124–127° (17 mm.).

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.43.

Fraction 1, 26.4 g. when mixed with a solution of *p*-toluenesulfonic acid monohydrate in 230 ml. of ethyl acetate, gave a crystalline precipitate weighing 31.2 g., m.p. 155–156°. Addition of hexane to the filtrate precipitated an additional 18.6 g., m.p. 138.0–138.5°. Similarly, from fraction 2 was obtained 2.5 g. of salt, m.p. 155–157°.

Anal. Calcd. for $C_{17}H_{23}NO_3S$: O, 14.93. Found: O, 14.91.

Tetracyclo[3:3:1:1^{3,9}:0^{2,4}]decane-6-ol (VI). The three crops of hydrotosylate were combined (0.163 mol.) and submitted to the Demjanov rearrangement according to Alder and Windemuth.[8] The product was distilled in a small spinning band column to give, after 4.2 g. of forerun, 7.5 g. (30.7%) of alcohol VI, b.p. 128° (22 mm.), n_D^{25} 1.5240.

Anal. Calcd. for $C_{10}H_{14}O$: O, 10.65. Found: O, 11.04.

A vapor phase chromatogram showed the presence of three components. Peak 1 (3.4%) is an impurity, while peaks 2 (5.4%) and 3 (91.2%) appear from the oxidation results (see below) to be the isomeric alcohols.

Tetracyclo[3:3:1:1^{3,9}:0^{2,4}]decane-6-one (VII). Oxidation of alcohol VI gave ketone VII in 49.1% yield, b.p. 126–129° (20 mm.), n_D^{25} 1.5138.

Anal. Calcd. for $C_{10}H_{12}O$: O, 10.8. Found: O, 11.42.

A vapor phase chromatogram showed the presence of two components in amounts of 5.8% and 94.2%.

(5) This compound was first prepared by Dr. H. E. Knipmeyer of the Central Research Department.

(6) J. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 2129 (1953).

(7) I am indebted to Prof. Harold Kwart for suggesting this procedure.

(8) K. Alder and E. Windemuth, *Ber.*, 71B, 1939, 2404 (1938).

The major constituent of the ketone was established as the 6- rather than the 7-keto derivative by formation of a monobenzal derivative, no dibenzal derivative being isolated.

The ketone, 470 mg. (3.17 mmol.) was dissolved in 5 ml. of 5% potassium hydroxide in methanol[9] and 1.1 ml. of benzaldehyde was added. After 20 hr. the mixture was diluted with 11 ml. of water and extracted with 10 ml. of hexane. The hexane layer was dried over magnesium sulfate and concentrated. Excess benzaldehyde was removed by maintaining the residue at 60° (0.25 mm.) for several hours. The cooled semicrystalline residue was recrystallized twice from 3 ml. portions of hexane to give 0.151 g. (0.639 mmol., 20.1%) of pale yellow monobenzal derivative, m.p. 74.0–77.0°.

Anal. Calcd. for $C_{17}H_{16}O$: O, 6.77. Found: O, 6.63.

The infrared spectra of all compounds encountered in this investigation were measured routinely and supported the proposed structures. In particular, these nortricyclene derivatives absorbed at 12.3–12.4 microns, as first noted by Roberts and co-workers.[10]

Acknowledgment. I am deeply indebted to the following individuals and their associates: to Mr. I. D. Plank for the microanalyses, Mr. H. E. Cupery for the pressure reactions, Mr. H. Thielke for the vapor phase chromatograms, Dr. D. C. England and Dr. H. E. Knipmeyer for permission to mention their unpublished work, to Mr. George Elechko for excellent technical assistance, and to Dr. P. W. Morgan for unfailing encouragement.

WILMINGTON 98, DEL.

(9) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958); K. Alder and R. Reubke, *Chem. Ber.*, **91**, 1525 (1958).

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

[CONTRIBUTION FROM THE "ASSIA" CHEMICAL LABORATORIES LTD.]

α-Hydrazino- Acids. I. α-Hydrazinoaliphatic Acids and α-(1-Methylhydrazino)aliphatic Acids

A. CARMI, G. POLLAK, AND H. YELLIN

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An improved method for the preparation of α-hydrazino-aliphatic acids is presented. The reaction is extended to the preparation of α-(1-methylhydrazino)-aliphatic acids, the structures of which are proved. The ultraviolet spectra are described.

Thiele[1] prepared α-hydrazinoisobutyric acid by the action of acetone semicarbazone on hydrocyanic acid. He also synthetized[2] α-hydrazinopropionic acid starting from acetaldehyde. Traube *et al.*[3] described the preparation of a series of α-hydrazino-aliphatic acids by the reduction of the isonitramino acids. Darapski *et al.*,[4] Bailey,[5] and Berger[6] obtained these compounds by the action of α-bromo acids on excess hydrazine in alcohol or in water.

Our interest in these compounds and their derivatives stems from their possible use as antimetabolites, especially in cancer chemotherapy.

We found the Darapski method convenient for the preparation of some of the higher members, as these hydrazino acids crystallize directly from the aqueous reaction mixture in fair yield. However, the preparation of the α-hydrazino acetic, propionic, and isobutyric acids is extremely cumbersome, requiring a Fischer esterification and a subsequent tedious saponification with barium hydroxide.

We found that by the use of ion exchange resins the isolation of these compounds is considerably simplified and the yields increased. When a weak anion exchanger is used, the addition of acetone is necessary to bind the hydrazine in the form of the ketazine, thus making the acid available for absorption on a weak anion exchanger (Method A).

The hydrazino acids are also absorbed on strong cation exchange resins, from which they can be eluted with ammonia and recovered by evaporation of the effluent (Method B). The yields by both methods are almost identical.

However, hydrazineacetic acid is not obtained directly in the highest purity by these methods. The preparation of the ester hydrochloride is still required, but saponification is conveniently carried out by a strong cation exchanger.

Berger[6] made a thorough study of the reaction between α-bromo-α-ethylbutyric acid and hydrazine and obtained α-hydroxy-α-ethylbutyric acid as the only product. He also failed to prepare the hydrazino diethylacetic acid by other methods and attributed the "non-formation" of this hydrazino acid to the influence of the tertiary carbon

(1) J. Thiele and K. Heuser, *Ann.*, **290**, 38 (1896).

(2) J. Thiele and J. Bailey, *Ann.*, **303**, 85 (1898).

(3) W. Traube and G. G. Longinescu, *Ber.*, **29**, 673 (1896); W. Traube and E. Hoffa, *Ber.*, **29**, 2729 (1896); W. Traube and E. Hoffa, *Ber.*, **31**, 146 (1898).

(4) A. Darapski and M. Prabhakar, *Ber.*, **45**, 1660 (1912); A. Darapski and M. Prabhakar, *J. prakt. Chem.*, **96**, 280 (1917); A. Darapski, *J. prakt. Chem.*, **146**, 219 (1936).

(5) J. Bailey and W. T. Read, *J. Am. Chem. Soc.*, **36**, 1758 (1914); J. Bailey and L. A. Mikeska, *J. Am. Chem. Soc.*, **38**, 1771 (1916).

(6) H. Berger, *J. prakt. Chem.*, **152**, 309 (1939).

TABLE I

α-1-METHYLHYDRAZINO ACIDS

Parent Acid[a]	M.P.,[b] °C.	Yield, %	Formula	Analysis N, % Calcd.	Analysis N, % Found[c]	m-Nitrobenzal Hydrazones M.P., °C.[b]
1. Acetic[d]	153–154	54	$C_3H_8N_2O_2$	26.9[e]	26.9	128–130
2. Propionic[d]	145	42	$C_4H_{10}N_2O_2$	23.7	23.7	115–117
3. n-Butyric[f]	122–124	47	$C_5H_{12}N_2O_2$	21.2	21.4	82–83
4. Isobutyric[f]	163–165	20	$C_5H_{12}N_2O_2$	21.2	21.2	121–123
5. n-Valeric[f]	123–124	28	$C_6H_{14}N_2O_2$	19.2	19.0	83–85
6. Isovaleric[f]	188–191	33	$C_6H_{14}N_2O_2$	19.2	19.3	74–75
7. n-Caproic[f]	130–132	27	$C_7H_{16}N_2O_2$	17.5	17.5	88–90
8. Isocaproic[g]	146–148	25	$C_7H_{16}N_2O_2$	17.5	17.8	85–87

[a] Procedures for representative compounds are described in the experimental part. [b] Uncorrected. [c] Analyses by Mr. E. Meier of the Microanalytical Department, Weizmann Institute of Science, Rehovoth, Israel. [d] Crystallized from absolute ethanol. Calcd.: C, 34.7; H, 7.74. Found: C, 34.5; H, 7.74. [f] Crystallized from isopropyl alcohol. [g] Crystallized from water.

atom in the α-position. The ready formation of α-hydrazino isobutyric acid was regarded by Berger as an exception.

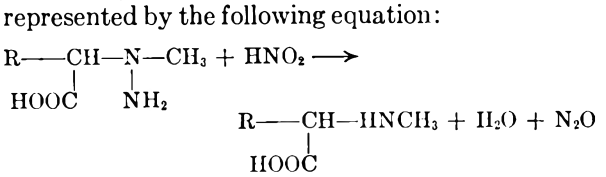
On repeating Berger's experiment and using our procedure we obtained α-hydrazino-α-ethylbutyric acid in fair yield, while the α-hydroxy acid and α-ethylcrotonic acid were side products. The latter seems to be formed directly by the dehydrobromination of α-bromo-α-ethylbutyric acid.

Working with a large excess of hydrazine in the cold the yield of α-hydrazino-α-ethylbutyric acid increases considerably.

α-Hydrazino-α-ethylbutyric acid shows properties similar to those of α-hydrazinoisobutyric acid.[1] At pressures of *ca.* 1 mm. it sublimes without decomposition (also observed by us in the case of hydrazinoisobutyric acid).

The above procedure was extended to the reaction between α-halo acids and methylhydrazine. Considering the electron-donating properties of the methyl group[7] it was expected that substitution would occur at the methyl bearing nitrogen. However, in view of the known exceptions to this rule,[8] we proceeded to prove the structure of the compounds by independent means. Attempts to reduce the N—N linkage with chromous chloride, titanous chloride and other reducing agents proved unsuccessful.

One line of evidence relies on the reaction with nitrous acid, in which gas is evolved and the corresponding *N*-methylamino acid isolated from the solution in almost theoretical yield. This was proved for α-(1-methylhydrazino)-acetic and -propionic acids. In analogy to the action of nitrous acid on *N*,*N*-diethylhydrazine[9] the reaction may be represented by the following equation:



(7) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, 80, 1895 (1958).

(8) Emil Fischer, *Ann.*, 190, 67 (1878).

(9) Emil Fischer, *Ann.*, 199, 308 (1879).

Confirmation of the structure was obtained by the reductive cleavage of the N—N bond with a large excess of Raney nickel in alcohol, a method used by Ainsworth and by Hinman.[10] All the compounds tested, *viz.* α-(1-methylhydrazino)-acetic, -propionic and -butyric acids gave ammonia in 80–90% yield.

The above proves conclusively that the compounds obtained by reaction of the halo acids with methylhydrazine have both substituents on the same nitrogen and are essentially free from isomers.

In view of this evidence it is surprising that it was not always possible to obtain the common hydrazones with benzaldehyde, salicylaldehyde etc. However, the *m*-nitrobenzaldehyde derivatives were readily obtained in good yield.

We have prepared the α-(1-methylhydrazino) acids described in Table I. All the compounds listed dissolve readily in water, giving practically neutral solutions, as can be expected from zwitter ions. The compounds are unstable in presence of air and reduce iodine and Fehling's solutions readily.

All the α-(1-methylhydrazino)-aliphatic acids and some α-hydrazino acids were submitted to the Sloan Kettering Institute for Cancer Research, New York, for tests.

Ultraviolet Spectra. The absorption of α-hydrazino and α-(1-methylhydrazino)-aliphatic acids was measured in the region between 220–350 mμ. Aliphatic acids, amino acids, and various hydrazine derivatives show no characteristic absorption in this region.[11–14] The α-hydrazino acids fall in line with these compounds (λ_{max} 276–278 mμ, ϵ_{max} 3–5).

(10) C. Ainsworth, *J. Am. Chem. Soc.*, 76, 5774 (1954); C. Ainsworth, *J. Am. Chem. Soc.*, 78, 1635 (1956); R. L. Hinman, *J. Org. Chem.*, 22, 148 (1957).

(11) G. A. Anslow, H. T. Hsieh, and R. C. Shea, *J. Chem. Phys.*, 17, 426 (1949).

(12) L. J. Seidel, A. R. Goldfarb, and S. Baldman, *J. Biol. Chem.*, 197, 285 (1952).

(13) Houben-Weyl, *Die Methoden der Organischen Chemie*, 3rd ed., III/2, page 704.

(14) P. Grammaticakis, *Bull. soc. chim. France*, 17, 690 (1950).

However the straight chain α-(1-methylhydrazino)-acids unexpectedly possess an appreciable absorption coefficient, and the absorption maximum shifts to longer wave lengths with increasing molecular weight (λ_{max} 285–332 mμ, ϵ_{max} 69–140). The corresponding branched chain acids absorb at shorter wave lengths and with much lower intensity (λ_{max} 299–325 mμ, ϵ_{max} 6–63).

EXPERIMENTAL[15]

Ethyl hydrazineacetate hydrochloride. To 500 g. (5 mol.) of 32% aqueous hydrazine was added gradually 94.5 g. (1 mol.) monochloroacetic acid. After 48 hr., 85 g. (approx. 2 mol.) sodium hydroxide was added and the solution distilled *in vacuo* to dryness (4 mol. of hydrazine was recovered). The residue was treated with 650 ml. ethanolic HCl (approx. 30% w./v.), refluxed gently, cooled, and saturated with gaseous HCl for 2 hr. The solution was boiled with 500 ml. absolute alcohol and filtered hot. The ester hydrochloride crystallized, yielding 103 g. (66.5%), m.p. 150–152° (lit. 150–153°[3]).

Hydrazineacetic acid. A solution of 46.5 g. (0.3 mol.) ethyl hydrazineacetate hydrochloride in 350 ml. water was refluxed with stirring in the presence of 15 g. Duolite C 20[16] (acid form) for 3 hr. The filtered solution was passed through a Duolite A 7[16] column (alkaline form), the effluent concentrated *in vacuo* to 50 g. and added dropwise into 250 ml. absolute alcohol. The crude acid was recrystallized from 20 ml. hot water and dried *in vacuo* over P_2O_5. The yield was 10 g. (37%), m.p. 152° (lit. 152° dec.[3]). From the mother liquor an additional 10 g., m.p. 145–147° was precipitated by ethanol.

Method A: α-hydrazinopropionic acid. To 150 ml. (2.3 mol.[17]) of 50% aqueous hydrazine was added gradually 51 g. (0.33 mol.) of α-bromopropionic acid and the mixture was allowed to stand for 24 hr. Excess hydrazine was distilled *in vacuo*. The residue was dissolved in 600 ml. water and 100 ml. acetone was added, lowering the *p*H from 8 to 4. The solution was passed through a Duolite A 7 column and concentrated *in vacuo* to dryness. The residue was dissolved in 40 ml. water and added dropwise into 500 ml. of absolute alcohol. The yield was 15 g. (48%), m.p. 182° (lit. 180°[6]). A second crop of 4 g. was obtained from the mother liquors. The *m*-nitrobenzal derivative crystallized from aqueous alcohol, m.p. 118–120°.

Method B: α-hydrazinoisobutyric acid. To 100 ml. (0.5 mol.) 16% aqueous hydrazine was added gradually 16.7 g. (0.1 mol.) of α-bromoisobutyric acid and allowed to stand for 48 hr. Excess hydrazine was distilled *in vacuo*, the residue dissolved in 200 ml. water and passed through a Duolite C 20 column. On evaporating the acid effluent 1.1 g. of a crystalline solid, m.p. 77–79° was isolated, which was identified as α-hydroxyisobutyric acid. After washing the column with water to neutrality, 700 ml. 4% ammonia was passed and the eluate concentrated to dryness. The solid residue was dissolved in 15 ml. water and 50 ml. absolute alcohol added, giving 3.6 g. (30.5%) product, m.p. 238–240° (lit. 237°[4]).

Method B: α-hydrazino-α-ethylbutyric acid. One tenth of a mole (19.5 g.) α-bromo diethylacetic acid was added dropwise with cooling to 64 g. (1 mol.) of 50% aqueous hydrazine. The reaction mixture was worked up as described under α-hydrazinoisobutyric acid. The acid effluent yielded 0.8 g. (6%) α-hydroxy-α-ethylbutyric acid, m.p. 79–80° (lit. 79–80°[18]). A mixed m.p. with an authentic sample showed no depression. From the alkaline eluate 10.3 g. (70%) α-hydrazino-α-ethylbutyric acid was obtained, m.p. (closed capillary) 225°.

Anal. Calcd. for $C_6H_{14}N_2O_2$: C, 49.3; H, 9.7; N, 19.2; O, 21.9. Found: C, 48.8; H, 9.7; N, 19.5; O, 22.4.

The *m-nitrobenzal derivative* melted at 112–114°.

Berger's procedure: α-hydrazino-α-ethylbutyric acid. To 32 g. (0.5 mol.) 50% aqueous hydrazine and 43 ml. of water was added dropwise 30 g. (0.154 mol.) α-bromodiethylacetic acid. The temperature rose to 70°. After 24 hr. the mixture was acidified with dilute hydrochloric acid to Congo red and 4.2 g. of an oil separated. This oil was brominated in carbon tetrachloride at −10°, whereby 2.95 g. of bromine was absorbed, giving, after crystallization from ether-ligroin, 2.5 g. of 2,3-dibromo-2-ethylbutyric acid, m.p. 116–117° (lit. 116.5°[19]), identified by a mixed m.p. with an authentic sample. The aqueous layer was extracted with ether, which on evaporation left 8.1 g. residue. By crystallization from petroleum ether 5.3 g. α-hydroxydiethylacetic acid was isolated. From the petroleum ether mother liquors 0.9 g. of an oil was recovered, which yielded on bromination 2.3 g. 2,3-dibromo-2-ethylbutyric acid.

The extracted aqueous layer was then passed through Duolite C 20 (acid form) and worked up as described under "Method B," yielding 8.3 g. (37%) of α-hydrazino α-ethylbutyric acid, m.p. 225°, identical with the compound obtained above.

Method A: α-(1-methylhydrazino)acetic acid. To 36 g. (0.76 mol.) methylhydrazine in 200 ml. water was added gradually 13.5 g. (0.143 mol.) monochloroacetic acid and left at room temperature for 4–5 days. The solution was worked up as described under α-hydrazinopropionic acid. The product was crystallized from absolute ethanol. Yield 8 g. (54.5%); m.p. 153–154°.

Method B: α-(1-methylhydrazino)isovaleric acid. To 18.5 g. (0.4 mol.) methylhydrazine in 200 ml. water was added gradually 18.2 g. (0.10 mol.) α-bromoisovaleric acid and left at room temperature. After 3 days, the solution was worked up as described under method B for α-hydrazinoisobutyric acid. The product was crystallized from 20 ml. water. Yield 33%.

Reaction of α-(1-methylhydrazino)propionic acid with sodium nitrite. A solution of 2.6 g. (0.022 mol.) α-(1-methylhydrazino)propionic acid in 20 ml. water was treated with 2 ml. acetic acid and 2.5 g. (0.018 mol.) sodium nitrite in 10 ml. water. After 30 min. the solution was made up to 50 ml. and passed through a column of Duolite C 20 (acid form). The alkaline eluate was concentrated *in vacuo*. A solid was obtained, which was identified by mixed m.p. (300–303° subl.) as *N*-methylalanine. Yield 1.5 g. (63%).

Acknowledgments. The authors wish to thank The "ASSIA" Chemical Laboratories Ltd. for making their laboratories available for this work. Thanks are also due to Dr. S. Sarel for useful discussion, and to Messrs. E. Levy and Y. Shvo for their help.

TEL-AVIV, ISRAEL

(15) All melting points are uncorrected.

(16) Manufactured by Chemical Process Co., Redwood City, Calif., U.S.A.

(17) The concentrations of hydrazine and methylhydrazine have, as far as we could observe, little effect on the yields.

(18) F. Tiemann and P. Friedlaender, *Ber.*, 14, 1974 (1881).

(19) R. Fittig, *Ann.*, 334, 102 (1904).

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Phenylnitromethane. I. An Improved Synthesis of α-Nitrostilbenes

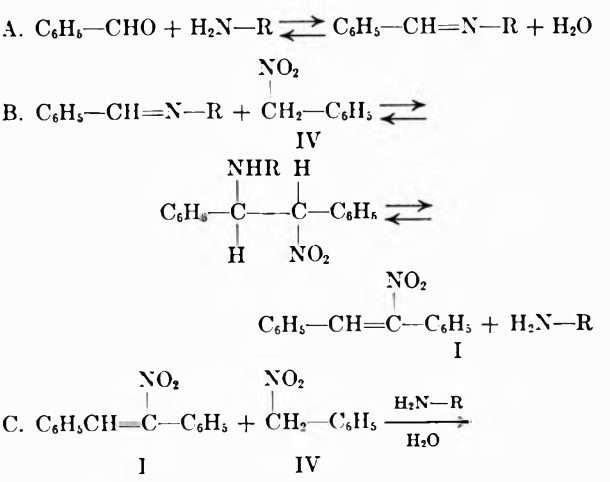
DALE N. ROBERTSON

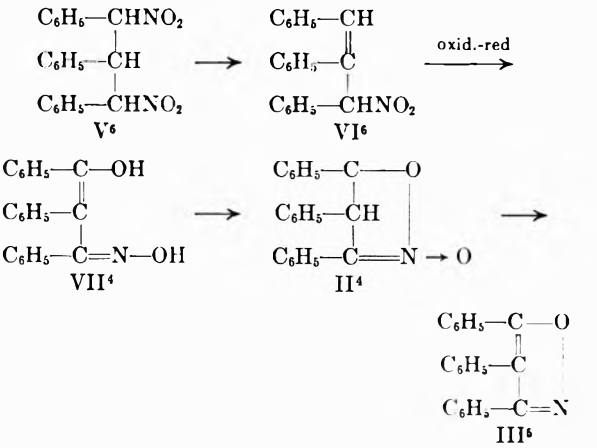
Received August 4, 1959

An improved synthesis of α-nitrostilbenes has been developed. High yields of pure products have been obtained by using Schiff's bases of aromatic aldehydes as intermediates and conducting the condensation with phenylnitromethane in acetic acid. The usual by-products, triphenylisoxazoline oxides and triphenylisoxazoles, are thus avoided. Comparative data with previous methods is included in tabular form. Nineteen new α-nitrostilbenes are reported.

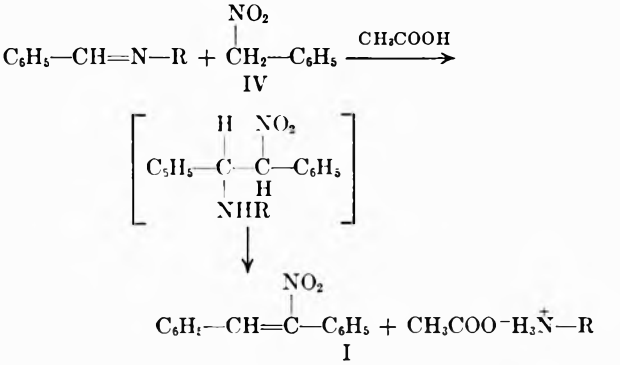
α-Nitrostilbenes have been prepared by the primary amine catalyzed condensation of aromatic aldehydes with phenylnitromethane[1] (α-nitrotoluene). Low yields are frequently encountered[1,2,3] and long reaction times (3–8 days) are usually required.[1,3] In addition, α-nitrostilbenes readily add phenylnitromethanes in the presence of ammonia[4] or aliphatic amines[5] to give, ultimately, triphenylisoxazoline oxide and triphenylisoxazole which are often troublesome by-products in the purification of α-nitrostilbenes.

α-Nitrostilbene (I) forms an isolatable addition product with piperidine and certain aromatic amines.[5] The adduct with piperidine is readily converted to triphenylisoxazoline oxide (II) and triphenylisoxazole (III). The reaction of other aliphatic amines with I leads directly to II and III, the adducts apparently being too unstable to isolate. Dornow and Boberg[5] have shown that the adduct of I with aniline can also be prepared in good yield by the reaction of phenylnitromethane (IV) with benzalaniline. I with IV in alcoholic ammonia gives II and III.[4] It seems clear, therefore, that the Knoevenagel reaction with aromatic aldehydes and phenylnitromethane, when catalyzed by primary amines, may be written as:





In considering this reaction, it was felt that a distinct improvement could be made by eliminating the water formed in reaction A and by tying up the basic amine formed in reaction B, thus excluding by-product formation according to reaction sequence C. This was readily accomplished by first forming the Schiff's base and contacting it with a solution of IV in an excess of glacial acetic acid at room temperature. The reaction may be represented by:

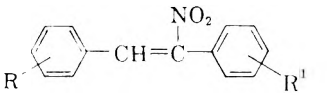


Crowell and Peck[7] conducted a kinetic study of the Knoevenagel reaction between nitromethane (VIII) and piperonal (IX) using butylamine (X) as catalyst, concluding that the Schiff's base was an intermediate. The Schiff's base reacted rapidly with VIII when catalyzed by butylammonium acetate whereas IX did not.

(1) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).
(2) C. T. Bahner, H. E. Dickson and L. Moore, *J. Am. Chem. Soc.*, **70**, 1982 (1948).
(3) P. Ruggli and B. Hegedus, *Helv. Chim. Acta*, **22**, 405 (1939).
(4) D. E. Worrall, *J. Am. Chem. Soc.*, **57**, 2299 (1935).
(5) A. Dornow and F. Boberg, *Ann.*, **578**, 94 (1952).
(6) F. Hein, *Ber.*, **44**, 2021 (1911).
(7) T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

TABLE I

SUBSTITUTED α-NITROSTILBENES[a]



	R	R¹	Reaction Time[b]	Yield, %[c]	M.P.[d]	Formula	Chlorine, % Calcd.	Found
XI	2-Chloro	—	C	87.3[e]	90–91	$C_{14}H_{10}ClNO_2$	13.65	13.37
			C	81.8				
XII	4-Chloro	—	B	74.7	113–114	$C_{14}H_{10}ClNO_2$	13.65	13.28
XIII	—	2-Chloro	C	54.6	92.8–93.5	$C_{14}H_{10}ClNO_2$	13.65	13.39
XIV	2,4-Dichloro	—	D	83.7	121–123	$C_{14}H_8Cl_2NO_2$	24.11	24.14
XV	3,4-Dichloro	—	C	65.3	110	$C_{14}H_8Cl_2NO_2$	24.11	23.84
XVI	2,6-Dichloro	—	D	83	136–136.5	$C_{14}H_8Cl_2NO_2$	24.11	24.00
XVII	2-Chloro	2-Fluoro	D	68.5	84.5–85.5	$C_{14}H_8ClFNO_2$	12.77	12.60
XVIII	2-Chloro	2-Chloro	A	63.3	120.5–121.5	$C_{14}H_8Cl_2NO_2$	24.11	24.66
XIX	2-Methoxy	2-Chloro	A	74.5	152–153	$C_{15}H_{12}ClNO_3$	12.24	12.14
XX	2-Ethoxy	2-Chloro	A	77	120–121	$C_{16}H_{14}ClNO_3$	11.67	11.41
XXI	2-Nitro	2-Chloro	E	80.8	155.8–156.6	$C_{14}H_8ClN_2O_4$	11.64	11.69
XXII	2,4-Dichloro	2-Chloro	B	78.3	90–91	$C_{14}H_8Cl_3NO_2$	32.37	32.12
XXIII	2,6-Dichloro-3-hydroxy	—	C	91 (crude)	170–171.3	$C_{14}H_9Cl_2NO_3$	22.86	22.48
							Bromine, % Calcd.	Found
XXIV	2-Bromo	—	B	85.6	91.5–92.5	$C_{14}H_{10}BrNO_2$	26.28	26.79
							Nitrogen, % Calcd.	Found
XXV	4-Carboethoxymethoxy	—	D	52	69.5–70.5	$C_{18}H_{17}NO_5$	4.28	4.43
XXVI	2-Ethoxy	—	A	67.1	108.7–109.4	$C_{16}H_{15}NO_3$	5.20	5.08
XXVII	2,4,6-Trimethyl	—	C	81.2	115–116	$C_{17}H_{17}NO_2$	5.24	5.32
							Carbon, % Calcd.	Found
XXVIII	2-Fluoro	—	C	51.8	79–80	$C_{14}H_{10}FNO_2$	69.12	69.12
XXIX	4-Hydroxy	—	F	33.2	144.5–147	$C_{14}H_{11}NO_3$	69.94	69.71

[a] Recrystallized from ethanol or acetic acid. [b] A = 5–30 min.; B = 2–7 hours; C = overnight; D = over weekend; E = 1 min. at 125°; F = 1 week. [c] With one exception yields are of purified product. [d] Determined in a Townson and Mercer Mark 4 melting point apparatus. [e] Schiff's base made with *n*-propylamine.

In view of the above, an attempt was made to condense IV with benzalbutylamine in methanol using butylammonium acetate as catalyst. No crystalline product could be isolated.

The reaction between benzaldehyde, IV and one equivalent of butylammonium acetate in acetic acid was very slow. Crystallization could not be induced (seeding) after 3 hr. and 20 hr. were required to obtain a 53.7% yield. Benzalbutylamine and IV in acetic acid began to deposit crystals (on seeding) after 30 min. and a yield of 60.8% was obtained in only 2 hr. A commercial grade of IV was used in these two reactions which probably accounts for the lower yields (compare XXX in Table II).

Raiford and Fox[8] used the system ammonium-acetate–acetic acid for the condensation of aromatic aldehydes with nitroalkanes to form β-nitrostyrenes, a method which bears some resemblance to the Schiff's base method of the present report. As commonly carried out, however, the method of Raiford and Fox often gives tars and low yields and seems to work best for hydroxy and alkoxy benzaldehydes. It was not satisfactory for the preparation of α-nitrostilbenes.

The method of Heinzelmann[9] for nitrostyrenes, wherein the condensation of a primary nitroparaffin with an aromatic aldehyde is carried out in an inert solvent and the water of reaction is removed azeotropically, likewise was not satisfactory for α-nitrostilbenes.

Adaptation of the Schiff's base method to the preparation of β-nitrostyrenes was not extensively investigated, although it has given good results in some cases[10] where the usual alkali hydroxide or amine catalyzed condensations were unsatisfactory and spectroscopic evidence (infrared) suggests that it may be widely applicable.

The Schiff's bases are conveniently formed by reaction of equimolar amounts of the appropriate aldehyde and amine in benzene solution, (200–500 ml. per mole of reactants) the water of reaction being removed by azeotropic distillation. In practice, it has been found best to remove the sol-

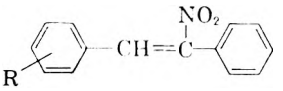
(8) L. C. Raiford and D. E. Fox, *J. Org. Chem.*, 9, 170 (1944).

(9) R. V. Heinzelmann, U. S. Patent 2,601,282 (June 24, 1952).

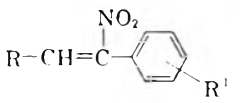
(10) D. N. Robertson, U. S. Patent 2,855,429 (October 7, 1958).

TABLE II

COMPARATIVE YIELDS: LITERATURE VS. SCHIFF'S BASE METHOD



	R[a]	Literature Yield, %	Literature Time, Hr.	Literature M.P.	Via Schiff's Base Yield,[b] %	Via Schiff's Base Time, Hr.	Via Schiff's Base M.P., °C.[c]
XXX	H[d]	60–70	8 days	75	88	88	73–74
					80.4	2	73–74
XXXI	2-Methoxy[e]	85	15	117.5–119	74	0.5	117.5–118
XXXII	4-Methoxy[d]	85	8 days	151	74.5	0.5	153
XXXIII	3,4-Dimethoxy[f]	Quant.	7 days	109	58.2	20	107–108
XXXIV	3,4-Methylenedioxy[d]	82	8 days	124	63.2	2	129–129.5
XXXV	3-Methoxy-4-hydroxy[g]	24	2–4 days	124.8–125.5	24.3	14 days	124–125
XXXVI	2-Methyl[h]	Not given	Not given	99	56.3	20	98.5–99.5
XXXVII	4-Methyl[h]	85	3–5 days	79	83.7	0.5	73–75.5
XXXVIII	2-Nitro[i]	21.5	72	106	45.2	0.5	101.5–102.5
XXXIX	3-Nitro[j]	7.5	96	112	71.8	20	112.8–113.8
XL	4-Nitro[k]	Not given	24	155	64.8	2.5	159.3–159.8



	R	R′						
XLI	2-Furfuryl[l]	—	93 (crude)	72	87–87.5	81.3	0.25	87.5–88
XLII	2-Thienyl[j]	—	32.3	3	123	81.4	2	126.5–127
XLIII	2-Furfuryl[j]	2-Chloro	34.9	72	101.1	82.4	0.2	103–104

[a] Recrystallized from ethanol or acetic acid. [b] Yields are of purified product. [c] Determined in Townson and Mercer Mark 4 melting point apparatus. [d] E. Knoevenagel and L. Walter, *Ber.*, **37**, 4508 (1904). [e] W. D. McPhee, E. S. Erickson, Jr., U. J. Salvador, *J. Am. Chem. Soc.*, **68**, 1866 (1946). [f] H. Kaufmann, *Ber.*, **52**, 1431 (1919). [g] R. Stewart and R. H. Clark, *Can. J. Res.*, **26B**, 7 (1948). [h] J. Meisenheimer, *et al.*, *Ann.*, **468**, 222 (1929). [i] P. Ruggli and B. Hegedus, *Helv. Chim. Acta*, **22**, 405 (1939). [j] C. T. Bahner, H. E. Dickson and L. Moore, *J. Am. Chem. Soc.*, **70**, 1982 (1948). [k] J. W. Baker and I. S. Wilson, *J. Chem. Soc.*, 844 (1927). [l] B. Reichert and W. Kuhn, *Ber.*, **74B**, 328 (1941).

vent prior to the next step in order to facilitate the work-up. It is not necessary to purify the Schiff's base, which may be poured directly into a solution of IV in glacial acetic acid (250 ml. per mol of IV is a convenient quantity). Although 0.5 to 2 hr. is usually sufficient reaction time (see Tables I and II), allowing the reaction to proceed overnight or even longer may give slightly higher yields (see Example XXX). Low yields and long reaction times were encountered only with the hydroxybenzaldehydes (XXIX and XXXV).

Room temperature is usually preferred. Lower yields were encountered in two experiments in which the reactants were brought to the boiling point and immediately quenched by pouring over crushed ice. In one instance, however, good results were obtained by a one minute reaction time at 125° (XXI).

Because of its availability, *n*-butylamine was used almost exclusively. A Schiff's base with *n*-propylamine was used once as a check and gave slightly better results under the same conditions (XI).

The presence of ethanol in the reaction mixture is definitely detrimental. In one preparation of XI a little alcohol was added to the reaction mixture and the yield was reduced (26.5%). A lower than average yield of XXXVIII was obtained and here again ethanol had been added during the reaction. The products, however, are stable in both ethanol and acetic acid, the preferred solvents for recrystallization.

EXPERIMENTAL

Schiff's bases. General procedure. A solution of 0.1 mol. each of an aromatic aldehyde and *n*-butylamine in 20–50 ml. of benzene in a 100 ml. round bottom flask is attached to a water separator (a modified Dean and Stark moisture trap) and refluxed until the theoretical amount of water has been collected (15 to 30 min.). The solvent is then removed by distillation, finally under aspirator pressure. The crude Schiff's base may be used directly in the next step.

α-Nitrostilbenes. General procedure. To a solution of 0.1 mol. of phenylnitromethane in 25 ml. of glacial acetic acid is added 0.1 mol. of the appropriate Schiff's base. The clear homogeneous mixture is allowed to stand at room temperature. If crystallization has not begun within 0.5 hr., a drop of the mixture is added to a little water in a watch crystal and scratched with a glass rod to obtain seed crystals. If this procedure fails, the mixture is allowed to stand overnight and another attempt is then made. When crystallization is complete, the solid is filtered, washed with water and recrystallized from ethanol or acetic acid. Alternatively, the reaction mixture may be poured into ice water to obtain the product.

In only two cases (XXIX and XXXV) are reaction times longer than overnight necessary.

MIDLAND, MICH.

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

Synthesis of Certain Chalcones and 3-Hydroxychromones

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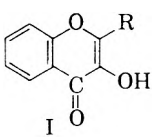
Certain new 3-hydroxychromones containing a heterocyclic or a polycyclic ring attached to the number 2 carbon atom of the chromone have been synthesized by preparing the corresponding hydroxychalcones, oxidizing the chalcones with alkaline hydrogen peroxide by the Algar-Flynn method, and purifying the products by column chromatography. In a few cases, the 3-hydroxychromones were also prepared directly by the Ranjorwa reaction. Properties of the purified compounds such as their ultraviolet spectra, infrared spectra, color reactions, and their melting points are recorded.

This paper reports our preparation, for biological studies, of certain new 3-hydroxychromones containing a heterocyclic or a polycyclic ring attached to the number 2 carbon atom of the chromone. The corresponding chalcones were also synthesized in every case.

Properties of the synthesized compounds, such as their ultraviolet spectra, infrared spectra, color reactions, and melting points have also been investigated.

The synthesized 3-hydroxychromones have the general formula I, where R = 9-anthracyl, 9-



I

phenanthryl, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 2-pyridyl-6-methyl, and 2-quinonyl, respectively.

One method tried for these syntheses was to prepare the 3-hydroxychromone in one step by the Ranjorwa reaction.[1] The Ranjorwa reaction, however, gave good results only in a few cases. The majority of the 3-hydroxychromones, therefore, were prepared by synthesizing first the corresponding chalcones and then by oxidizing the chalcones to 3-hydroxychromones by the Algar-Flynn[2] method, with alkaline hydrogen peroxide. In every case, each product obtained was purified by column chromatography. For these syntheses, 2-hydroxyacetophenone and an aldehyde of the appropriate polycyclic or heterocyclic compound were used. In one preparation only, 2-hydroxy-5-methylacetophenone was used instead of 2-hydroxyacetophenone.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tennessee.

1-(2-Hydroxyphenyl)-3-(9-anthracyl)propenone. Two general methods were employed for the preparation of this and other chalcones synthesized.

First general method for preparation of chalcones. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol. To this solution, 5 ml. of 50% KOH was added in portions. The color of the solution became orange. The flask was then stoppered and kept at room temperature (approximately 25°) for 48 hr. The resulting deep red solution was diluted with water, and the chalcone was precipitated by bubbling a current of carbon dioxide through the solution. The red precipitate was crystallized from acetone, m.p. 166–167°. The yield was 1.9 g. (58%).

Second general method for preparation of chalcones. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol and 5 ml. of 50% KOH was slowly added to it. The flask was shaken mechanically for 4 hr. The solution, which had now become deep red, was acidified with 5% ice cold HCl. The red precipitate formed was crystallized from acetone, m.p. 166–167°. The yield was 2.1 g. (64.8%).

The 1-(2-hydroxyphenyl)-3-(9-anthracyl)propenone obtained by both methods was purified further by column chromatography. A chromatographic column was prepared by adding a slurry of Magnesol brand magnesium silicate (Food Machinery and Chemical Corp., N. Y.) in methanol to a chromatographic tube and packing the absorbant under 10 lb. of pressure. This column of Magnesol was washed with 50 ml. of methanol. The solution of chalcone in methanol was poured onto the column, and the pressure was reduced to 5 lb. A small amount of impurity remained adsorbed on the top of the column, but most of the chalcone passed through the column. The chalcone was crystallized from acetone, m.p. 166–167°.

2-(9-Anthracyl)-3-hydroxychromone by the Algar-Flynn reaction. One gram (0.003 mol.) of 1-(2-hydroxyphenyl)-3-(9-anthracyl)propenone was dissolved in 50 ml. of 95% ethanol, and then 20 ml. acetone and 6 ml. of 1*N* potassium hydroxide were added. This red solution was heated on a water bath, and 10 ml. of 30% H_2O_2 was added. There was a vigorous reaction, and the solution slowly turned yellow. The mixture was then heated on a water bath for 30 min. and allowed to stand for 2 hr. Yellow crystals deposited and were separated and then recrystallized from benzene, m.p. 331–332°. The yield was 0.2 g. (17.9%). From the alcoholic solution, a small amount of another yellow crystalline substance, m.p. 246–247°, was isolated. This latter compound has not been identified.

2-(9-Anthracyl)-3-hydroxychromone by the Ranjorwa reaction. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol, and 5 ml. of 50% KOH was added slowly. The flask was shaken mechanically for 1 hr., with the solution exposed to air. The flask was then stoppered and kept at room temperature. The procedure was repeated daily for 30 days. At the end of the 30 days, the red sodium salt that had deposited in the flask was separated and treated with dilute HCl. The red

(1) S. D. Limaye and D. B. Limaye, *Rasayanam*, **2**, No. 2, 41 (1952); *Chem. Abstr.*, **47**, 4879 (1953).

(2) J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, **42B**, 1 (1934).

TABLE I

MELTING POINTS, YIELDS, AND COLOR REACTIONS OF CHALCONES

Compound	M.P.	Yield (%)	Color Reactions H_2SO_4 (Conc.)	Color Reactions $SbCl_5$ in CCl_4
1-(2-Hydroxyphenyl)-3-(9-anthracyl)propenone	166–167	58[a]	Dk G	Bl[b]
1-(2-Hydroxy-5-methyl phenyl)-3-(9-anthracyl)propenone	171–172	62[a]	Dk G	V[b]
1-(2-Hydroxyphenyl)-3-(9-phenanthryl)propenone	158–159	92.6	R	R-Br[b]
1-(2-Hydroxyphenyl)-3-(1-naphthyl)propenone	115–116	16.4	R	R[b]
1-(2-Hydroxyphenyl)-3-(2-naphthyl)propenone	155–156	54.9	R	R[b]
1-(2-Hydroxyphenyl)-3-(2-thienyl)propenone	99–100	58.7[a]	O	Dp O
1-(2-Hydroxyphenyl)-3-(2-pyridyl)propenone	101–102	53.3	O	R[b]
1-(2-Hydroxyphenyl)-3-(3-pyridyl)propenone	161–162	25.8	O	O
1-(2-Hydroxyphenyl)-3-(2-pyridyl-6-methyl)propenone	96–97	37.5	O	R[b]
1-(2-Hydroxyphenyl)-3-(2-quinonyl)propenone	125–126	29.0	R	R[b]

Bl = Blue; Br = Brown; Dk = Dark; Dp = Deep; G = Green; O = Orange; R = Red; V = Violet.
[a] Prepared by first method described; others were synthesized by the second method. [b] Formation of a precipitate.

salt turned yellow, and was crystallized from benzene, m.p. 331–332°.

The 2-(9-anthracyl)-3-hydroxychromone from both syntheses was purified further by chromatography. A chromatographic column was prepared by adding a slurry of Magnesol in dry benzene to a chromatographic tube. The absorbant was packed under a pressure of 10 lb. The column was washed with anhydrous benzene by pouring 50 ml. of the anhydrous benzene onto the absorbant and passing it through the column under a pressure of 10 lb. The benzene solution of the chromone was next passed through the Magnesol column, under a pressure of 5 lb. The column was developed with additional benzene. The chromone was present just at the top of the column in a yellow zone, and a chalcone appeared as an orange zone just below it. Immediately after washing the column with anhydrous benzene, the Magnesol was extruded from the top of the column, and cut by a stainless steel spatula into three portions. The top zone contained impurities and was set aside. The second zone was eluted with acetone, and the desired chromone was obtained after evaporation of the acetone. The chromone was crystallized from benzene, m.p. 331–332°.

Acetate of 2-(9-anthracyl)-3-hydroxychromone. The synthesized 2-(9-anthracyl)-3-hydroxychromone (0.5 g.) was refluxed for 1 hr. with acetic anhydride (2 ml.) and pyridine (3 drops). The resulting mixture was poured onto crushed ice. The yellow solid formed was crystallized from 95% ethanol as yellow needles, m.p. 194–195°.

Synthesis and properties of various chalcones. The various chalcones synthesized are listed in Table I. Of those listed, 1-(2-hydroxyphenyl)-3-(2-pyridyl)propenone, 1-(2-hydroxyphenyl)-3-(3-pyridyl)propenone, 1-(2-hydroxyphenyl)-3-(2-pyridyl-6-methyl)propenone, and 1-(2-hydroxyphenyl)-3-(2-quinonyl)propenone could be synthesized only by the second general method. Both methods were successful for preparation of all the other chalcones listed. Melting points, percentage yields of synthesis, and color reactions of each chalcone in concentrated H_2SO_4 and in $SbCl_5$ in carbon tetrachloride are also recorded in Table I.

Synthesis of various 3-hydroxychromones. The 3-hydroxychromones synthesized in this study are listed in Table II. All of these were prepared from the corresponding chalcone of Table I by the Algar-Flynn reaction. In only three cases as indicated in Table II, was the Ranjorwa reaction also successful. The melting points, percentage yields of synthesis by the Algar-Flynn reaction, and analytical data are also included in Table II.

The acetate of each 3-hydroxychromone was prepared. The melting point and analytical data for each acetate are also recorded in Table II.

Color reactions of 3-hydroxychromones. The color reactions produced by the synthesized chromones on treatment with common flavonoid color-producing reagents are reported in Table III.

Ultraviolet absorption spectra of 3-hydroxychromones. Ultraviolet absorption spectra of absolute ethanol solutions of the synthesized chromones were obtained using a Beckman spectrophotometer, Model DU. Two drops of 2% alcoholic $AlCl_3$ were then added to each solution and the new absorption spectrum of each recorded. The resulting shifts are given in Table III.

Infrared absorption spectra. Infrared spectra of these synthesized chromones were taken in chloroform solution on a Perkin-Elmer Infracord spectrophotometer. The absorption frequencies for the carbonyl group of the synthesized chromones were found to be between 1620 $cm.^{-1}$ and 1650 $cm.^{-1}$, and those for the hydroxyl group were between 3445 $cm.^{-1}$ and 3460 $cm.^{-1}$, as recorded in Table III. The absorption peaks for the hydroxyl group were generally not sharp, and in the case of 2-(2-pyridyl-6-methyl)-3-hydroxychromone and of 2-(2-quinonyl)-3-hydroxychromone, they were absent. Hergert and Kurth[3] reported values in the range 1627–1657 $cm.^{-1}$ and 3270–3340 $cm.^{-1}$ for the carbonyl and hydroxyl absorption frequencies, respectively, of 3 naturally occurring flavone aglycones studied. They found that the hydroxyl band was broad and not sharply defined for 2 of these 3 flavonols. For 2 naturally occurring flavonol aglycones studied, Inglett[4] found values of 1655 $cm.^{-1}$ for the carbonyl and 3130 $cm.^{-1}$ to 3340 $cm.^{-1}$ for the hydroxyl group.

The 1-naphthaldehyde used was purchased from L. Light & Co. Ltd. of England, and the other aldehydes and the acetophenone compounds used were purchased from Aldrich Chemical Co., Milwaukee, Wis.

Acknowledgment. We thank Mr. Peter Klaboe and Miss K. Lakshmi of the Physics Dept., University of Oklahoma, for assistance with the infrared determinations. We appreciate very much the support, in part, for this research by the National Institutes of Health.

NORMAN, OKLA.

(3) H. L. Herger and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).
(4) G. E. Inglett, *J. Org. Chem.*, **32**, 93 (1958).

TABLE II

MELTING POINTS, YIELDS, AND ANALYSES OF 3-HYDROXYCHROMONES AND THEIR ACETATES

Compound	M.P., °C.	% Yield Algar-Flynn Synthesis	Analyses		Acetate of 3-Hydroxychromone		
			Calcd.	Found	M.P., °C.	Analyses	
						Calcd.	Found
2-(9-Anthracyl)-3-hydroxychromone[a]	331–332	17.9	C, 81.64; H, 4.17	C, 81.49; H, 4.18	194–195	C, 78.94; H, 4.24	C, 78.97; H, 4.29
2-(9-Anthracyl)-3-hydroxy-6-methylchromone[a]	305–306	34.1	C, 81.80; H, 4.58	C, 81.82; H, 4.76	283–285	C, 79.17; H, 4.60	C, 79.10; H, 4.73
2-(9-Phenanthryl)-3-hydroxychromone	248–249	16.9	C, 81.64; H, 4.17	C, 81.47; H, 4.15	179–181	C, 78.94; H, 4.24	C, 78.68; H, 4.16
2-(1-Naphthyl)-3-hydroxychromone[a]	231–232	36.1	C, 79.15; H, 4.19	C, 79.07; H, 4.06	190–192	C, 76.35; H, 4.27	C, 76.52; H, 4.43
2-(2-Naphthyl)-3-hydroxychromone	208–209	25.0	C, 79.15; H, 4.19	C, 78.98; H, 4.14	145–146	C, 76.35; H, 4.27	C, 76.41; H, 4.35
2-(2-Thienyl)-3-hydroxychromone	205–206	24.6	C, 63.92; H, 3.30; S, 13.13	C, 64.01; H, 3.34; S, 13.18	152–153	S, 11.20	S, 11.21
2-(2-Pyridyl)-3-hydroxychromone	178–179	46.1	C, 70.29; H, 3.79; N, 5.85	C, 70.04; H, 3.57; N, 5.84	138–140	N, 4.98	N, 5.08
2-(3-Pyridyl)-3-hydroxychromone	207–208	21.7	C, 70.29; H, 3.79; N, 5.85	C, 70.43; H, 3.71; N, 5.95	109–110	N, 4.98	N, 5.08
2-(2-Pyridyl-6-methyl)-3-hydroxychromone	208–209	63.4	N, 5.53	N, 5.61	118–119	N, 4.74	N, 4.87
2-(2-Quinonyl)-3-hydroxychromone	253–254	34.6	N, 4.84	N, 5.01	181–182	N, 4.23	N, 4.17

[a] Also synthesized by the Ranjorwa reaction.

TABLE III

COLOR REACTIONS, SPECTRAL SHIFTS WITH $AlCl_3$, AND INFRARED SPECTRAL DATA OF 3-HYDROXYCHROMONES

Compound	Color Reactions[a]					Spectral Shifts with $AlCl_3$			Infrared Spectral Data	
	5% $FeCl_3$ Soln.	H_2SO_4 (conc.)	$SbCl_5$ in CCl_4	Mg and HCl	Appearance on Paper Chromatogram under Ultraviolet	Max., mμ	Max., mμ, with $AlCl_3$	Shift, mμ, with $AlCl_3$	Hydroxyl Cm.$^{-1}$	Carbonyl Cm.$^{-1}$
2-(9-Anthracyl)-3-hydroxychromone	Y	O-R	Y	—	Bl	325	385	60	3445	1620
2-(9-Anthracyl)-3-hydroxy-6-methylchromone	Y	R-Br	Y-Br	—	Bl	322	385	57	3445	1620
2-(9-Phenanthryl)-3-hydroxychromone	Y	R-Br	G	Y	V	332	390	58	3445	1620
2-(1-Naphthyl)-3-hydroxychromone	Br	Y	Y-Br	Y	Y	333	390	57	3445	1620
2-(2-Naphthyl)-3-hydroxychromone	Br	Y	Y-Br	Y	Y	355	420	65	3445	1620
2-(2-Thienyl)-3-hydroxychromone	Y	Y	Y-Br	Y	Y	333	390	57	3445	1620
2-(2-Pyridyl)-3-hydroxychromone	Br	Y	Y	Y	Y	345	405	60	3460	1645
2-(3-Pyridyl)-3-hydroxychromone	Br	R-Br	Y	Y	G-Y	340	400	60	3440	1620
2-(2-Pyridyl-6-methyl)-3-hydroxychromone	Br	Y	Y	Y	Y-G	350	400	50	—	1645
2-(2-Quinonyl)-3-hydroxychromone	O	Y	Y-Br	Y	O	322	400	78	—	1650
Quercetin[b]						377	431	58		
Kaempferol[b]						367.5	426	58		

[a] Bl, Blue; Br, Brown; G, Green; O, Orange; R, Red; Y, Yellow. [b] Data from Jurd and Geissman [*J. Org. Chem.*, **21**, 1400 (1956)].

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Heterocyclic Vinyl Ethers. XVII. Benzo-1,4-oxathiadiene-2-aldehyde, 2-Methylbenzo-1,4-oxathiadiene and 3-Methylbenzo-1,4-oxathiadiene[1]

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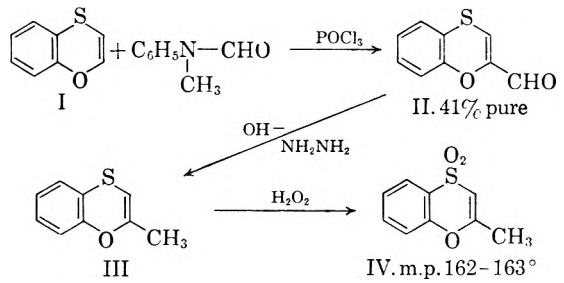
The electrophilic formylation of benzo-1,4-oxathiadiene (I) has been shown to give benzo-1,4-oxathiadiene-2-aldehyde (II). This orientation of substitution is somewhat anomalous in view of known electrical effects of oxygen and sulfur. The synthesis of 2-methyl- and 3-methylbenzo-1,4-oxathiadiene, as well as derivatives of these new heterocycles, is described.

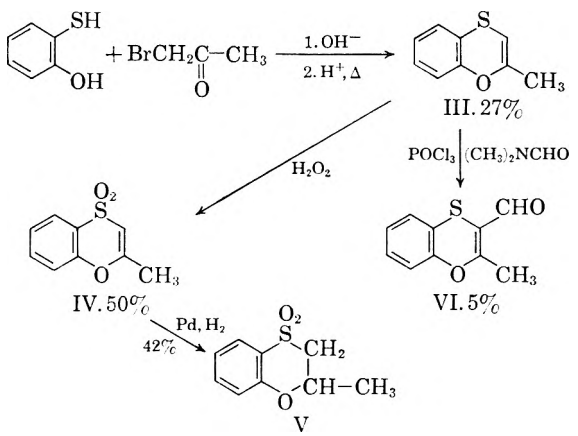
We have now examined the structure of the aldehyde, obtained[3] by reaction of benzo-1,4-oxathiadiene (I) with *N*-methylformanilide or *N*,*N*-dimethylformamide and phosphorus oxychloride (the Vilsmeyer Reaction), and have established the structure benzo-1,4-oxathiadiene-2-aldehyde (II) for this product.

Reduction of the aldehyde II with hydrazine and alkali (Wolff-Kishner) afforded an oil (22% calculated as III), which was characterized by conversion into the solid sulfone IV by oxidation. This sulfone was subsequently shown to be identical with an authentic sample of 2-methylbenzo-1,4-oxathiadiene sulfone.

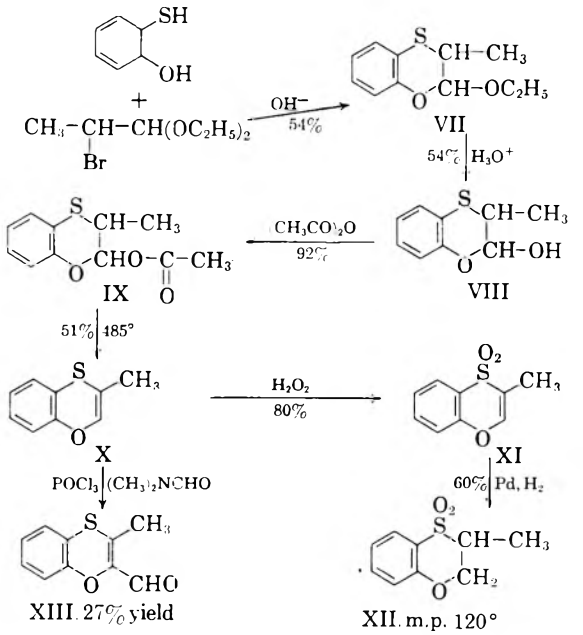


The independent synthesis of 2-methylbenzo-1,4-oxathiadiene (III), the sulfone IV, 3-methylbenzo-1,4-oxathiadiene (X), as well as other derivatives of these new heterocyclics is summarized in the following equations.

2-Methylbenzo-1,4-oxathiadiene (III)



3-Methylbenzo-1,4-oxathiadiene (X)



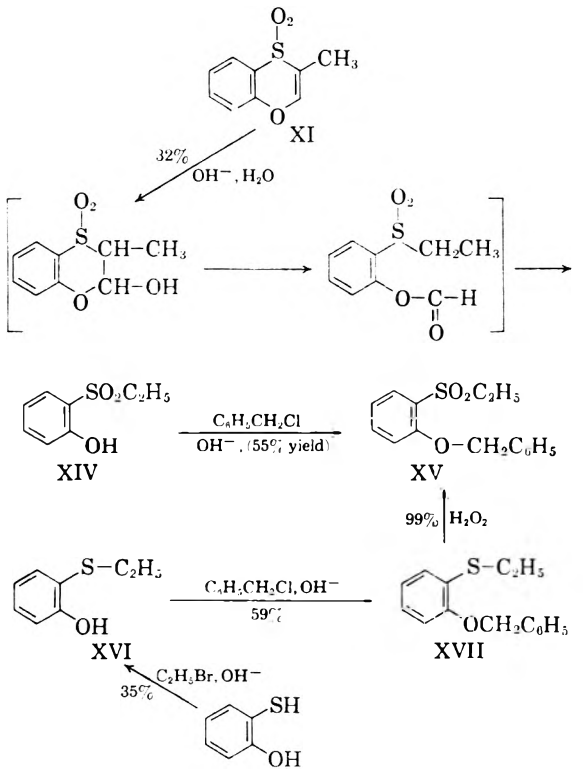
The structures of the aldehydes VI and XIII were not established; however, the preferential formylation of benzo-1,4-oxathiadiene (I) in the 2- position (I→II) is considered convincing evidence for the assignment of structure XIII, and is also consistent with the significant difference in yield noted for the formylation of the 2-, and 3-methyl derivatives (5 and 27%, respectively).

The syntheses employed for 2- and 3-methylbenzo-1,4-oxathiadiene (III and X), from monothiocatechol, were not considered unambiguous. Final confirmation of these structures was obtained by the alkaline hydrolysis of XI, together with the reactions summarized in the following equations. The two samples of XV were identical.

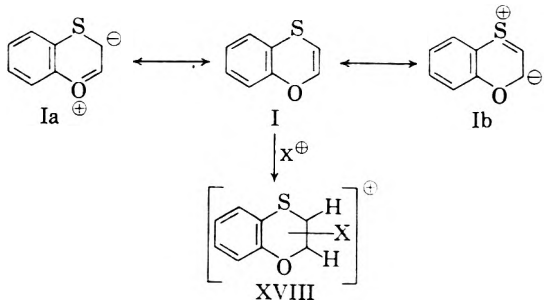
(1) Supported in part by Office of Ordnance Research, U. S. Army, Contract No. DA-11-022-ORD-571.

(2) Sinclair Oil Co. Fellow, 1958–59. From the PhD. Thesis of Gordon L. Willette, The University of Minnesota, 1959.

(3) W. E. Parham and John D. Jones, *J. Am. Chem. Soc.*, 76, 1068 (1954).

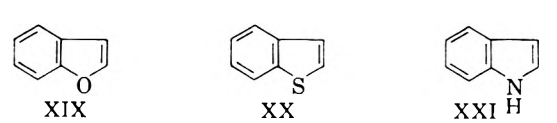


The Vilsmeyer Reaction is an example of an electrophilic substitution reaction.[4] The formation of II from I establishes the fact that simple *p*-orbital stabilization of the ground state of I (Ia-Ib) or the transition state XVIII, is not sufficient to explain the observed orientation, since it is well

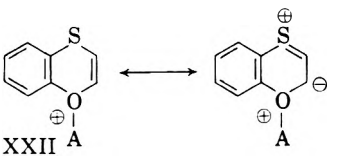


established that the oxygen-carbon $2p2p$ π-bond is stronger than the sulfur-carbon $3p2p$ π-bond (*i.e.*, Ia is more important than Ib).

Electrophilic substitution of benzofuran (XIX), benzothiophene (XX), and iodole (XXI) occurs preferentially in the 2-, 3-, and 3- positions, respectively.[5] Although the oxygen-carbon and nitrogen-carbon resonance intergrals are thought to be higher than the sulfur-carbon resonance intergral,[6] resonance in the ground or transition states would seem to predict the same orientation for each of these heterocycles. Substitution of benzo-1,4-oxathiadiene in the 2- position is consistent with the orientation observed for benzofuran and benzothiophene; however, the differences noted are not readily explained.



Attention may be called to the fact that the orientation observed for I is consistent with the possibility that the species undergoing substitution



is a conjugate acid of I involving the oxygen atom, as shown in XXII.

EXPERIMENTAL

3-Methylbenzo-1,4-oxathiadiene (X) *and derivatives. 2-Ethoxy-3-methylbenzo-1,4-oxathiene* (VII). This reaction was carried out under nitrogen and with vigorous stirring. Diethyl α-bromopropionacetal[7] (162.5 g., 0.770 mol.) was added dropwise to a solution prepared from potassium hydroxide (56.7 g., 0.770 mol.) in absolute ethanol (400 ml.) and monothiocatechol (97.0 g., 0.770 mol.). The resulting mixture was heated at the reflux temperature for 2 hr., then cooled, treated with anhydrous magnesium sulfate (*ca.* 10 g.), and finally filtered. The salts were washed with absolute ethanol, and the combined filtrate and washings were concentrated at reduced pressure. The cooled residue was treated with saturated ethereal hydrogen chloride, and the resulting mixture was allowed to stand, out of contact with air, for 34 hr. The acidic solution was neutralized with sodium carbonate, water was then added, and the organic material was separated with ether. The ether solution was dried over magnesium sulfate and distilled, affording 88 g., 54% yield, of 2-ethoxy-3-methylbenzo-1,4-oxathiene (VII, b.p. 125–130°/2 mm.).

2-Hydroxy-3-methylbenzo-1,4-oxathiene (VIII). A mixture of VII (122 g., 0.576 mol.) and 3% aqueous sulfuric acid (500 ml.) was heated at the reflux temperature for 39 hr., and the resulting mixture was distilled with steam until the distillate was clear. The residue remaining from the steam distillation was cooled (25°), made basic by addition of solid sodium bicarbonate, and was then extracted with ether. The solid obtained from the dried ether extract was recrystallized from methylene chloride–petroleum ether (60–68°), and pure VIII was obtained (56.0 g., 53.5% yield, m.p. 64–64.5°).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 58.96; H, 6.03.

2-Acetoxy-3-methylbenzo-1,4-oxathiene (IX). The procedure employed was essentially identical with that previously described for acetylation of 2-hydroxybenzo-1,4-oxathiene.[8] From VIII (56.0 g., 0.308 mol.) there was obtained 63.5 g. (92% yield) of IX (b.p. 105–115°/0.7 mm.).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 59.14; H, 5.67.

3-Methylbenzo-1,4-oxathiadiene (X). The deacetoxylation of 2-acetoxy-3-methylbenzo-1,4-oxathiene (IX, 10.0 g., 0.045 mol.) in dry benzene was carried out by pyrolysis at

(4) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(5) *Heterocyclic Compounds*, Vol. 2, R. C. Elderfield, editor: Chapter 1, p. 18 by R. C. Elderfield and V. B. Meyer; Chapter 4, p. 147 by D. K. Fukushima; Vol. 3, Chapter 1, by P. L. Julian, E. W. Meyer, and H. C. Printy, John Wiley & Sons, New York, N. Y.

(6) *Cf.* H. H. Jaffe, *J. Chem. Phys.*, **20**, 279 (1950).

(7) A. H. Williams and F. N. Woodward, *J. Chem. Soc.*, 38 (1948).

a temperature of 480–490°, by a procedure essentially identical with that previously described for the deacetoxylation of 2-acetoxybenzo-1,4-oxathiene.[3] 3-Methylbenzo-1,4-oxathiadiene (X, 3.76 g., 51% yield, n_D^{26} 1.5890) was collected at 74–91°/0.75 mm. by distillation. A sample was redistilled for analysis (b.p. 77°/1 mm., $n_D^{26.7}$ 1.5965).

Anal. Calcd. for C_9H_8OS: C, 65.85; H, 4.91. Found: C, 65.62; H, 5.24.

3-Methylbenzo-1,4-oxathiadiene sulfone (XI) was prepared from X (0.73 g., 0.0044 mol.) by oxidation in the usual manner[3] with 30% hydrogen peroxide in hot glacial acetic acid (15 ml.). The crude product (0.7 g., 80% yield, m.p. 107°) was purified by recrystallization from ethanol. Pure XI melted at 115–115.5°.

Anal. Calcd. for $C_9H_8O_3S$: C, 55.10; H, 4.11. Found: C, 55.15; H, 4.22.

3-Methylbenzo-1,4-oxathiene sulfone (XII). A mixture of XI (0.1 g.), absolute ethanol (25 ml.), and palladium black (0.05 g.) was stirred for 3 days in an atmosphere of hydrogen at room temperature. 3-Methylbenzo-1,4-oxathiene sulfone was isolated from the ethanol solution, and was recrystallized from carbon tetrachloride-petroleum ether (60–68°); 0.05 g., 60% yield, m.p. 119–120.5°.

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.54; H, 5.09. Found: C, 54.40; H, 5.21.

3-Methylbenzo-1,4-oxathiadiene-2-aldehyde (XIII). The procedure employed was essentially identical with that described below for the formylation of 2-methylbenzo-1,4-oxathiadiene. The aldehyde (XIII), obtained from 3-methylbenzo-1,4-oxathiadiene (X, 3.76 g., 0.023 mol.), was purified by isolation as the bisulfite adduct, and by final recrystallization frm petroleum ether (60–68°); 1.1 g., 27% yield, canary-yellow, m.p. 66–68°.

Anal. Calcd. for $C_{10}H_8O_2S$: C, 62.50; H, 4.20. Found: C, 62.44; H, 4.30.

The infrared spectrum of this product showed carbonyl absorption at 1655 cm.$^{-1}$

The 2,4-dinitrophenylhydrazone of 3-methylbenzo-1,4-oxathiadiene-2-aldehyde was prepared in the usual way from a solution of the corresponding bisulfide addition product (0.5 g.) in ethanol (20 ml.). The derivative melted at 243–244° (from nitromethane).

Anal. Calcd. for $C_{16}H_{12}O_5SN_4$: C, 51.62; H, 3.25; N, 15.05. Found: C, 52.38; H, 3.40; N, 14.82.

2-Methylbenzo-1,4-oxathiadiene (III) *and derivatives.* A solution of potassium hydroxide (25.5 g. assaying 85% KOH, 0.395 mol.) in absolute ethanol (200 ml.) was added slowly to monothiocatechol[3] (50 g., 0.395 mol., b.p. 72–76°/3 mm., $n_D^{25.5}$ 1.6072) in an atmosphere of nitrogen. Bromoacetone (54.12 g., 0.395 mol.) was then added dropwise, and the resulting solution was heated at the reflux temperature under nitrogen, and with stirring, for 2 hr. The mixture was then cooled to 25°, anhydrous magnesium sulfate (5 g.) was added, and the resulting mixture was filtered. The precipitate was washed with absolute ethanol, and the combined filtrate and ethanol washings was concentrated at reduced pressure. The residue was cooled (25°), and saturated ethereal hydrogen chloride (30 ml.) was added. The acidic solution was allowed to stand (out of contact with air) for 24 hr., and was then neutralized with solid sodium carbonate. The mixture was filtered, and the filtrate was distilled. Crude *2-methylbenzo-1,4-oxathiadiene* (III, 17.10 g., n_D^{27} 1.6020, 26.5% yield) was collected at 78–90°/1.1 mm.). A higher boiling fraction (10.8 g., b.p. 92–120°/1.4 mm.) was not examined.

A sample of crude III (1 g., 0.006 m.) was oxidized with 30% hydrogen peroxide (15 ml.) in boiling glacial acetic acid. The crude sulfone (0.6 g., 50% yield) was obtained as a solid when water was added to the cold acetic acid solution. Pure 2-methylbenzo-1,4-oxathiadiene sulfone (IV, m.p. 162–163°) was obtained by recrystallization of the crude sulfone from methylene chloride-petroleum ether (60–68°).

Anal. Calcd. for $C_9H_8O_3S$: C, 55.10; H, 4.11. Found: C, 55.03; H, 4.12.

A solution of IV (0.1 g., 0.005 mol.) in ethanol (25 ml.) was reduced with palladium and hydrogen at atmospheric pressure (48 hr.). The product, presumably *2-methylbenzo-1,4-oxathiene sulfone* (V), was recrystallized from petroleum ether (60–68°) to give a white solid (0.04 g., 40% yield) melting at 67–69°. This product was not analyzed further.

Formylation of 2-methylbenzo-1,4-oxathiadiene (III). A mixture of *N,N*-dimethylformamide (22.5 g., 0.308 mol.) and phosphorus oxychloride (25.0 g., 0.163 mol.), which had been allowed to stand overnight,[8] was cooled in an ice bath, and 2-methylbenzo-1,4-oxathiadiene (III, 18.74 g., 0.113 m., b.p. 73.5–86°/0.07 m., $n_D^{26.5}$ 1.5920–1.5950) was added slowly in portions. The mixture, after being allowed to stand at 25° for 24 hr., was dissolved in chloroform (200 ml.), and the resulting solution was added to a mixture of ice and water (*ca.* 300 g.). After the ice had melted, the chloroform layer was separated and washed with dilute sodium carbonate until all acid was removed. The chloroform layer was dried over magnesium sulfate, concentrated to 50 ml., and shaken with a mixture of ether (100 ml.) and saturated sodium bisulfite (200 ml.). The bisulfite adduct (*ca.* 2 g.) which formed was collected and washed with cold absolute ethanol, then washed again with cold ether. The pale yellow adduct was suspended in water, and sodium carbonate was added until the solution was basic to litmus. The resulting mixture was then extracted with ether, the ether extract was dried with magnesium sulfate and finally concentrated. The crude aldehyde (1.1 g., 5% yield, m.p. 136–139°) was recrystallized from methylene chloride-petroleum ether (60–68°), and then sublimed under vacuum, affording a product tentatively assigned structure VI (m.p. 140–141°).

Anal. Calcd. for $C_{10}H_8O_2S$: C, 62.50; H, 4.20. Found: C, 62.37; H, 4.33.

The infrared spectrum of the aldehyde showed carbonyl absorption at 1650 cm.$^{-1}$

Proof of structure of 2- and 3-methylbenzo-1,4-oxathiadiene. Hydrolysis of 3-methylbenzo-1,4-oxathiadiene sulfone (XI). A solution prepared from XI (0.8 g., 0.004 mol.), ethanol (10 ml.), and potassium hydroxide (3*N*, 10 ml.) was heated at the reflux temperature for 5 hr. The cold solution was dried with magnesium sulfate and distilled. 2-Ethylsulfonylphenol (XIV) was obtained as a colorless oil (0.24 g., 32% yield, b.p. 122–125°/1 mm.). A sample (0.15 g.) of this product was treated with phenylisocyanate (3 ml.) and pyridine (1 drop) and the mixture was heated at 100° for 15 min. The precipitate was treated with chloroform, the insoluble urea was removed, and the *phenylurethane* of XIV was recrystallized from carbon tetrachloride. The resulting urethane melted at 149–151°.

Anal. Calcd. for $C_{15}H_{15}O_4SN$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.75; H, 5.11; N, 5.19.

2-Benzyloxyphenyl ethyl sulfone (XV). (a) A solution containing XIV (2 g., 0.017), prepared as described above, potassium carbonate (1 g.), benzyl chloride (1 g., 0.008 mol.), and acetone (25 ml.) was heated at the reflux temperature for 16 hr. Water (10 ml.) was then added to the cold mixture, and the resulting mixture was extracted with ether. 2-Benzyloxyphenyl ethyl sulfone (1 g., 55% yield, m.p. 107–108° from 95% ethanol) was obtained from the ether extract.

Anal. Calcd. for $C_{15}H_{16}O_3S$: C, 64.95; H, 5.82. Found: C, 64.88; H, 5.81.

(b) Monothiocatechol (23.22 g., 0.184 mol.) in ethanol (100 ml.) was added dropwise to a solution, under nitrogen, of potassium hydroxide (11.79 g., 0.183 mol.) in ethanol (100 ml.). The solution was stirred, ethyl bromide (20.06 g., 0.184 mol.) in ethanol (50 ml.) was added slowly, and the resulting mixture was stirred at 25° for 2 hr. The mixture was filtered, and the filtrate was concentrated at reduced pressure. Water and sulfuric acid were added to the residue,

(8) A. H. Weston and R. J. Michaels, Jr., *Org. Syntheses*, **31**, 108 (1951).

which was then distilled with steam. The ether-soluble material from the distillate was extracted with 10% sodium hydroxide, and the alkaline layer was then acidified with 10% sulfuric acid. The oil which separated was collected in ether, and the extract was dried with magnesium sulfate and distilled. *2-Ethylmercaptophenol* (XVI, 10 g., 35% yield, $n_D^{25.5}$ 1.5681) was collected at 59–60°/0.6 mm.

A sample of 2-ethylmercaptophenol (5.57 g., 0.0362 mol.) was benzylated with benzyl chloride by a procedure essentially identical with that described above. 2-Ethylmercaptophenol benzyl ether (XVII, 5.16 g., 58% yield, $n_D^{25.5}$ 1.5960) was collected at 148–149°/1 mm.

Ethylmercaptophenyl benzyl ether was oxidized in hot glacial acetic acid with hydrogen peroxide (30%) by a procedure identical with that described elsewhere in this report. 2-Benzyloxyphenyl ethyl sulfone (XV) was obtained in quantitative yield; m.p. 106–107.5° (from ethanol).

Anal. Calcd. for $C_{15}H_{16}O_3S$: C, 64.95; H, 5.82. Found: C, 64.85; H, 5.70.

Samples of 2-benzyloxyphenyl ethyl sulfone, prepared by procedures (a) and (b) showed no depression of melting point upon admixture. Furthermore, X-ray diffraction patterns of these materials were identical.

Proof of structure of benzo-1,4-oxathiadiene-2-aldehyde (II). *Reduction to 2-methylbenzo-1,4-oxathiadiene* (III). A mixture of benzo-1,4-oxathiadiene aldehyde[3] (II, 2.5 g., 0.014 mol.), hydrazine (8 ml., 95%), triethylene glycol (50 ml.), and pulverized potassium hydroxide (1 g.) was heated at the reflux temperature for 2 hr. Material was then allowed to distill until the temperature of the solution reached 120°.

(a) The aqueous distillate was extracted with ether (100 ml.), the ether was dried with magnesium sulfate and concentrated. The residue (0.5 g., 22% calcd. as C_9H_8OS) was oxidized with 30% hydrogen peroxide (5 ml.) in hot glacial acetic acid. The solid sulfone, obtained from the acetic acid by addition of water, was recrystallized from 95% ethanol. The sulfone weighed 0.4 g. and melted at 161–162.5°. This material caused no depression in melting point when admixed with authentic 2-methylbenzo-1,4-oxathiadiene sulfone (m.p. 162–163°).

(b) In one experiment the residue from the steam distillation was extracted with ether, and the extract was dried and distilled. The organic distillate (b.p. 54–62°/1.3 mm., *ca.* 2 g.) was washed with water and the insoluble oil (1 g.) was oxidized with hydrogen peroxide, as described above. The resulting product was recrystallized from methylene chloride–petroleum ether (60–68°). This procedure afforded a small amount of white solid melting at 63.5–64.5°.

Anal. Calcd. for $C_8H_8O_3S$: C, 52.16; H, 4.37; S, 17.38; M.W. 184.21. Found: C, 52.29, 52.52; H, 4.76, 4.05; S, 16.99, 17.91; M.W. (freezing point of benzene) 203, 203; M.W. (Rast in camphor), 117, 201.

The identity of this material was not established.

MINNEAPOLIS 14, MINN.

[CONTRIBUTION NO. 184 FROM THE RESEARCH CENTER OF THE UNITED STATES RUBBER CO.]

The Chemistry of Maleimide and Its Derivatives. I. *N*-Carbamylmaleimide

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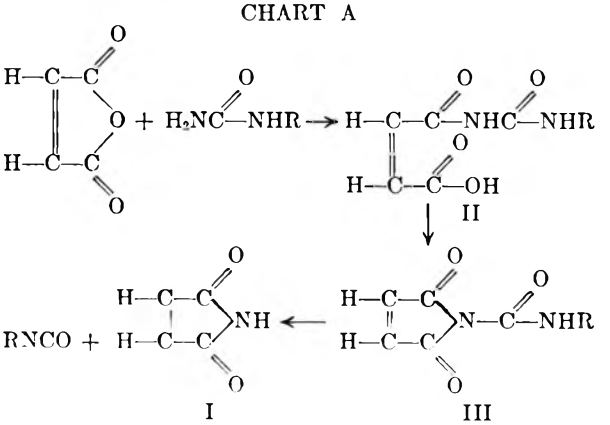
Carefully controlled condensation of maleic anhydride with urea or monosubstituted ureas, and cyclization of the maleuric acids to *N*-carbamylmaleimides followed by decomposition in dimethylformamide provide a practical route to maleimide. *N*-Carbamylmaleimides react with primary and secondary alcohols to yield esters of maleuric acid. *N*-Carbamylmaleimide and the maleurate esters have been copolymerized with several vinyl-type monomers.

Interest in the chemistry of maleimide (I) and its derivatives, and more particularly in their polymerizability, has been limited by the lack of a practical method of preparing such compounds. Until recently, the synthesis of maleimide was usually effected by chromic acid oxidation of pyrrole[1] or by acid-catalyzed cyclization of maleamide.[2] We have noted that these methods provide low yields and that neither is suitable for the preparation of appreciable amounts of maleimide. In our search for a more satisfactory method, we have devised the synthesis outlined in Chart A wherein the desired compound is obtained by thermal decomposition of the new structure, *N*-carbamylmaleimide (IIIa). Homologs of IIIa such as IIIb, c, and d are also readily available from this sequence of reactions.

CHART A



It is the purpose of this paper to describe the synthesis of III and to point out some of its reactions.

(1) G. Plancher and F. Cattadori, *Atti reale accad. naz. Lincei*, [5] **13**, I, 489 (1904).

(2) I. J. Rinkes, *Rec. trav. chim.*, **48**, 961 (1929).

TABLE I

N-CARBAMYLMALEAMIC ACIDS (II)

R	Yield, %	M.P., (Dec.) °C.	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
H	50–95	161–162[a]					17.72	17.68	158	139
										159
C_6H_5	32	162–163[b]	56.3	57.02	4.26	4.36	11.95	11.83	234	232
				57.23		4.39		11.79		
n-C_4H_9	58	105.5–107.0[c]	50.50	51.29	6.54	6.75	13.05	13.03	214	214
				51.39		6.67		13.01		
tert-C_4H_9	85	151.5–153.5[c]	50.50	50.54	6.54	6.64	13.05	13.0	214	210
				50.73						

[a] Recrystallized from acetic acid. [b] Recrystallized from ethyl acetate. [c] Recrystallized from water.

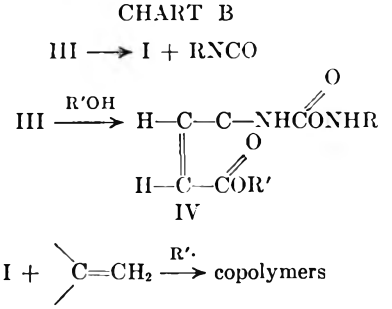
Preparation of N-carbamylmaleimides (III). We have effected a substantial improvement in the method of Dunlap and Phelps[3] for preparing *N*-carbamylmaleamic acid (IIa) by allowing equimolar amounts of maleic anhydride and urea to react in glacial acetic acid solution at 50–60° for twelve hours.[4] Yields became practically quantitative if mother liquors were re-used in subsequent reactions. It was demonstrated that the improvement in rate resulted from a catalytic effect exerted by IIa. A search for other catalysts showed that tertiary amines depressed the yield of IIa, while neither sulfuric acid nor acetate ion had any effect; dichloroacetic acid was a poorer solvent than was acetic acid. Anhydrous conditions were essential since as little as four per cent of water in the solvent completely inhibited the reaction. It was necessary to keep the reaction temperature within the 50–60° range in order to obtain good yields of readily purified product. At higher temperatures, the reaction became so violently exothermic as to be difficult or impossible to control, and carbon dioxide was evolved vigorously. That this gas-evolution resulted from decomposition of the product was indicated by the fact that simply refluxing IIa in acetic acid caused evolution of carbon dioxide. Other possible side-reactions include rearrangement of IIa to *N*-carbamylfumaramic acid, cyclization of IIa to IIIa by maleic anhydride and formation of derivatives of aspartic acid. The products of these possible reactions could seriously complicate the isolation and purification of IIa.

Homologs of IIa (Table I) were prepared from the appropriately substituted ureas. It was discovered that the substituted carbamylmaleamic acids were less stable than the parent compound; *N*-(phenylcarbamyl)-(IIa) and *N*-(*n*-butylcarbamyl)maleamic acid (IIc) underwent partial isomerization to the corresponding fumaramic acid derivatives on protracted warming in aqueous solution. Conversion to the *trans* isomer was avoidable by using organic recrystallization solvents such as ethyl acetate or methanol. IIa was not isomerized in aqueous solution, but it was noted that the melting point of crude IIa was not improved by recrystallization from this solvent. *N*-Carbamylfumaramic acid (Table II) and its homologs were prepared in excellent yield by refluxing II in methanol or acetic acid containing a trace of mineral acid.

The cyclization[5] of IIa was most satisfactorily accomplished by heating a suspension of the compound in two or three times its weight of acetic anhydride at 80–100° until the solid dissolved. The reaction was very slow at lower temperatures, and decomposition of the product to I and cyanuric acid became appreciable above 100°. On cooling, yields in excess of 90% of *N*-carbamylmaleimide (IIIa), m.p. 157–158°, crystallized from solution. It was possible to replace part of the acetic anhydride with acetic acid, but the product then had a lower melting point. Recrystallization of pure IIIa from acetic acid yielded the same material which bore a strong odor of acetic acid and was assumed to be a solvate. Acetic acid could not be completely pumped off the product under vacuum but could be removed by recrystallization from acetic anhydride or nitromethane.

Chemical properties of N-carbamylmaleimide (III). Certain of the chemical reactions of III are outlined in Chart B.

CHART B



(3) F. L. Dunlap and I. K. Phelps, *Am. Chem. J.*, 19, 492 (1897).

(4) R. H. Snyder, U. S. Patent 2,717,908, September 13, 1955.

(5) R. H. Snyder, U. S. Patent 2,788,349, April 9, 1957.

TABLE II

N-CARBAMYLFUMARAMIC ACIDS

R	M.P., (Dec.) °C.	Analyses							
		Carbon		Hydrogen		Nitrogen		Neut. Equiv.	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	224					17.7	17.3	158	159
C_6H_5	208–210	56.3	56.9	4.26	4.33				
			56.6		4.20				
n-C_4H_9	202–204	50.5	50.4	6.55	6.44	13.05	13.44		
			50.8		6.66		13.48		

TABLE III

N-CARBAMYLMALEIMIDES (III)

R	Yield, %	M.P., °C.	Analyses							
			Carbon		Hydrogen		Nitrogen		Neut. Equiv.	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	92.5	157–158[a]					20.0	19.7	140	139
								19.8		
C_6H_5	71	140–141[b]	61.0	61.8	3.73	3.80	13.0	13.0	216	215
				62.1		3.88		13.1		
n-C_4H_9	74	66.5–68.0[c]	55.1	55.7	6.16	6.21	14.3	14.2	196	211
				55.8		6.25		14.7		
tert-C_4H_9	23	107–109[c]	55.1	55.6	6.16	6.10	14.3	14.3	196	184
				55.9		6.14		14.2		

[a] Recrystallized from acetic anhydride. [b] Recrystallized from benzene. [c] Recrystallized from benzene–petroleum ether (b.p. 60–70°).

Thermal decomposition. The literature contains references[6,7] to the successful pyrolysis of *N*-carbamylimides to yield imides and cyanuric acid. IIIa sublimed under vacuum at 150° but decomposed at 180° to yield some I and a large amount of a complex polymer. In the presence of zinc chloride better yields of I were obtained at 130–150°, while the most satisfactory yields (60–80%) were obtained from decompositions run in dimethylformamide at 100°. Reaction periods of about one hour followed by rapid separation of I from the liquors favored higher yields. Homologs of IIIa have been decomposed similarly to produce high yields of isocyanates and very low yields of I.

Reaction of III *with alcohols.*[8,9] III reacted with primary and secondary alcohols, but not with tertiary alcohols or phenols, at 80–100° to yield alkyl *N*-carbamylmaleamates (IV) (Table IV).

Higher reaction temperatures were found to cause undesirable decomposition. In the case of methanol and ethanol, the reaction was complete in about thirty minutes even at room temperature, but higher primary alcohols and all glycols and secondary alcohols reacted more sluggishly, 25 to 30% yields of ester resulting from several hours of heating in the recommended temperature range. However, electrophilic substances sharply accelerated the reaction and provided excellent yields of the esters in an hour or two at 80–100° whether the reaction was run in excess alcohol or an inert medium such as dioxane, acetonitrile or petroleum ether (b.p. 60–70°). Zinc chloride, cadmium chloride, and ferric chloride catalyzed the acylation smoothly, but aluminum chloride catalyzed the acylation reaction and then isomerized[10] the products to alkyl *N*-carbamylfumaramates. As compared to their *cis*-isomers, the fumaramates were higher melting, less soluble, and had an ultraviolet absorption maximum in the 220 millimicron region which was not observed in the case of the *cis*-isomers.

Copolymerization of III *and* IV *with vinyl monomers.* Both III and IV copolymerized readily with such monomers as styrene, vinyl acetate, and butadiene. The *N*-carbamylfumaramates have not proved to be useful monomers because of their very poor solubility in most organic liquids.

EXPERIMENTAL[11]

Melting points are uncorrected.

N-Carbamylmaleamic acid (IIa). A stoppered flask containing 1000 g. of glacial acetic acid, 300 g. (5.0 mol.) of

(6) A. Piutti, *Ann.*, **214**, 17 (1892); *Gazz. Chim. ital.*, **12**, 169 (1892).

(7) C. S. Smith and C. J. Cavallitto, *J. Am. Chem. Soc.*, **61**, 2218 (1939).

(8) Amines and mercaptans also react with III, but ring-opening and addition to the double bond are frequently concurrent, resulting in complex products.

(9) R. H. Snyder and P. O. Tawney, U. S. Patent **2,854,438**, Sept. 20, 1958.

(10) R. J. Kelly and C. E. Bryan, U. S. Patent **2,809,190**, Oct. 8, 1957.

(11) Analyses were performed by the Analytical Research Department of the Research Center or by the Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

TABLE IV

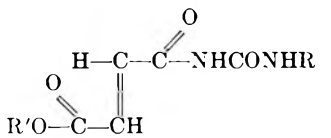
ALKYL *N*-CARBAMYLMALEAMATES (IV)

R	R′	Yield, %	M.P., °C.	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	Methyl	88.6	113–114					16.29	16.36
H	Ethyl	70	111–112					15.05	15.01
									14.84
H	*i*-Propyl	75.5	113–114					14.00	13.95
									13.97
H	*n*-Butyl	47	96–99					13.09	13.25
									13.33
H	Allyl		109–111					14.13	14.02
									13.99
H	Benzyl	50	130–131					11.28	11.25
H	β-Hydroxyethyl	60	131–131.5					13.85	13.59
									13.71
H	β-Chloroethyl	66	116–119					12.68	12.62
									12.84
H	N-Morpholinyl-ethyl	74	121.5–122.5					15.5	15.3
									15.2
H	Ethylene[a]	73	184–186					16.37	16.31
									16.26
n-Butyl	Benzyl	78	65.5–66.5	63.1	63.8	6.58	6.69	9.20	9.34
					63.8		6.71		9.34
tert-Butyl	Benzyl	90	70–72.5	63.1	63.3	6.58	6.63	9.20	9.22
					63.2		6.63		9.14
tert-Butyl	*i*-Propyl	88	96–97	56.2	56.9	7.81	7.88	10.90	10.99
					57.1		7.85		10.99
Phenyl	Benzyl	77	131–133.5	66.7	66.7	4.97	4.99	8.63	8.48
Phenyl	*i*-Propyl	61	132–133	60.8	61.4	5.83	5.72	10.11	10.17
					61.1		5.74		10.19
H	*n*-Dodecyl	79	119–119.5	62.5	62.3	9.2	9.2	8.6	8.7

[a] bis-Maleurate.

TABLE V

ALKYL *N*-CARBAMYLFUMARAMATES



R	R′	M.P., °C.	Nitrogen Analysis: Calcd.	Found
H	Methyl	228–230	16.28	16.18
				16.18
H	β-Chloro-ethyl	189.5–190.5	12.68	12.62
				12.59

urea and 500 g. (5.1 mol.) of maleic anhydride was heated at 50° for 12 hr. and then left overnight at room temperature. The crystalline product, collected on a filter, washed with 250 ml. of glacial acetic acid and dried at 50°, weighed 405 g. (a 56% yield) and melted at 161–162° (dec.). The mother liquors and washings were recharged with 300 g. of urea and 500 g. of maleic anhydride and heated at 56° for only 5 hr. After standing overnight at room temperature, 620 g. (77% yield) of product, m.p. 159–161° (dec.) was collected. Two successive repetitions of this process produced 83.8 and 97.5% yields of product, m.p. 156–159° (dec.) and 157–160° (dec.) respectively. The average yield was 86%.

N-(n-Butylcarbamyl)maleamic acid (IIc). A mixture of 19.6 g. (0.2 mol.) of maleic anhydride, 23.4 g. (0.2 mol.) of *N*-*n*-butylurea and 50 ml. of acetic acid was heated at 55° for 11 hr. Evaporation of solvent left a viscous residue which, when poured into ice water, yielded 25.0 g. (58%) of a white solid, m.p. 102–105°. Recrystallization from water yielded pure *N*-(*n*-butylcarbamyl)maleamic acid, m.p. 105.5–107.0°.

N-Carbamylmaleimide (IIIa). *N*-Carbamylmaleamic acid (1000 g., 6.3 mol.) was added to 3240 g. of acetic anhydride which had been heated to 90–95°. The suspension was stirred vigorously at 90–97° for 35 min. at which time the solid had dissolved. After a hot filtration the filtrate was cooled to room temperature, and the precipitated solid was filtered off and washed with 150 g. of acetone. After vacuum drying, the product weighed 680 g. (76.7%) and melted 155–158°. A sample recrystallized from acetic anhydride had m.p. 157–158°.

Maleimide (I). A 5-l. flask fitted with a stirrer and thermometer was charged with 1680 g. of dimethylformamide and heated to 90–95° by means of a water bath. Heating was stopped and 840 g. (6.0 mol.) of IIIa was added with stirring. The water bath absorbed heat evolved by the exothermic reaction so that the reaction temperature did not exceed 111°. At the end of the exothermic period, heat was applied to maintain the temperature at 95–99° for a total reaction time of 1 hr. The mixture was cooled to room temperature and left overnight. Precipitated cyanuric acid was filtered off and dimethylformamide was removed from the filtrate under vacuum. The product was then distilled rapidly at 96–105° at 5 millimeters to yield 85.9% of crude maleimide. After recrystallization from ethyl acetate, the product had m.p. 92–94° undepressed by admixture with[12] material obtained by pyrolysis of 3,6-*endo*-methylene-Δ^4-tetrahydrophthalimide.

N-Carbamylfumaramic acid. A solution of 1 g. of IIa in 20 ml. of acetic acid containing a drop of concentrated sulfuric acid was warmed on a steam bath for 20 min. Separa-

(12) P. O. Tawney, U. S. Patent 2,524,145, Oct. 3, 1950.

tion of the *trans*-acid began soon after the heating started. On cooling, 0.75 g. of product separated and was filtered off.

n-Butyl N-carbamylmaleamate (IV. R = H, R′ = *n*-C_4H_9). A mixture of 1184 g. of *n*-butanol, 560 g. (4.0 mol.) of IIIa, 8 g. of zinc chloride and 150 g. of petroleum ether (b.p. 60–70°) was refluxed at 85° until solution was complete. The solution was filtered and cooled, depositing 782 g. (92%) of the ester, m.p. 96–99°.

Methyl N-carbamylfumaramate. Addition of 0.1 g. of aluminum chloride to 5.0 g. (0.036 mol.) of IIIa in 50 ml. of methanol caused an immediate exothermic reaction and precipitation of a quantitative yield of methyl *N*-carbamylfumaramate, m.p. 228–230°.

Copolymerization of IIIa *with vinyl acetate.* A solution of 10 g. (0.07 mol.) of IIIa, 25 ml. (0.27 mol.) of vinyl acetate and 0.1 g. of benzoyl peroxide in 194 ml. of dioxane was heated at 80° in a water bath for 6 hr. The polymer solution was poured into 1 l. of acetone. After filtration and drying, the polymer weighed 5.5 g. (17% conversion), was soluble in dimethylformamide and, with hydrolysis, in 10% aqueous sodium hydroxide, had intrinsic viscosity 0.13 and analyzed for 57.6% nitrogen. This analysis corresponds to a ratio of IIIa to vinyl acetate of 1:1.2 from a feed ratio of 1:3.8.

Copolymerization of methyl N-carbamylmaleamate (IV. R = H, R′ = CH_3) *with styrene.* A mixture of 20 g. (0.192 mol.) of styrene, 20 g. (0.116 mol.) of IV and 0.8 g. of benzoyl peroxide in 40 g. of acetone was heated for 4.75 hr. in a water bath held at 70°. The clear solution, which still contained some undissolved IV, was poured into stirred methanol to precipitate the polymer. The precipitate was filtered off and dried overnight in an evacuated desiccator. The material was then triturated with methanol and again dried overnight in a vacuum desiccator. The product weighed 11.6 g. (29% conversion) and was soluble in dioxane and acetic acid. Nitrogen analysis (6.05, 6.05%) indicated that the monomer ratio (IV:styrene) in the polymer was 1:2.8 from a feed ratio of 1:1.65. The polymer had an intrinsic viscosity in dioxane of 0.11.

Acknowledgment. The following assisted in some of the preparations described: G. H. Brice, F. S. Elkins, A. N. Johnson, M. D. Kellert, and K. A. Leibbrand.

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WAYNE, N. J.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY AND THE RESEARCH AND DEVELOPMENT DIVISION SMITH KLINE & FRENCH LABORATORIES]

Synthesis of Phenothiazines. III. Derivatives of Hydroxy- and Mercaptophenothiazines[1]

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Received August 11, 1959

The preparation of seven phenothiazines is reported; they are 2-hydroxy-, 2-benzoyloxy-, 2-methylmercapto-, 2- and 4-trifluoromethylmercapto-, 2-methylsulfonyl-, and 2-trifluoromethylsulfonylphenothiazine. Various new intermediates are described.

The early French work in the phenothiazine field, following the lead of chloropromazine, resulted in the synthesis of the 2-methyl and 2-methoxy derivatives.[4] Further work in France[5] and in Switzerland,[6] as well as independent work in our laboratories, produced the 2-methylmercapto- and 2-methylsulfonyl-phenothiazines. The development of the potent 10-aminoalkyl-2-trifluoromethylphenothiazines[7,8] has led us to study the 10-aminoalkyl-2-trifluoromethylmercapto- and 2-trifluoromethylsulfonylphenothiazines. The present paper describes the preparation of the novel 2-substituted phenothiazine intermediates. The synthesis of a number of 10-alkylated phenothiazines derived from them will be described later.

Many methods for preparing phenothiazines have been reported in the literature.[9] These include: (A) the thionation of an appropriately substituted diphenylamine with sulfur[10] and a catalyst,[11,12] (B) the copper-catalyzed dehydrohalogenation of substituted 2-amino-2′-halodiphenyl sulfides,[13] and (C) the Smiles rearrangement of 2′-amido-2-

(1) These compounds were prepared at the Research Institute of Temple University under a contract with Smith Kline & French Laboratories. Papers I and II of this series are considered to be those referred to in ref. (7) and (34).

(a) To whom inquiries may be addressed.

(2) Research Institute of Temple University.

(3) Smith Kline & French Laboratories.

(4) P. Charpentier, *et al.*, *Compt. rend.*, **235**, 59 (1952).

(5) Rhône-Poulenc, Belgian Patent **552,836** (1957).

(6) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fisher, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061 (1958).

(7) P. N. Craig, E. A. Nodiff, J. J. Lafferty, and G. E. Ullyot, *J. Org. Chem.*, **22**, 709 (1957).

(8) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957).

(9) S. P. Massie, *Chem. Revs.*, 54, 797 (1954).

(10) A. Bernthsen, *Ber.*, **16**, 2896 (1883).

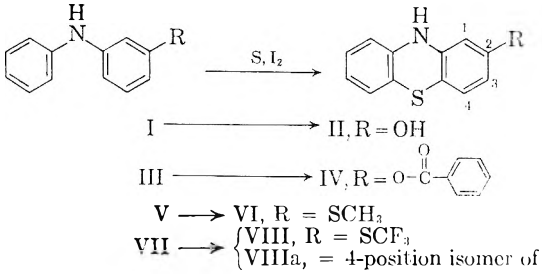
(11) E. Knoevenagel, *J. prakt. Chem.*, **89**, 11 (1914).

(12) F. Ackermann, German Patent **224,348** (1909).

(13) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Patent **2,769,002** (1956).

nitrodiphenyl sulfides followed by ring closure with loss of nitrous acid.[14,15]

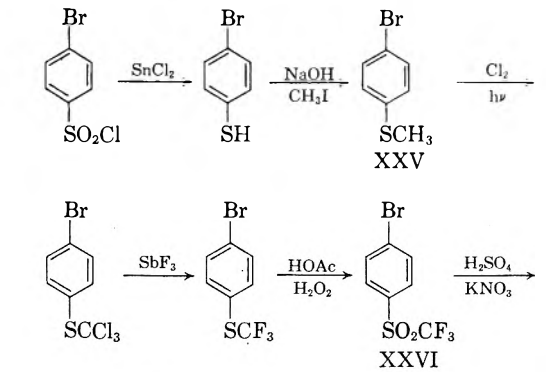
Five of the phenothiazines reported here were made by method (A) using the appropriate 3-substituted diphenylamines as shown by the accompanying equation. Single attempts to prepare 2-methylsulfonyl- and 2-acetoxyphenothiazine, using Method (A), gave evolution of hydrogen sulfide, but no phenothiazines could be characterized in the products of the reactions.

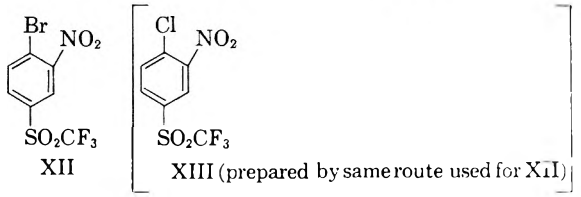


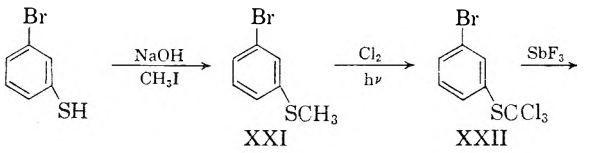
The reaction of resorcinol with aniline in the presence of calcium chloride gave the 3-hydroxydiphenylamine (I).[16,17] The benzoate (III)[18] and the acetate (X) were prepared from I. The remaining diphenylamines were prepared by the method of Goldberg[19] from acetanilide and the appropriately 3-substituted bromobenzenes.

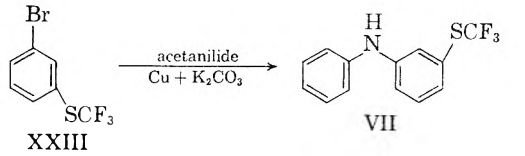
Two other phenothiazines were prepared according to Method (B), starting with *o*-bromothiophenol and the appropriately substituted *o*-halonitrobenzenes.

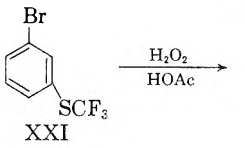
The routes used to prepare some of the required intermediates are outlined in the flow diagrams.

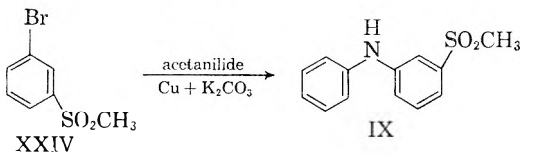


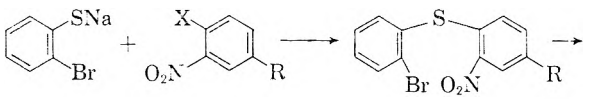






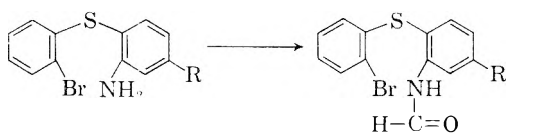






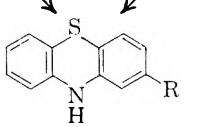
XI, X = Cl, R = SO_2CH_3
XII, X = Br, R = SO_2CF_3
XIII, X = Cl, R = SO_2CF_3

XIV, R = SO_2CH_3
XV, R = SO_2CF_3



XVI, R = SO_2CH_3
XVII, R = SO_2CF_3

XVIII, R = SO_2CF_3



XIX, R = SO_2CH_3
XX, R = SO_2CF_3

The preparation of most of the intermediates was routine. However, several points in these syntheses are of interest.

It was found that 2′-bromo-2-nitro-4-methylsulfonyldiphenylsulfide (XIV) exists in two crystalline modifications. These forms show identical elemental analyses but melt at 132–133° (α) and 158–160° (β). On standing overnight, at room temperature, exposed to air, the low melting form (α) converts to the high melting form (β). The melting point of the (β) form is not depressed upon admixture with the high melting form prepared from the (α) modification. The infrared spectra show some differences, but the work of Jones and

(14) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).
(15) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).
(16) A. Calm, *Ber.*, **16**, 2786 (1883).
(17) V. Merz and W. Weith, *Ber.*, **14**, 2343 (1881).
(18) K. v. Auwers, *Ann.*, **364**, 171 (1909).
(19) I. Goldberg, *Ber.*, **40**, 4541 (1907).

Sandorfy[20] and Ebert and Gottlieb[21] on spectra and polymorphism indicates that this is not unusual. In one reaction the products (XIV) were found to consist of 35% as the (α) modification and 55% as the (β) form. In a similar reaction the only compound isolated was 78% as the (α) form. On reduction and cyclization both forms gave the same amine (XVI) and the same phenothiazine (XIX).

The synthesis of 2′-bromo-2-nitro-4 trifluoromethylsulfonyldiphenylsulfide (XV) was accomplished, in one case, by the reaction between sodium *o*-bromothiophenolate and 3-nitro-4-chlorophenyl trifluoromethylsulfone (XIII) and, in another, by the same reaction using the bromo analog of XIII. The bromo analog (XII) gave a 92% yield of XV after refluxing in ethanol for four hours. The chloro compound (XIII) gave only a 46% yield of XV after refluxing for as long as eighteen hours.

The cyclization of 2′-bromo-2-amino-4-trifluoromethylsulfonyldiphenylsulfide (XVII) to 2-trifluoromethylsulfonylphenothiazine (XX) was very sensitive to time and to the purity of the starting material (XVII). Thus, starting material which melted 110–113° gave yields of XX of 30% or less, while material melting only slightly higher (112–113°) increased the yield to 60%. If XVII were refluxed in *N*,*N*-dimethylformamide (DMF) for longer than 6.5 hr. or if it were impure, the copper catalyst was partly consumed and XVII was converted to a purple substance which was soluble only in water and DMF. To eliminate the critical nature of this cyclization it was found expedient to formylate XVII. On cyclization, the formyl derivative (XVIII) gave 60–80% of the phenothiazine (XX) after refluxing for only 1.25 hr. The formyl group was removed during the reaction.[22]

The configuration of the phenothiazines (XIX and XX) obtained by Method (B) is unequivocal, as only one isomer is possible. Method (A), however, when applied to 3-substituted diphenylamines, can give both the 2- and 4-substituted phenothiazines, depending on whether thionation takes place *o*- or *p*- to the substituent. Various authors[4,6,8,9,22–24] have investigated this situation and from their work have proposed criteria for the assignment of structure. Thus the 2-isomer is obtained in greater abundance, is less soluble, and melts higher.[25] In the infrared the 2-isomers should show a deep band in region 12.0–12.5μ (asymmetric trisubstituted benzene) while the 4-isomers show a deep band in the region 12.5–13.2μ (vicinal trisubstituted benzenes).

The 2-methylmercapto-, 2-trifluoromethylmercapto- and 4-trifluoromethylmercaptophenothiazines show the expected peaks (12.4μ, 12.3μ and 12.8μ respectively). However, the unambiguously prepared 2 - methylsulfonylphenothiazine (XIX) has a very weak peak at 12.5μ and an unexpected strong peak at 13.0μ. The similarly prepared 2-trifluoromethylsulfonylphenothiazine (XX) has a moderate peak at 12.4μ but again an unexpected strong peak at 13.0μ. The benzoyloxy phenothiazine has only a weak peak at 12.6μ in the region 12.0–13.2μ. The final assignment of orientation in phenothiazines should not be made solely on the basis of infrared spectra.[22]

The phenothiazines reported here gave a characteristic deep red color with concentrated nitric acid except for 2-hydroxyphenothiazine, which gave a green color in this test.

EXPERIMENTAL[26]

3-Acetoxydiphenylamine (X).[27] Acetylation of 3-hydroxydiphenylamine (I)[16,17] was carried out with acetic anhydride in pyridine. Recrystallization from ethanol gave 80% of white crystals, m.p. 86–87°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.99; H, 6.04.

2-Hydroxyphenothiazine (II). A mixture of 1.6 g. (0.0087 mol.) of I, 0.51 g. (0.016 mol.) sulfur and a few crystals of iodine was heated in a test tube, under dry nitrogen, for 1 hr. at 130–140°. The hard, black reaction mass was extracted with benzene and the extracts were concentrated and treated with petroleum ether to give a flocculent yellow precipitate. Vacuum sublimation, followed by recrystallization from benzene, gave 0.2 g. (11%) of pale yellow glistening platelets. It was not possible to get a clear melting point even under nitrogen. Successive portions of II were plunged into a melting point bath whose temperature was gradually increased. At a bath temperature of 215° the solid melted momentarily to a clear yellow liquid before decomposing (lit.,[27(a)] 207–209°).

Anal. Calcd. for $C_{12}H_9NOS$: C, 56.95; H, 4.21. Found: C, 57.07; H, 4.57.

3-Benzoyloxydiphenylamine (III). Benzoylation of I with benzoylchloride in pyridine gave 73% of III, m.p. 125–126° after two crystallizations from ethanol (lit.[18] m.p. 125.5–126.5°).

2-Phenothiazinyl benzoate (IV). A mixture of 251 g. (0.87 mol.) of III, 50 g. of (1.56 mol.) sulfur and 3.8 g. of iodine was stirred for 1.5 hr. at 160° under dry nitrogen. The extremely hard, green-black reaction mixture was crushed and

(20) R. N. Jones and C. Sandorfy, *Technique of Organic Chemistry*, Vol. 9, *Chemical Applications of Spectroscopy*, A. Weissberger, ed., Interscience Publishers Inc., New York, 1956, pp. 294–296.

(21) A. A. Ebert, Jr., and H. B. Gottlieb, *J. Am. Chem. Soc.*, **74**, 2806 (1952).

(22) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955), reported a similar removal of a formyl group during the synthesis of various trifluoromethylphenothiazines by Smiles rearrangement of appropriate 2′-formamido-2-nitrodiphenylsulfides.

(23) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(24) J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).

(25) The known 2-isomers generally melt above 130° and the 4-isomers melt below 120°.

(26) All melting and boiling points are uncorrected.

(27) This compound is mentioned in Swiss Patent No. **283,320** (1952) as having been made from the sodium salt of *m*-hydroxydiphenylamine and acetyl chloride. No data are given. (a) After completion of the work described herein, this compound was reported by J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fisher, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz. [*Helv. Chim. Acta*, **42**, 259 (1959)].

boiled with 2 l. of benzene. A small amount of black tar was filtered and the benzene solution was decolorized from opaque black to clear maroon by stirring with chromatographic alumina. Concentration and recrystallization from benzene of the resulting cake gave 68 g. (24%) of yellow crystals, m.p. 195.0–196.5°. An analytical sample, obtained by vacuum sublimation followed by crystallization from benzene melted 196–197°.

Anal. Calcd. for $C_{19}H_{13}NO_2S$: C, 71.45; H, 4.10. Found: C, 71.45; H, 4.21.

3-Bromophenyl methyl sulfide (XXI). Diazotization of *m*-bromoaniline, followed by treatment with potassium ethyl xanthate gave *m*-bromothiophenol.[28,29] To a vigorously stirred mixture of 137.5 g. (0.73 mol.) of *m*-bromothiophenol, 380 ml. of 2*N* sodium hydroxide (0.76 mol.) and 670 ml. of water cooled to 10°, was added 105 g. (0.74 mol.) of methyl iodide during 0.5 hr. An additional 50 g. of methyl iodide was then added during 5 min. The reaction mixture was stirred at room temperature for 1.5 hr., extracted with ether and the extracts were dried over anhydrous magnesium sulfate. The yield of XXI was 133 g. (90%), b.p. 83–85/1 mm.; n_D^{23} 1.6243 (lit.[30] b.p. 121°/14 mm.; n_D^{20} 1.6240).

3-Methylmercaptodiphenylamine (V). A mixture of 102 g. (0.5 mol.) XXI, 81 g. (0.6 mol.) of acetanilide, 48 g. (0.35 mol.) of anhydrous potassium carbonate, and 1.7 g. of copper-bronze powder was heated to 220° during 2 hr., and then was stirred and refluxed at an external temperature of 220–230° for 20 additional hr. The final internal temperature was 200°. The black, viscous reaction mixture was extracted with acetone, the acetone was removed under reduced pressure and the dark brown oily residue was refluxed with 500 ml. of 20% ethanolic potassium hydroxide for 4.5 hr. The reaction mixture was poured into a l. of saturated salt solution, extracted with ether, dried over anhydrous magnesium sulfate, and concentrated. Crystallization of the dark brown, viscous residue from petroleum ether (b.p. 35–75°) gave 69 g. (64%) of glistening white crystals, m.p. 54–55°. Another crystallization from the same solvent provided an analytical sample, m.p. 55.0–55.5°.

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.51; H, 6.09; N, 6.51. Found: C, 72.25; H, 5.98; N, 6.56.

This compound (m.p. 59–61°) was reported by Bourquin *et al.*[6] from the decarboxylation of *N*-(3-methylmercaptophenyl)anthranilic acid.

2-Methylmercaptophenothiazine (VI). A mixture of 96.6 g. (0.45 mol.) V, 26.2 g. (0.82 mol.) of sulfur, and 1.45 g. of iodine was stirred, under nitrogen, for 1 hr. at an internal temperature of 135°. The hard brown reaction cake was dissolved in boiling benzene, treated with Norit and chromatographic alumina and concentrated under reduced pressure. Crystallization of the resulting solid from benzene gave 47 g. (43%) of off-white solid, m.p. 137.5–139.5°. A *pure white* analytical sample was obtained by vacuum sublimation followed by crystallization from ethanol; m.p. 138–139° (lit.[6] *pale yellow* solid, m.p. 138–140°).

Anal. Calcd. for $C_{13}H_{11}NS_2$: C, 63.63; H, 4.52. Found: C, 63.35; H, 4.56.

3-Bromophenyl trichloromethyl sulfide (XXII). Chlorine gas was introduced through a coarse fritted gas dispersing tube into a solution of 284.5 g. (1.4 mol.) of 3-bromophenyl methyl sulfide (XXI) in 1.5 l. of dry chloroform. During chlorine introduction the solution was irradiated with a 150 watt lamp and maintained at +15 to 18°. Chlorine was introduced for 7.5 hr., for a total weight increase of 180 g. Dissolved chlorine was removed with a vigorous nitrogen stream, the solvent was removed under reduced pressure and the residue distilled to give 396 g. (92%) of yellow oil, b.p. 102–104°/1 mm.; n_D^{30} 1.6178.

Anal. Calcd. for $C_7H_4BrCl_3S$: C, 27.43; H, 1.32. Found: C, 27.68; H, 1.54.

3-Bromophenyl trifluoromethyl sulfide (XXIII). A finely ground mixture of 142 g. (0.47 mol.) of XXII and 110 g. (0.62 mol.) of antimony trifluoride was heated in a 250 ml. Claisen flask to 150°. When the initial reaction subsided, the temperature was rapidly raised and the fraction boiling at 190–205° was collected. This fraction was dissolved in ether and washed with 6*N* hydrochloric acid (4 × 150 ml.) and water (2 × 200 ml.). The ether solution was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was distilled to give 73 g. (62%) of colorless liquid, b.p. 192–194°/760 mm.; 103–105°/40 mm.; n_D^{25} 1.5117. This material was used directly in the next step without further purification.

3-Trifluoromethylmercaptodiphenylamine (VII). A mixture of 160 g. (0.62 mol.) of XXIII, 100 g. (0.74 mol.) of acetanilide, 53 g. (0.37 mol.) of anhydrous potassium carbonate, and 2.1 g. of copper-bronze powder was treated as described in the synthesis of V. The residue remaining after removal of the acetone was refluxed for 5 hr. with a mixture of 180 ml. of concentrated hydrochloric acid and 500 ml. of ethanol, poured into 2.5 l. of cold water, and made just alkaline with 20% sodium hydroxide. This mixture was extracted with ether and the extract was dried over anhydrous magnesium sulfate to give 121 g. (72%) of pale yellow oil, b.p. 115–119°/0.3 mm. An analytical sample boiled at 116°/0.3 mm.; n_D^{30} 1.5829.

Anal. Calcd. for $C_{13}H_{10}F_3NS$: C, 57.98; H, 3.74. Found: C, 57.87; H, 3.99.

2-Trifluoromethylmercaptophenothiazine (VIII). A mixture of 117 g. (0.44 mol.) of VII, 25 g. (0.78 mol.) of sulfur, and 1.8 g. of iodine was stirred under nitrogen at 145–160° for 1.5 hr. The reaction mass was dissolved in a liter of boiling benzene, treated with a mixture of Darco G-60 and chromatographic alumina, and concentrated to give a yellow solid. A yield of 58 g. (45%) of glistening yellow crystals, m.p. 165–166°, was obtained on crystallization from carbon tetrachloride.

Anal. Calcd. for $C_{13}H_8F_3NS_2$: C, 52.16; H, 2.69; N, 4.68. Found: C, 51.88; H, 2.69; N, 4.72.

4-Trifluoromethylmercaptophenothiazine (VIIIa). The carbon tetrachloride mother liquor obtained from the crystallization of VIII was concentrated to give a yellow solid. Crystallization from ligroin (b.p. 66–75°) gave 3 g. (2%) of VIIIa, m.p. 82–84°.

Anal. Calcd. for $C_{13}H_8F_3NS_2$: C, 52.16; H, 2.69; N, 4.68. Found: C, 52.34; H, 3.05; N, 4.78.

3-Bromophenyl methyl sulfone (XXIV). A mixture of 22.4 g. (0.2 mol.) of 30% hydrogen peroxide and 20 ml. of glacial acetic acid was added with vigorous stirring, during 35 min., to a mixture of 20 g. (0.1 mol.) of XXI and 140 ml. of glacial acetic acid heated to 40°. When the mildly exothermic reaction had subsided, an additional 10 g. of 30% hydrogen peroxide was added during 5 min. After refluxing for 3 hr. and standing at room temperature overnight the reaction mixture was poured into 400 ml. of cold water. The solid was slurried with cold water, dried and crystallized from carbon tetrachloride to give 20 g. (85%) of glistening white plates, m.p. 99–101°.

This compound was prepared by Twist and Smiles[31] by bromination of methyl phenyl sulfone, m.p. 103°.

3-Methylsulfonyldiphenylamine (IX). This compound was prepared in the same manner as V. Crystallization from carbon tetrachloride followed by recrystallization from benzene–petroleum ether (30–60°) gave 30% of white crystals, m.p. 103–104°. The mixed melting point with XXIV was 70–85°.

(28) H. F. Wilson and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 5200 (1950).

(29) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, Coll. Vol. III, 809 (1955).

(30) Previously prepared by K. Brand, W. Gabel, and E. Rosenkranz (*Ber.*, **70**, 296 (1937)) by means of the Sandmeyer reaction on *m*-aminophenyl methyl sulfide.

(31) R. F. Twist and S. Smiles, *J. Chem. Soc.*, 1248 (1925).

Anal. Calcd. for $C_{13}H_{13}NSO_2$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.34; H, 5.38; N, 5.57.

Attempted thionation of IX. A mixture of 3.16 g. (0.013 mol.) of IX, 0.74 g. (0.023 mol.) of sulfur and 0.095 g. of iodine was gradually heated in a test tube to 210°. Hydrogen sulfide evolution was extremely slow. Vacuum sublimation of the green, brittle reaction mixture at 180° and 0.05 mm. gave only a trace of yellow solid, m.p. 168–170°. This solid turned green on standing and gave a deep red color with concentrated nitric acid.

2'-Bromo-2-nitro-4-methylsulfonyldiphenylsulfide (XIV). Chlorobenzene was converted to 4-chlorophenyl methyl sulfone using methanesulfonyl chloride and aluminum chloride.[32] Nitration with concentrated sulfuric acid and potassium nitrate gave 3-nitro-4-chlorophenyl methyl sulfone (XI).[31,33] To a mixture of 94.5 g. (0.5 mol.) of *o*-bromothiophenol,[34] 1.5 l. of ethanol, 150 ml. of water and 20 g. (0.5 mol.) of sodium hydroxide was added, with rapid stirring, a suspension of 118 g. (0.5 mol.) of XI in 1 l. of ethanol. The voluminous yellow solid which immediately formed redissolved on heating to reflux temperature. Stirring and refluxing were continued 2 hr. Two identical reactions of this size were filtered hot and combined. From the hot filtrate there separated immediately 135 g. (35%) of long yellow needles, m.p. 131–133°. On cooling, the filtrate yielded an additional 213 g. (55%) of short yellow needles, m.p. 158–160°. On standing overnight, exposed to air at room temperature, the low melting form changed to the high melting form.

Anal. Calcd. for $C_{13}H_{10}BrNO_4S_2$: C, 40.21; H, 2.60. Found: C, 40.54; H, 2.70.

A similar run carried out with 0.05 mol. of XI gave exclusively the long yellow needles, m.p. 132–133° (78%).

Anal. Calcd. for $C_{13}H_{10}BrNO_4S_2$: C, 40.21; H, 2.60; N, 3.61. Found: C, 40.56; H, 2.89; N, 3.64.

2'-Bromo-2-amino-4-methylsulfonyldiphenyl sulfide (XVI). Eleven and six-tenths grams (0.03 mol.) of XIV was added during 0.75 hr., to a mixture of 51.3 g. (0.23 mol.) of stannous chloride dihydrate in 45 ml. of concentrated hydrochloric acid at 50°. The temperature did not rise above 70° during the addition. The clear, pale-yellow reaction mixture was refluxed for 2 hr. and made strongly alkaline with 40% potassium hydroxide. The alkaline mixture was extracted with benzene and the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting pale-yellow oil solidified on standing and gave 7.0 g. (66%) of pure white crystals on crystallization from ethanol, m.p. 125–126°.

Anal. Calcd. for $C_{13}H_{12}BrNO_2S_2$: C, 43.58; H, 3.38; N, 3.91. Found: C, 43.65; H, 3.41; N, 4.21.

2-Methylsulfonylphenothiazine (XIX). A mixture of 78 g. (0.22 mol.) of XVI, 700 ml. of dimethylformamide (DMF), 35 g. (0.25 mol.) of anhydrous potassium carbonate and 3.5 g. of copper-bronze powder was stirred and refluxed for 24 hr. The clear, deep-orange reaction mixture was filtered and the filtrate was diluted with 3 l. of cold water. A green gum formed initially but solidified on standing. The crude solid was dried *in vacuo*, dissolved in benzene, and stirred simultaneously with Norit and chromatographic alumina. Concentration under reduced pressure gave 46.5 g. (77%) of pale yellow solid, m.p. 156.5–158°. An analytical sample melted 158–159° after vacuum sublimation and crystallization from benzene–carbon tetrachloride (lit.[5] m.p. 164°).

Anal. Calcd. for $C_{13}H_{11}NS_2O_2$: C, 56.29; H, 4.00. Found: C, 56.13; H, 3.99.

An attempt to carry out this cyclization in the absence of a solvent and using cuprous iodide instead of copper-bronze was unsuccessful.

4-Bromophenyl methyl sulfide (XXV). 4-Bromobenzenethiol was prepared by reduction of commercial 4-bromobenzenesulfonyl chloride with stannous chloride dihydrate and anhydrous hydrogen chloride in glacial acetic acid.[28,35] Methylation was carried out as described for the synthesis of XXI to give 84% of white solid, m.p. 36.5–38°. A small quantity was further purified by distillation, b.p. 92.5–94°/2.5 mm.; m.p. 39–40°.[35]

This compound was prepared previously by Holt and Reid[36] from 4-aminophenyl methyl sulfide using the Sandmeyer reaction (m.p. reported to be 27°).

4-Bromophenyl trifluoromethyl sulfone (XXVI). Compound XXV was chlorinated and then fluorinated with antimony trifluoride to give 4-bromophenyl trifluoromethylsulfide.[37] Oxidation with 30% hydrogen peroxide in glacial acetic acid, as described in the synthesis of XXIV, gave 93% of white solid, m.p. 59.5–61.5°. This material was dried and used without crystallization. Compound XXVI was previously prepared[37] from 4-aminophenyl trifluoromethylsulfone using the Sandmeyer procedure (lit.[37] m.p. 64–65°).

The oxidation of XXV was also carried out in this laboratory using chromic anhydride in glacial acetic acid. The yields were lower than those obtained with hydrogen peroxide.

4-Chlorophenyl trifluoromethylsulfone (XXVII). Oxidation of 4-chlorophenyl trifluoromethylsulfide,[38] using the same procedure as in the synthesis of XXIV, gave 93% of the sulfone (XXVI), m.p. 55–56° on crystallization from ethanol (lit.[38] m.p. 55–56°).

This oxidation was carried out previously[38] using chromic anhydride in glacial acetic acid.

3-Nitro-4-bromophenyl trifluoromethylsulfone (XII). Seventy-five grams (0.26 mol.) of XXVI were suspended in 240 ml. of concentrated sulfuric acid. The suspension was heated to 80°, at which temperature it became a clear yellow solution. To this solution, maintained at 80–90°, were added, during 55 min., 45.5 g. (0.46 mol.) of solid potassium nitrate. The temperature was maintained at 90° for 2 additional hr. The reaction mixture was poured onto 2 l. of crushed ice and the resulting precipitate was crystallized from ethanol to give 74.8 g. (86%) of white crystals; m.p. 87–89°. An analytical sample was recrystallized from ethanol; m.p. 88–89°.

Anal. Calcd. for $C_7H_3BrF_3NO_4S$: C, 25.16; H, 0.91. Found: C, 25.23; H, 1.04.

3-Nitro-4-chlorophenyl trifluoromethylsulfone (XIII). Nitration of 4-chlorophenyl trifluoromethylsulfone was carried out as described in the synthesis of XII. The yield of fine white needles was 74%; m.p. (from ethanol) 54–55°. A second crystallization from ethanol gave the analytical sample, m.p. 55–56°.

Anal. Calcd. for $C_7H_3ClF_3NO_4S$: C, 29.03; H, 1.04. Found: C, 29.20; H, 1.03.

2'-Bromo-2-nitro-4-trifluoromethylsulfonyldiphenylsulfide (XV). A solution of 71.5 g. (0.21 mol.) of XII in 750 ml. of ethanol was added to a solution of 8.4 g. (0.21 mol.) of sodium hydroxide, 63 ml. of water, 39.9 g. (0.21 mol.) of *o*-bromothiophenol and 625 ml. of ethanol. The resulting yellow solution was refluxed 4 hr. and concentrated to 300 ml. under reduced pressure. The yellow prisms which separated were washed with water in a Waring blendor and then further washed with 300 ml. of ethanol. The yield was 85 g. (92%); m.p. 144–146°.

(32) W. E. Truce and C. W. Vriesen, *J. Am. Chem. Soc.*, **75**, 5032 (1953).

(33) J. F. Bunnett, *et al.*, *J. Am. Chem. Soc.*, **75**, 642 (1953).

(34) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).

(35) E. D. Amstutz, E. A. Fehnel, and J. W. Woods, *J. Am. Chem. Soc.*, 69, 1922 (1947).

(36) H. S. Holt and E. E. Reid, *J. Am. Chem. Soc.*, 46, 2330 (1924).

(37) L. M. Yagupolsky and M. S. Marenets, *J. Gen. Chem. U.S.S.R.*, 24, 885 (1954). (Eng. Trans.)

(38) I. G. Farbenind, A.-G., French Patent 820,796 (1937).

Anal. Calcd. for $C_{13}H_7BrF_3NO_4S_2$. C, 35.30; H, 1.60. Found: C, 35.16; H, 1.67.

A similar synthesis of XV using XIII instead of XII gave only a 46% yield after refluxing for as long as 18 hr.

2'-Bromo-2-amino-4-trifluoromethylsulfonyldiphenylsulfide (XVII). A vigorous stream of hydrogen chloride gas was passed into a suspension of 450 g. (2.0 mol.) of stannous chloride dihydrate in 450 ml. of glacial acetic acid and 35 ml. of water until the suspension cleared (*ca.* 10 min.). The temperature of this solution was raised to 65° and 74 g. (0.17 mol.) of XV was added in portions during 1 hr., keeping the temperature at 70–80°. After about two-thirds of the stannous chloride had been added a white solid began to form. On completion of the addition, the reaction mixture was stirred at 85–90° for 2 additional hr. The mixture was filtered and the filtrate was poured onto crushed ice. The resulting precipitate was recrystallized from 95% ethanol to give 58 g. (84%) of white crystals; m.p. 112–113°.

Anal. Calcd. for $C_{13}H_9BrF_3NO_2S_2$: C, 37.87; H, 2.20. Found: C, 38.06; H, 2.40.

2'-Bromo-2-formamido-4-trifluoromethylsulfonyldiphenylsulfide (XVIII). A mixture of 100 g. (0.22 mol.) of XVII and 1 l. of 90% formic acid was refluxed for 20 hr. and poured over 6 l. of crushed ice. The resulting precipitate was washed with water and crystallized from ethanol to give 77 g. (72%) of white needles; m.p. 102.5–103°.

Anal. Calcd. for $C_{14}H_9BrF_3NO_3S_2$: C, 38.19; H, 2.06. Found: C, 38.44; H, 2.17.

2-Trifluoromethylsulfonylphenothiazine (XX) (from XVII). A mixture of 28 g. (0.07 mol.) of XVII, 250 ml. of DMF, 11.6 g. (0.08 mol.) of anhydrous potassium carbonate and 1.4 g. of copper-bronze powder was stirred and refluxed under dry nitrogen, for 6.5 hr. The reaction was then stopped even though carbon dioxide was still being evolved. The reaction mixture was filtered hot, the solid material washed with 25 ml. of DMF and the combined filtrate and washings were poured into 3 l. of water. A yellow colloid formed initially but on standing overnight an orange precipitate separated. The precipitate was dissolved in ethanol, treated with a mixture of chromatographic alumina and Darco G-60, and the solution was diluted with water to give 14 g. (60%) of orange crystals; m.p. 146–147°.

Anal. Calcd. for $C_{13}H_8F_3NO_2S_2$: C, 47.12; H, 2.43. Found: C, 47.27; H, 2.56.

A similar small scale (0.003 mol.) cyclization which was allowed to stir and reflux for 24 hr. gave only 30% of XX.

(*From* XVIII). A mixture of 11 g. (0.025 mol.) of XVIII, 125 ml. of DMF, 4.2 g. (0.03 mol.) of anhydrous potassium carbonate and 0.5 g. of copper-bronze powder was refluxed and stirred, under dry nitrogen, until carbon dioxide evolution was complete (1.25 hr.). The reaction mixture was filtered and washed as in Method A and the combined filtrate and washings were poured into a l. of cold water. On standing at room temperature for 2 hr. the initially formed yellow colloid gave 6.6 g. (80%) of orange crystals, m.p. 145–146° (XX). A mixed melting point with the material obtained from XVII showed no depression.

Acknowledgment. The authors wish to express their appreciation to Dr. James W. Wilson for his advice and suggestions concerning this work. The assistance of the Research Analytical Section of Smith Kline & French Laboratories for obtaining spectral and analytical data is gratefully acknowledged.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH AND THE DEPARTMENT OF CHEMISTRY, TEMPLE UNIVERSITY]

Azacyclooctane Derivatives[1]

JULIUS DIAMOND,[2a] WILLIAM F. BRUCE,[2b] CARL GOCHMAN,[2b] AND FLOYD T. TYSON[2c]

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Preparation of 1-methyl-4-phenyl-4-carbethoxyazacyclooctane and α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane is described. These substances showed less analgesic activity than their analogs with six-membered rings.

The preparation of ethoheptazine[3] has made available a seven-membered ring analog of meperidine. This new compound has proved to have valuable analgesic properties without addiction potential.[4] Continuing this study, we have now made the eight-membered ring analog of meperidine to permit study of the effect of further ring enlargement, and particularly because the morphine molecule can be considered to contain an eight-membered heterocyclic ring. In addition to the eight-membered ring analog in this series, namely 1-methyl-4-phenyl-4-carbethoxyazacyclooctane (VI), we have also prepared α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane (XVII), which is an eight-membered ring analog of alphaprodine, a more potent analgesic than either ethoheptazine or meperidine.[5]

Formation of the azacyclooctane ring was ac-

(1) Taken in part from the dissertation of J. Diamond, submitted to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy (1955).

(2) (a) Present address: Lincoln Laboratories, Decatur, Ill. (b) Wyeth Institute for Medical Research, Philadelphia 1, Pa. (c) Department of Chemistry, Temple University, Philadelphia 22, Pa.

(3) The generic name for 1-methyl-4-phenyl-4-carbethoxyazacycloheptane, also known as Zactane®. J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.*, **22**, 399 (1957); J. Diamond and W. F. Bruce, U. S. Patent 2,666,050 (1954) [*Chem. Abstr.*, **49**, 4031 (1955)]; F. F. Blicke and E.-P. Tsao, *J. Am. Chem. Soc.*, **75**, 5587 (1953).

(4) J. Seifter, D. K. Eckfeld, I. A. Letchack, E. M. Gore, and J. M. Glassman, *Federation Proc.*, **13**, 403 (1954); A. J. Grossmann, M. Golbey, W. C. Gittinger, and R. C Batterman, *J. Am. Geriatrics Soc.*, **4**, 187 (1956).

(5) The synthesis of an azacycloheptane analog of α-prodine will be reported in a subsequent paper.

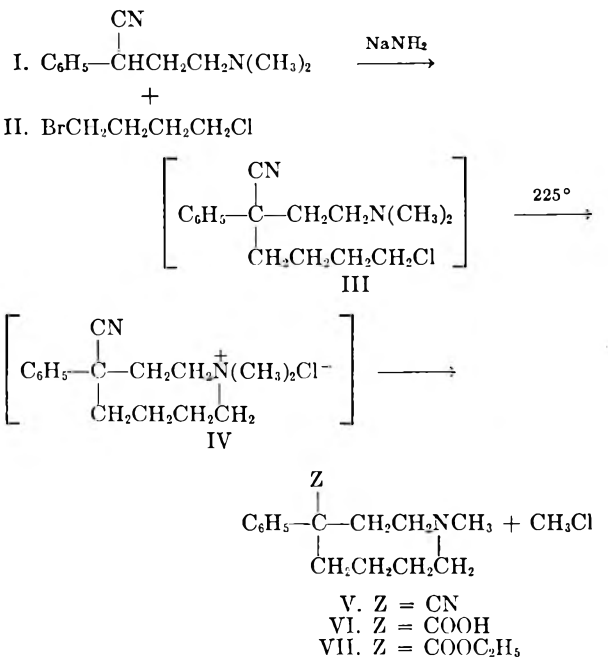


Figure 1

complished in the one case, as shown in Fig. 1, by first treating 2-phenyl-4-dimethylaminobutyronitrile (I) with tetramethylene chlorobromide (II). The sodio derivative of I, formed with sodamide, reacted with II in ether at −20° to −25° to produce 1-dimethylamino-3-phenyl-3-cyano-7-chloroheptane (III) which, because of its tendency to react with another molecule of itself, was not isolated. Upon heating a solution of this compound in 2,6,8-trimethylnonanol-4 at 225°, cyclization and dechloromethylation occurred to produce 1-methyl-4-phenyl-4-cyanoazacyclooctane (IV) in 21.9% over-all yield from I. This is half the yield obtained in the preparation of the nitrile in the seven-membered ring series by a similar process, no doubt a consequence of the less ready formation of eight-membered rings.

The direct conversion of III to V was resorted to after several unsuccessful attempts were made to cyclize III in nitrobenzene to the isomeric azacyclooctane quaternary salt IV. By contrast, a seven-membered ring quaternary salt was readily obtained in yields of 65–80% in this solvent by an analogous synthesis.[3]

Hydrolysis of the azacyclooctane nitrile (V) with 80% sulfuric acid at 115–120° produced the carboxylic acid (VI) which was not isolated, but was converted to VII by esterification with ethanol in the presence of sulfuric acid.

The eight-membered ring structures for V and VII were assigned on the basis of the elemental analyses, C-methyl values and molar refraction measurements. The C-methyl values, determined by the method of Kuhn and Roth,[6] confirmed the absence of a C-methyl group in the nitrile (V) and the presence of only one C-methyl group in the ester (VII). All isomeric contracted ring structures, such as VIII and IX, containing an extranuclear C-methyl group were thereby ruled out. Alicyclic structures X and XI were eliminated as a result of elementary analyses and molecular refraction (Fig. 2).

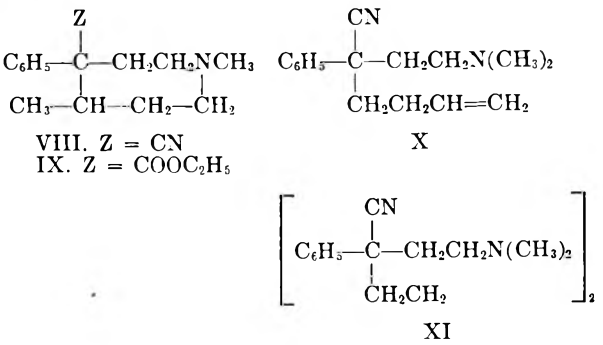


Figure 2

The preparation of XVII was accomplished, as shown in Fig. 3, by condensing methyl methacrylate (XII) with methylamine to give methyl ω-methylaminoisobutyrate (XIII).[7] By treating XIII with 5-chlorovaleronitrile in *n*-butyl ether at 110–115° over potassium carbonate for 16 hr. a new tertiary amine, 4-cyanobutyl-2-carbomethoxypropylmethylamine (XIV) resulted. Upon reaction of this compound in tetralin with sodium hydride at 150° for 1.5–2 hr. followed by hydrolysis and decarboxylation, without isolation of the intermediates, a keto tertiary amine (XV) was obtained which on analysis had the composition of 1,3-dimethylazacyclooctanone-4. The ketone function in this compound was shown upon its conversion by phenyllithium to a phenylaminocarbinol (XVI). Esterification with propionic anhydride gave the propionate (XVII).

A pharmacological evaluation of VII with ethoheptazine and meperidine showed that the analgesic potency of the new compound is considerably less than that of the others, coupled with increased toxicity. Study of XVII is not yet completed.[8]

EXPERIMENTAL[9]

1-Methyl-4-phenyl-4-cyanoazacyclooctane (V). A solution of 141 g. (0.75 mol.) of 2-phenyl-4-dimethylaminobutyronitrile[10] in 300 ml. of ether was added dropwise to 35.1 g. (0.90 mol.) of sodamide suspended in 700 ml. of anhydrous ether. The reaction was conducted at 30–35° with stirring under a nitrogen atmosphere. The mixture was then heated at its reflux temperature for 2 hr., cooled to −30°, and a solution of 153 g. (0.89 mol.) of tetramethylene chlorobromide in 300 ml. of ether was added dropwise at −25 to −20°. Upon completing the addition, the mixture was al-

(6) R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933).

(7) D. R. Howton, *J. Org. Chem.*, **10**, 277 (1945).

(8) J. Seifter, private communication.

(9) All melting points were determined in an oil bath and are uncorrected; microanalyses by Dr. G. Ellis and associates.

(10) C. E. Kwarther and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946).

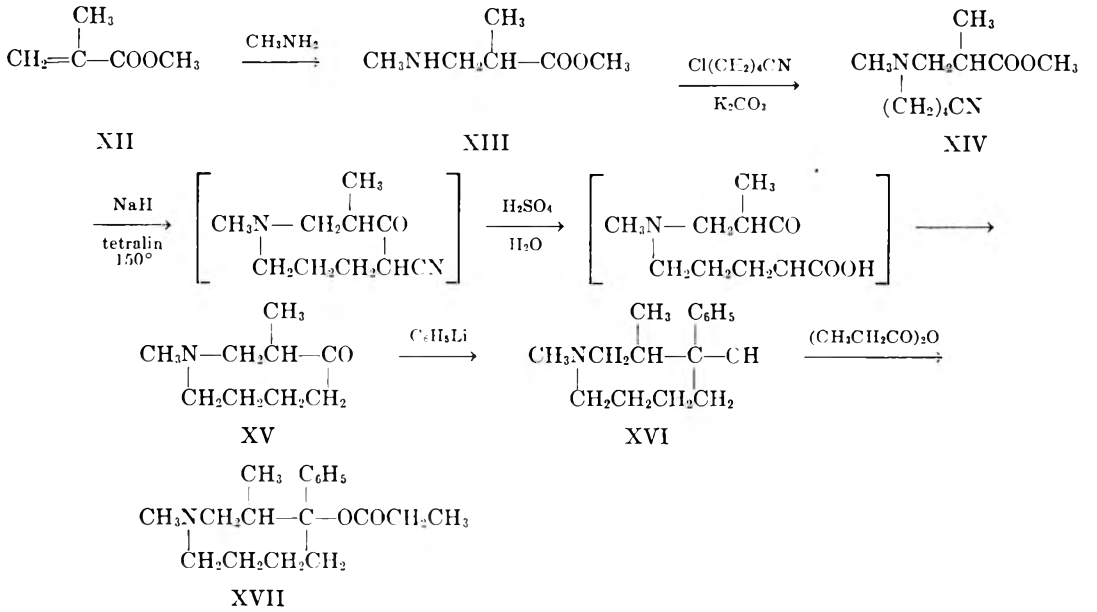


Figure 3

lowed to warm to room temperature and stand overnight. The precipitated inorganic salts were filtered off and the ether removed from the filtrate under reduced pressure. The liquid residue contained 1-dimethylamino-3-phenyl-3-cyano-7-chloroheptane (III).

One liter of 2,6,8-trimethylnonanol-4 was added to the residue and the solution added with stirring during 1.5 hr. to 1 l. of refluxing trimethylnonanol, b.p. 225°. The solution was heated at its reflux temperature for an additional 2 hr., then cooled under nitrogen and extracted with dilute hydrochloric acid. The acid extract was washed with ether, made alkaline with aqueous sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The product was rapidly distilled away from a large quantity of resinous material at 140–160° at 0.3–0.4 mm. Redistillation of the crude material gave 37.4 g. (21.9%) of V, pale yellow liquid, b.p. 130–134° at 0.3 mm.; n_D^{27} 1.5270; d_4^{27} 1.010.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.82; N, 12.75; C—CH_3, 0.00; M_D 69.54. Found: C, 79.06; H, 9.32; N, 12.57; C—CH_3, 0.00; M_D 69.48.

The *picrate*, m.p. 158–159°, was formed in acetone-methanol.

Anal. Calcd. for $C_{21}H_{23}N_5O_7$: C, 55.18; H, 5.07; N, 15.32. Found: C, 55.33; H, 4.89; N, 15.13.

1-Methyl-4-phenyl-4-carbethoxyazacyclooctane (VII). A mixture of 9.1 g. (0.04 mol.) of V, 10.6 g. of 98% sulfuric acid, and 2.6 g. of water was heated at 115–125° for 3 hr. The resulting sirupy solution which contained 1-methyl-4-phenyl-4-carboxyazacyclooctane (VI) was cooled somewhat and 75 ml. of absolute ethanol added. After refluxing this solution for 16 hr., the excess ethanol was distilled off at atmospheric pressure. The cooled residue was poured slowly into an ice-cold saturated solution of sodium carbonate, and extracted with ether. Distillation of the dried and filtered extract gave 5.2 g. (46.9%) of VII, a colorless liquid, b.p. 130–133° at 0.3 mm.; n_D^{28} 1.5215; d_4^{26} 1.042. In a second reaction using 27.3 g. of V, 15.5 g. (45.9%) of VII was also obtained.

Anal. Calcd. for $C_{17}H_{25}N_2$: C, 74.18; H, 9.15; N, 5.08; C—CH_3, 5.46; M_D 80.70. Found: C, 74.07; H, 9.06; N, 4.99; C—CH_3, 5.59; M_D 80.68.

The *methiodide*, m.p. 165–167° dec., was formed in acetone-ether.

Anal. Calcd. for $C_{15}H_{28}INO_2$: C, 51.82; H, 6.76; N, 3.36; I, 30.5. Found: C, 51.92; H, 6.86; N, 3.09; I, 30.5.

4-Cyanobutyl-2-carbomethoxypropylmethylamine (XIV). Methyl β-methylaminoisobutyrate (XIII), boiling from 115–125° at 150 mm., n_D^{28} 1.4200, was prepared in 39% yield by the method of Howton,[7] except that the reaction mixture was worked up after standing overnight instead of 3 days. A mixture of 100 g. (0.85 mol.) of ω-chlorovaleronitrile, 111.5 g. (0.85 mol.) of XIII, and 120 g. (0.87 mol.) of anhydrous potassium carbonate in 300 ml. of *n*-butyl ether was stirred and heated at 110–115° for 16 hr. The solid was collected on a filter and was washed with ether. The filtrate was extracted three times with dilute hydrochloric acid. The combined acid extracts were washed with ether to remove traces of neutral material, then made alkaline with sodium hydroxide and extracted with ether. This extract was dried over anhydrous potassium carbonate, filtered, concentrated, and distilled to give 70.0 g. (39%) of XIV, a colorless liquid boiling from 117–122° at 0.20 mm., n_D^{24} 1.4465.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.20; H, 9.49; N, 13.20. Found: C, 62.41; H, 9.46; N, 13.31.

1,3-Dimethylazacyclooctanone-4 (XV). A mixture of 6.2 g. (0.125 mol.) of a 48.6% dispersion of sodium hydride in mineral oil and 350 ml. of tetralin was placed under nitrogen in a 1-l. 3-necked flask. After dropwise addition of 25.9 g. (0.122 mol.) of XIV to this mixture, stirring and heating at 150° was carried on for 2 hr., during which time the gray mixture became rose colored. Heating was discontinued and when the mixture had cooled somewhat, 10 ml. of methanol was added to destroy any unreacted sodium hydride. The mixture was then washed with water and with 100 cc. of 50% sulfuric acid. The acid extract was refluxed for 15 hr., during which time carbon dioxide evolution gradually decreased to zero. After the acid solution was cooled, diluted with an equal volume of water, and extracted with ether to remove neutral by-products, the product was obtained upon making the solution basic by adding 40% sodium hydroxide and extracting it with ether. After drying the ether over anhydrous potassium carbonate, filtering, concentrating, and distilling the product, 2.0 g. (10.5%) of a colorless liquid (XIV) boiling from 110–118° at 38–40 mm. was obtained.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.60; H, 11.03; N, 9.03. Found: C, 69.64; H, 10.89; N, 9.24.

α-1,3-Dimethyl-4-phenyl-4-propionoxyazacyclooctane (XVII). To a solution of phenyllithium prepared by adding 7.1 g. of bromobenzene to a mixture of 0.635 g. (0.091 g.-atom) of lithium shot and 50 ml. of anhydrous ether under nitrogen, followed by 2 hr. of reflux, was added at −20°, 2.0 g. (0.0129 mol.) of XIV in 25 ml. of toluene. After 0.5 hr., the reaction mixture was warmed to room temperature and allowed to stand overnight. A solution of 6.66 g. (0.0475 mol.) of propionic anhydride in 25 ml. of toluene with 2 drops of concentrated sulfuric acid as a catalyst was added and the solution was concentrated until the temperature of the distillate reached 105°, when the temperature was held at this point for 3 hr. After the solution was cooled and made alkaline by adding 20 ml. of 5% sodium hydroxide solution, the product was extracted from the toluene layer by washing with dilute hydrochloric acid, the acid extract washed with ether to remove traces of neutral material, and made alkaline by adding cold 4*N* sodium hydroxide. The product was taken up in ether, dried over anhydrous potassium carbonate, filtered, concentrated, and distilled to give 1.0 g. (27%) of amber liquid (XVII) boiling from 90–92° at 0.20 mm., n_D^{24} 1.5262. While two DL mixtures are possible, no evidence for more than one form, designated α, has been found in this product.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.41. Found: C, 74.88; H, 9.76.

The *picrate*, melting at 128–130°, was formed in ether and was recrystallized from 1-butanol.

Anal. Calcd. for $C_{24}H_{30}N_4O_9$: C, 55.60; H, 5.85; N, 10.80. Found: C, 55.73; H, 5.49; N, 10.41.

The *acid citrate*, melting at 134–135°, was formed in absolute ethanol.

Anal. Calcd. for $C_{24}H_{35}NO_9$: C, 59.90; H, 7.31; N, 2.91. Found: C, 60.97; H, 7.13; N, 2.98.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

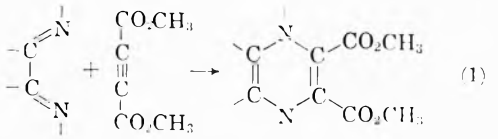
Reaction of 2-Phenylquinoxaline and of 2,3-Diphenylquinoxaline with Dimethyl Acetylenedicarboxylate[1]

ERLING GROVENSTEIN, JR., WILLIAM POSTMAN, AND JAMES W. TAYLOR

Received June 26, 1959

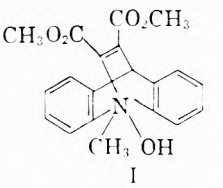
2,3-Diphenylquinoxaline reacts with dimethyl acetylenedicarboxylate in methanol to give a yellow product which consists of 1 mole each of 2,3-diphenylquinoxaline, dimethyl acetylenedicarboxylate, and methanol. On the basis of its reactions and ultraviolet absorption spectra, this product is assigned the structure 1-(1,2-dicarbomethoxyvinyl)-2,3-diphenyl-2-methoxy-1,2-dihydroquinoxaline (IV) in neutral or basic solution in methanol, while in acidic methanol it exists as 1-(1,2-dicarbomethoxyvinyl)-2,3-diphenylquinoxalinium cation (VI). 2-Phenylquinoxaline reacts similarly with dimethyl acetylenedicarboxylate to give a product which after long exposure to the atmosphere was isolated as 1-(1,2-dicarbomethoxyvinyl)-3-phenyl-2-hydroxy-1,2-dihydroquinoxaline (VIII). Reaction of 2,3-diphenylquinoxaline with hydrogen peroxide in acetic acid gave under the present conditions *N,N'*-dibenzoyl-*o*-phenylenediamine in addition to the previously reported *N,N'*-dioxo-2,3-diphenylquinoxaline.

The addition of dienophiles to 1-aza- and 1,4-diaza-1,3-dienes might be expected to occur in a manner analogous to the ordinary Diels-Alder reaction, thus for a 1,4-diaza-1,3-diene with dimethyl acetylenedicarboxylate as indicated in Equation 1. Such reactions, however, generally



(1)

appear to proceed in other ways if reaction occurs at all.[2] However, dehydroindigo undergoes 1,4-addition of dienophiles such as styrene to its two heterocyclic nitrogens[3] and acridine adds dimethyl acetylenedicarboxylate in methanol, according to Diels and Thiele,[4] to give chiefly an adduct which was formulated as stucture I. The report of Diels and Thiele encouraged us to investigate the reaction of dimethyl acetylenedicarboxylate with 2-phenyl- and 2,3-diphenylquinoxaline. During the course of the present work, Acheson and Burstall[5] showed that the product of Diels and Thiele had structure IIa in neutral



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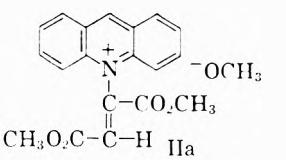
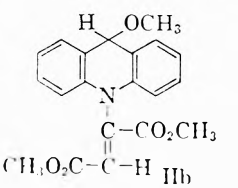


IIa



IIb

(1) Based chiefly upon the following theses at the Georgia Institute of Technology: W. Postman, Ph.D. Thesis, June, 1953; J. W. Taylor, M.S. thesis, June, 1958.

(2) M. C. Kloetzal, *Org. Reactions*, **4**, 1 (1948); H. L. Homes, *Org. Reactions*, **4**, 60 (1948).

(3) R. Pummerer, H. Fiesselmann, and O. Müller, *Ann.*, **544**, 206 (1940); R. Pummerer and E. Stieglitz, *Ber.*, **75**, 1072 (1942).

(4) O. Diels and W. E. Thiele, *Ann.*, **543**, 79 (1940).

(5) R. M. Acheson and M. L. Burstall, *J. Chem. Soc.*, 3240 (1954).

methanol and IIb in alkaline methanol. Similar structures were reported by Acheson and Bond[6] for the product from phenanthridine and by Acheson and Jefford[7] for the product from 2,3-benzacridine with dimethyl acetylenedicarboxylate in methanol.

Adduct from 2,3-Diphenylquinoxaline. Dimethyl acetylenedicarboxylate and 2,3-diphenylquinoxaline in methanol upon standing gave a yellow adduct whose elemental analysis, methoxyl content, and molecular weight were in agreement with that required for an adduct from 1 mol. each of dimethyl acetylenedicarboxylate, diphenylquinoxaline, and methyl alcohol. The adduct could be distilled *in vacuo* with little decomposition and could be recrystallized from solvents such as acetonitrile and carbon tetrachloride. The methanol in the adduct is, therefore, rather firmly bound, a fact which is also required by molecular weight determination in triphenylmethane. On the other hand, reaction of the adduct in ether solution with perchloric acid, picric acid, or ferric chloride gave crystalline products of composition expected for replacement of one methoxyl by perchlorate, picrate, or tetrachloroferrate(III) anion. A chloride could apparently be obtained by a similar procedure, but it proved too unstable for analysis.

When the yellow adduct was refluxed with ethanolic hydrochloric acid, 2,3-diphenylquinoxaline was recovered in nearly 70% yield. Reaction of the adduct with two molar equivalents of ethanolic potassium hydroxide gave some 45% yield of 2,3-diphenylquinoxaline, 16% of desoxybenzoin (benzyl phenyl ketone), 17% of quinoxaline-2-carboxylic acid, and 22% yield of carbon dioxide.

The adduct in acetone showed no reaction with a dilute solution of potassium permanganate at room temperature. The adduct, however, was oxidized by a hot solution of sodium dichromate in acetic acid; only 2,3-diphenylquinoxaline was recovered from the oxidation mixture. The adduct was oxidized by hydrogen peroxide in acetic acid in low yield to *N,N'*-dibenzoyl-*o*-phenylenediamine; this same product was obtained along with *N,N'*-dioxo-2,3-diphenylquinoxaline by oxidation of 2,3-diphenylquinoxaline under similar conditions.

The most outstanding result from the cleavage of the adduct by acid, base, or oxidizing agents—in so far as it relates to the structure of the adduct—was the isolation of 2,3-diphenylquinoxaline or its oxidation product. This result suggests that the adduct retains the structural skeleton of 2,3-diphenylquinoxaline and provides evidence against the attachment of dimethyl acetylenedicarboxylate to 2,3-diphenylquinoxaline by way of a C—C bond.

(6) R. M. Acheson and G. J. F. Bond, *J. Chem. Soc.*, 246 (1956).

(7) R. M. Acheson and G. W. Jefford, *J. Chem. Soc.*, 2676 (1956).

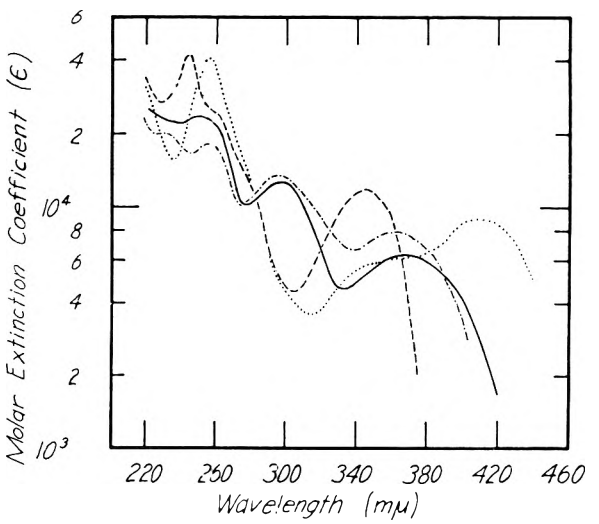
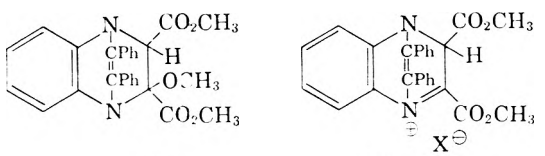


Fig. 1. Ultraviolet absorption spectra of adduct (IV) from 2,3-diphenylquinoxaline in methanol or in methanolic 0.1*N* $NaOCH_3$ (———) and in methanolic 0.1*N* $HClO_4$ or HCl (.....); adduct (VIII) from 2-phenylquinoxaline in methanol (-·-·-·); 2,3-diphenylquinoxaline in methanol (- - - -)

The isolation of quinoxaline-2-carboxylic acid suggests that at least one (possibly two) of the acetylenic carbon atoms of dimethyl acetylenedicarboxylate is joined to a heterocyclic nitrogen atom of 2,3-diphenylquinoxaline.

In Fig. 1 are presented the ultraviolet absorption spectra of the adduct in neutral, alkaline, and acidic methanol. The adduct gives the same spectrum in neutral methanol as in 0.1*N* methanolic $NaOCH_3$; however, the spectrum is appreciably altered in 0.1*N* methanolic $HClO_4$ or HCl. By way of comparison the spectrum of 2,3-diphenylquinoxaline differs significantly from that of its adduct with acetylenic ester; moreover, the spectrum of 2,3-diphenylquinoxaline is essentially the same in neutral methanol and in 0.1*N* methanolic HCl. The adduct and especially its derivatives with acids absorb more intensely at longer wave lengths than does 2,3-diphenylquinoxaline.

These data cannot be explained satisfactorily in terms of a structure such as IIIa for the adduct Structure IIIa could not undergo a ready ionization



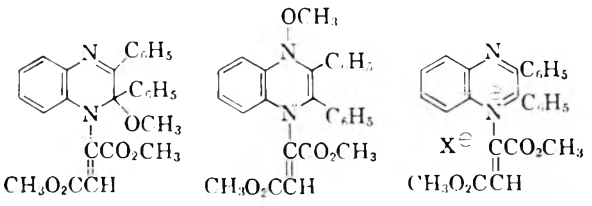
IIIa IIIb

(Ph = C_6H_5, X^- = Cl^-, ClO_4^-, *etc.*)

with dilute acids to give IIIb because IIIb is a highly strained structure, having a double bond at a bridgehead in violation of Bredt's rule. Conceivably III might undergo a more complex ionization to give VI. A more decisive argument against IIIa is that such a compound would not be

expected to be colored,[8a] as it has merely a *cis*-stilbene unit as its most extended chromophore (the nitrogen atoms of IIIa are not conjugated with the double bonds because of unfavorable geometry[8b] for orbital overlap).

Structure IV is therefore proposed for the adduct from 2,3-diphenylquinoxaline with dimethyl acetylenedicarboxylate in methanol. This structure is analogous to those proposed by Acheson[5,6,7] and co-workers and moreover offers an explanation for the ready ionization by dilute acids, as IV would be expected to combine with acids to give the more fully aromatic structure VI. Structure IV is favored



IV V VI

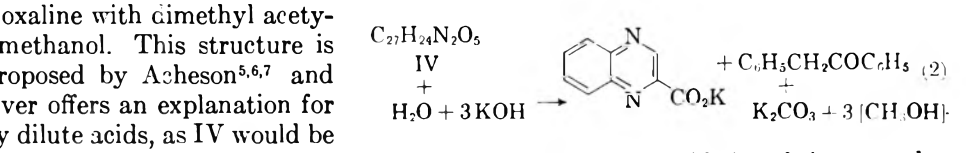
a, X = $FeCl_4$
b, X = Picrate
c, X = ClO_4

over V for the adduct because it more satisfactorily accounts for the color of the adduct,[8a] because bond energy calculations[9] indicate that IV should be about 6 kcal. per mole more stable than V, and because IV might be expected to have more resonance energy than V because of more effective conjugation. The relationship between IV and VI is analogous to the tautomeric change recognized by Hantzsch[10] and by Kehrmann.[11]

Dilute solutions ($2\times10^{-5}M$) of the perchlorate VIc in absolute methanol showed ultraviolet absorption which was almost identical with that of the adduct IV under similar conditions. This result indicates that VI undergoes extensive methanolysis to give IV under even weakly acidic conditions.

No direct evidence concerning the stereochemistry of IV was established, but the structure of IV suggests that it was formed by a type of Michael addition. Such additions frequently take place with acetylenic compounds[12] to give mainly products of *trans* addition. Moreover a *trans* structure was suggested for the closely related addition products of Acheson[5,6,7] and co-workers.

The alkaline hydrolysis of IV follows two routes: one regenerates 2,3-diphenylquinoxaline while the other follows Equation 2. The reaction leading to

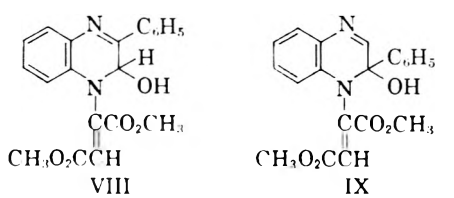


(2)

quinoxaline-2-carboxylic acid is of interest but the present results cannot distinguish between the several likely paths.

Adduct from 2-Phenylquinoxaline. 2-Phenylquinoxaline with dimethyl acetylenedicarboxylate in methanol gave a viscous oil under conditions similar to those employed with 2,3-diphenylquinoxaline. While the oil resisted usual methods of crystallization, upon solution in carbon tetrachloride followed by standing in an open evaporating dish for three weeks the oil was converted into a yellow crystalline product. This product, after recrystallization from carbon tetrachloride and methyl ethyl ketone, had the correct analysis, molecular weight, and methoxyl content for an adduct composed of 1 mol. each of 2-phenylquinoxaline, dimethyl acetylenedicarboxylate, and water. Oxidation of the adduct by potassium permanganate in aqueous acetone gave 2-hydroxy-3-phenylquinoxaline and 2-phenylquinoxaline. 2-Phenylquinoxaline was not oxidized by potassium permanganate under similar conditions. Reaction of the adduct with two molar equivalents of alcoholic potassium hydroxide gave some 2-phenylquinoxaline but mostly yielded a dibasic acid which resisted attempts at purification. The crude dibasic acid reacted with potassium hydroxide to give 2-phenylquinoxaline.

The ultraviolet absorption spectrum of the adduct from 2-phenylquinoxaline is shown in Fig. 1. This spectrum is similar to that of the adduct (IV) from 2,3-diphenylquinoxaline. The adduct from 2-phenylquinoxaline is accordingly assigned structure VIII and the dibasic acid is evidently the free acid corresponding to VIII, as it possesses a



VIII IX

similar ultraviolet absorption spectrum. The isomeric structure IX for the adduct is improbable both because of the ultraviolet absorption spectrum and because IX, unlike VIII, would not be expected to undergo ready oxidation by potassium permanganate to give 2-hydroxy-3-phenylquinoxaline.

(8) a. *cf.* J. N. Murrell, *J. Chem. Soc.*, 296 (1959). b. *cf.* B. M. Wepster, *Rec. trav. chim.*, **71**, 1159 (1952).

(9) Based on values given by Y. K. Syrkin as quoted by A. E. Remick, "Electronic Interpretation of Organic Chemistry," 2nd ed., John Wiley and Sons, New York, 1949, p. 142.

(10) A. Hantzsch, *Ber.*, **32**, 575 (1899); A. Hantzsch and M. Kalb, *Ber.*, **32**, 3109 (1899). For a recent survey see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 575–586.

(11) F. Kehrmann and C. Natcheff, *Ber.*, **31**, 2425 (1898); F. Kehrmann and M. Woulfson, *Ber.*, **32**, 1042 (1899). For recent examples with quinoxaline derivatives see: K. Brand and E. Wild, *Ber.*, **56**, 105 (1923); J. Druey and A. Huni, *Helv. Chim. Acta*, **35**, 2301 (1952).

(12) A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Edwards Arnold and Co., London, 1950, Vol. II, pp. 201, 218.

EXPERIMENTAL[13]

Dimethyl acetylenedicarboxylate was prepared from the monopotassium salt of acetylenedicarboxylic acid by the procedure of Huntress, Lesslie, and Bornstein.[14] 2,3-Diphenylquinoxaline was prepared in 81% yield from equimolar quantities of *o*-phenylenediamine and benzil in refluxing glacial acetic acid by the method of Bost and Towell.[15]

2-Phenylquinoxaline. Phenylglyoxal hydrate,[16] prepared from 147 g. (1.10 mol.) of phenylglyoxal, and *o*-phenylenediamine (119 g., 1.10 mol.) were refluxed in 700 ml. of 95% ethyl alcohol for 2.5 hr. The reaction mixture was chilled in an ice bath and filtered to give, after drying, 177 g. (78% yield) of crude product. Recrystallization from 800 ml. of alcohol with aid of animal charcoal for decolorization gave 131 g. of product of m.p. 76–77°. The most highly purified sample had m.p. 77.5–78.5° (recorded,[17] m.p. 78°).

1-(1,2-Dicarbomethoxyvinyl)-2,3-diphenyl-2-methoxy-1,2-dihydroquinoxaline (IV). Dimethyl acetylenedicarboxylate (34.2 g., 0.241 mol.) and 2,3-diphenylquinoxaline (34.0 g., 0.121 mol.) were mixed in 240 ml. of anhydrous methanol and were kept in a stoppered flask at room temperature with occasional shaking for 6 days. The yellow precipitate which formed was separated by filtration and weighed 33.2 g. (m.p. 144–148°). By concentration of the filtrate *in vacuo* an additional 8.7 g. of crude product was obtained to give a total yield of 76%. Recrystallization of the first batch of crystals once and the second batch twice from acetonitrile gave 34.0 g. (61.5% yield) of yellow crystals of IV, m.p. 156–157°. Compound IV, for analysis, was also recrystallized from carbon tetrachloride and from methyl ethyl ketone.

Anal. Calcd. for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14; CH_3O, 20.41 (three methoxyl groups per mole); mol. wt., 456.5. Found: C, 71.19; H, 5.58; N, 6.26; CH_3O, 20.24; mol. wt. 465 ± 50 (in triphenylmethane after procedure described by Schneider[18]).

In working up the mother liquors from the preparation of IV sometimes about 1 g. of a red product was obtained. This red compound after recrystallization from acetonitrile had m.p. 214.5–215° (dec.) but was not further characterized.

Compound IV could be distilled with some decomposition at a pressure of 0.05 to 0.1 mm. and a bath temperature of about 250°. Compound IV underwent slow decomposition upon storage at room temperature.

Tetrachloroferrate(III) *of IV.* A solution prepared from 1.4 g. of ferric chloride hexahydrate and 45 ml. of anhydrous ethyl ether was filtered to remove undissolved ferric chloride and was then mixed with 25 ml. of an ether solution containing 1.5 g. of IV. Yellow crystals precipitated in the form of needles. The crystals were dissolved in acetonitride and were reprecipitated by addition of anhydrous ether. The product had m.p. 182–183°.

Anal. Calcd. for $C_{26}H_{21}Cl_4FeN_2O_4$: C, 50.19; H, 3.40; Cl, 22.80; N, 4.50; ash (Fe_2O_3), 12.84. Found: C, 50.31; H, 3.34; Cl, 22.69; N, 4.61; ash, 12.81.

Picrate of IV. Compound IV (1.3 g.) was dissolved in 20 ml. of a saturated solution of picric acid in anhydrous ethyl ether. Minute yellow crystals formed. These were dissolved in acetonitrile and precipitated by addition of ethyl ether. Repetition of this recrystallization technique gave a product of m.p. 169.3–170.5°.

Anal. Calcd. for $C_{32}H_{23}N_6O_{11}$: C, 58.80; H, 3.55; N, 10.72. Found: C, 58.33; H, 3.60; N, 10.72.

Perchlorate of IV. In 25 ml. of anhydrous ethyl ether 1.5 g. of compound IV was dissolved and the solution was added to an ethereal solution of perchloric acid, prepared by shaking 20 ml. of 70% perchloric acid with 25 ml. of anhydrous ethyl ether and separating the ether phase. The yellow product (1.0 g.) which precipitated had m.p. 222.5–223° (dec.). Solution of the product in 20 ml. of methyl ethyl ketone and addition of anhydrous ethyl ether gave 0.89 g. of purified product, m.p. 228–229° (dec.).

Anal. Calcd. for $C_{26}H_{21}ClN_2O_8$: C, 59.49; H, 4.03; Cl, 6.76; N, 5.34. Found: C, 59.84; H, 4.05; Cl, 6.81; N, 5.35.

The perchlorate undergoes decomposition on storage, thus after 12 days a sample had m.p. about 219°.

Use of the same procedure with 1.5 g. of 2,3-diphenylquinoxaline resulted in the formation of 0.92 g. of a yellow perchlorate of m.p. 254–255.5°. A mixture of equal parts of this solid with the perchlorate of IV had m.p. 205–216°.

Reaction of IV with HCl. Compound IV (1.5 g.) in 25 ml. of anhydrous ethyl ether was added to 50 ml. of anhydrous ether which was 0.6*M* in hydrogen chloride. A yellow solid immediately precipitated. Suction filtration gave a solid which on momentary contact with air was converted to an oil.

Compound IV (2.0 g.) was stirred with 10 ml. of 95% ethyl alcohol to give a slurry, 1.0 ml. of concentrated hydrochloric acid was added, and the mixture was refluxed on the steam bath for 1 hr. The solvent was allowed to evaporate partially at room temperature. A product (0.87 g., 70% yield calculated as 2,3-diphenylquinoxaline) was separated by filtration and had m.p. near 105°. Recrystallization from ethyl alcohol gave a product of m.p. 124.5–125.5° which showed no depression of melting point when admixed with a sample of pure 2,3-diphenylquinoxaline (m.p. 125.5–126.5°). Continued evaporation of the reaction mixture gave a dark red semisolid mass.

Reaction of IV with KOH. Compound IV (20.0 g., 0.0439 mol.) was refluxed on a steam bath for 2 hr. with 125 ml. of ethyl alcohol and 53 ml. (0.088 mol.) of 1.66*N* aqueous KOH. The mixture was cooled in an ice bath and filtered. The crystalline precipitate was washed well with water and after drying weighed 5.6 g. (45% yield calculated as 2,3-diphenylquinoxaline). The product was recrystallized from ethyl alcohol to give 4.4 g. of crystals of m.p. 125.8–126.6°, which showed no depression of melting point when mixed with 2,3-diphenylquinoxaline. The mother liquors from washing the 5.6 g. of crude 2,3-diphenylquinoxaline were found to liberate upon acidification 106 ml. (S.T.P.) of carbon dioxide (22% yield on the assumption that 1 mol. of IV should yield 1 mol. of CO_2).

The filtrate from which the 2,3-diphenylquinoxaline had been removed was evaporated *in vacuo*. The concentrated solution deposited 3.3 g. of a brown solid which upon recrystallization from ethyl alcohol gave 1.4 g. (16% yield calculated as desoxybenzoin) of pale yellow crystals, m.p. 47–50°. The product was recrystallized from benzene-cyclohexane, *n*-hexane, and finally twice from ethyl alcohol to give white crystals of m.p. 55–56°. This product was identified as desoxybenzoin by its m.p. and mixed m.p. with an authentic sample of desoxybenzoin[19] and by the identity of its ultraviolet absorption spectrum with that of desoxybenzoin.

The mother liquor from which the crude desoxybenzoin had been removed was further concentrated on the steam

(13) Melting points are corrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill. Ultraviolet absorption spectra were determined by means of a Beckmann quartz spectrophotometer, model DU or DK.

(14) E. H. Huntress, T. E. Lesslie, and J. Bornstein, *Org. Syntheses*, **32**, 55 (1952). We are indebted to the authors for supplying us with these directions before their publication.

(15) R. W. Bost and E. E. Towell, *J. Am. Chem. Soc.*, **70**, 904 (1948).

(16) H. A. Riley and A. R. Gray, *Org. Syntheses*, **Coll. Vol. II**, 509 (1943).

(17) O. Hinsberg, *Ann.*, **292**, 246 (1896); O. Fischer and E. Schindler, *Ber.*, **39**, 2243 (1906).

(18) F. Schneider, "Qualitative Organic Microanalysis," John Wiley and Sons, New York, N. Y., 1946, p. 112.

(19) Prepared by the procedure of C. F. H. Allen and W. E. Barker, *Org. Syntheses*, **Coll. Vol. II**, 156 (1943).

bath. There deposited, on cooling, a dark yellow solid (3.0 g.) which was separated by filtration and was then converted into a slurry with 25 ml. of water and again filtered. The aqueous filtrate was strongly acidified with hydrochloric acid. The precipitate which formed weighed 1.3 g. (17% yield calculated as quinoxaline-2-carboxylic acid) and melted at about 204°. After decolorization with charcoal and three recrystallizations from ethyl alcohol the pure white product melted at 212° (dec.). This compound was identified as quinoxaline-2-carboxylic acid on the basis of its m.p. and mixed m.p. with authentic quinoxaline-2-carboxylic,[20] and by comparison of its ultraviolet absorption spectrum with that of the authentic sample.

Oxidation of IV. Solutions of IV in methanol or acetone showed no reaction at room temperature when treated with a dilute aqueous solution of $KMnO_4$. When 3.0 g. (0.0066 mol.) of IV was refluxed for 15 min. with 3.0 g. (0.011 mol.) of sodium dichromate in 21 ml. of glacial acetic acid, a green solution resulted. The solution was poured onto ice and extracted with ether and the ether extract was washed with ammonium hydroxide. From the ether extract 1.1 g. of semisolid residue was obtained. Two recrystallizations from methanol gave white crystals of m.p. 122–123° which gave no depression of m.p. with a pure sample of 2,3-diphenylquinoxaline.

To a slurry of 8.0 g. of IV in 27 ml. of glacial acetic acid was added a solution of 67 ml. of 30% hydrogen peroxide in 40 ml. of acetic acid. The mixture was heated on a steam bath for 2 hr., cooled to room temperature, and filtered. The insoluble product weighed 0.57 g. and after two recrystallizations from acetophenone was a white compound of m.p. 309–310° (dec.) and gave the following analysis.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.92; H, 5.10; N, 8.86. Found: C, 75.78; H, 5.38; N, 9.06.

This compound (VII) had the same melting point and mixed melting point and the same infrared absorption spectrum as a sample of *N,N'*-dibenzoyl-*o*-phenylenediamine prepared by oxidation (see below) of 2,3-diphenylquinoxaline with hydrogen peroxide.

Oxidation of 2,3-diphenylquinoxaline. To a mixture of 25 ml. of acetic acid and 50 ml. of 30% hydrogen peroxide was added 3.0 g. of 2,3-diphenylquinoxaline partially dissolved in 25 ml. of ethanol. The mixture was subjected to reflux for 40 hr. and was then allowed to cool undisturbed for 24 hr. The crystals which precipitated were separated by filtration and were washed with enough hot methanol to dissolve an orange impurity and leave 1.33 g. of white crystals. The combined mother liquor and methanol wash from these crystals upon evaporation gave 1.58 g. of yellow crystals (m.p. 193–195°). A repetition of this preparation gave 1.55 g. of the yellow product but only 0.08 g. of the white product; the cause for the variation in yield is unknown. After two recrystallizations from ethyl alcohol the yellow product had m.p. 210–211° (dec.) and gave the following analysis:

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.59; H, 4.62; N, 8.94.

This analysis agrees with that expected for *N,N'*-dioxo-2,3-diphenylquinoxaline. This amine oxide has been analyzed previously only for carbon and hydrogen and is reported[21] to melt in the range of 208 to 216°.

The white product from the hydrogen peroxide oxidation after several recrystallizations from acetic acid or acetophenone had m.p. 309–310° (dec.). This substance as noted above was identical with compound VII from oxidation of IV. Previous reports[21] of the reaction of 2,3-diphenylquinoxaline with hydrogen peroxide under milder conditions than the present have not indicated the formation of a high melting product of properties analogous to VII, although 2,3-diphenylquinoxaline monoxide (m.p. 197°) has been found under some conditions. Compound VII corresponds in elementary analyses to a monohydrate of 2,3-diphenylquinoxaline monoxide; however VII could be recrystallized from acetic acid or acetophenone and could be sublimed at 260° (0.02 mm.) without loss of water. The white product of m.p. 309–310° (dec.) was eventually found[22] to be identical, as indicated by mixed melting point and infrared spectral determinations, with a sample of *N,N'*-dibenzoyl-*o*-phenylenediamine, prepared[23] from *o*-phenylenediamine.

1-(1,2-Dicarbomethoxyvinyl)-2-hydroxy-3-phenyl-1,2-dihydroquinoxaline (VIII). Dimethyl acetylenedicarboxylate (66.8 g., 0.470 mol.) and 2-phenylquinoxaline (97.0 g., 0.471 mol.) were dissolved in 760 ml. of anhydrous methanol and the solution was allowed to stand in a stoppered flask for 1 week at room temperature. The solvent was removed *in vacuo* and there remained a dark red viscous oil. Attempts to crystallize the product from acetonitrile under customary conditions were unsuccessful; however, crystals were obtained by the following procedure. The oil was dissolved in 170 ml. of carbon tetrachloride and the solution was left at room temperature for 3 weeks in an evaporating dish which was open to the atmosphere. During this period, the solid material which formed a crust over the solution was broken up from time to time. The residue in the evaporating dish was filtered and washed thoroughly with ether. The insoluble portion consisted of yellow crystals whose surface was red in color. The crude solid after removal of solvent weighed 114 g. (66% yield calculated as VIII) and had m.p. 128–138°. Five recrystallizations alternately from carbon tetrachloride and then methyl ethyl ketone gave yellow crystals of VIII of m.p. 139.5–140.5° (with some decomposition to give a red melt).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65; CH_3O, 16.94 (two methoxyl groups per mole); mol. wt., 366.4. Found: C, 65.87; H, 4.90; N, 7.57; CH_3O, 16.1; mol. wt., 387 ± 40 (in triphenylmethane after procedure described by Schneider[18]).

Compound VIII undergoes slow decomposition upon storage.

Reaction of VIII with KOH. While VIII dissolved to only a small extent in a mixture of equal parts of water and methanol, solution was complete after shaking for 5 min. in a mixture of equal parts of 10% aqueous KOH and methanol. Under similar conditions adduct IV was not visibly more soluble in presence than in absence of KOH.

Compound VIII (10.0 g., 0.0273 mol.) in 60 ml. of ethyl alcohol and 32.0 ml. (0.0552 mol.) of 1.725*N* aqueous potassium hydroxide was heated on a steam bath under conditions for reflux for 2.5 hr. The reaction mixture was cooled to room temperature, diluted with 250 ml. of water, and extracted with ether until the ether extracts acquired only a pale yellow color. The ether extracts yielded 0.76 g. (13.5% yield calculated as 2-phenylquinoxaline) of a brown residue which after recrystallization from ethyl alcohol and decolorization with animal charcoal had m.p. 74–76°. A mixed melting point with a pure sample of 2-phenylquinoxaline (m.p. 77.5–78.5°) showed no depression. The aqueous solution from the ether extractions was acidified with hydrochloric acid. The brown precipitate which separated was filtered and washed well with water. This brown product after drying at room temperature in a dessicator over Drierite weighed 9.2 g. and had m.p. 143–145° (dec. with evolution of gas). All attempts to obtain this product in a purer condition by recrystallization were unsuccessful. The titration curve for this acid showed two end points as expected for the dibasic acid corresponding to VIII and the ultraviolet absorption spectrum had maxima

(20) Prepared by the procedure of B. R. Brown, *J. Chem. Soc.*, 2577 (1949).

(21) S. Maffei, *Gazz. chim. ital.*, **76**, 239 (1946); F. Linsker and R. L. Evans, *J. Am. Chem. Soc.*, **68**, 403 (1946); J. K. Landquist and G. J. Stacey, *J. Chem. Soc*, 2828 (1953).

(22) We wish to acknowledge helpful discussions from Dr. J. W. Huffman and Dr. J. R. Dyer concerning the structure of this product.

(23) O. Hinsberg and L. v. Udránsky, *Ann.*, **254**, 254 (1889); E. Bamberger and B. Berlé, *Ann.*, **273**, 346 (1893).

at the same locations as for VIII but with somewhat altered intensities. A 5.0 g. sample of the crude acid was heated under reflux for 1.5 hr. with 30 ml. of ethyl alcohol and 25.0 ml. of 1.72*N* aqueous KOH. The reaction mixture after dilution with water gave 1.25 g. of crude 2-phenylquinoxaline in the ether extract.

Oxidation of VIII. Compound VIII (10.0 g., 0.0273 mol.) was dissolved in 150 ml. of acetone and a saturated aqueous solution of $KMnO_4$ (170 ml. in all) was added in small portions, with shaking, until the color of the permanganate persisted for a few minutes. During this addition the reaction mixture warmed spontaneously to 35–40°. The precipitate which separated was filtered, was made into a slurry with water, and was acidified with hydrochloric acid. Sodium bisulfite was then added until the manganese dioxide dissolved. The resulting solution was filtered and the precipitate was washed well with water. The precipitate weighed 1.4 g. (23% yield calculated as 2-hydroxy-3-phenylquinoxaline) and after one recrystallization from methyl ethyl ketone had m.p. 244–245°. Recrystallization from methyl ethyl ketone and then from ethyl alcohol gave a very pale yellow product of m.p. 248.5–249.0°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.62; H, 4.60; N, 12.52. This compound is identified as 2-hydroxy-3-phenylquinoxaline and gave no depression of melting point with an authentic sample prepared[24] by condensation of *o*-phenylenediamine with benzoylformic acid.[25]

The acetone solution, from which the 2-hydroxy-3-phenylquinoxaline had been removed by filtration, upon evaporation deposited 2.44 g. (24% yield) of crude 2-phenylquinoxaline (m.p. *ca.* 76–78°) contaminated somewhat with 2-hydroxy-3-phenylquinoxaline.

To a solution of 2-phenylquinoxaline (0.56 g.) in 15 ml. of acetone was added a few drops of a saturated aqueous solution of $KMnO_4$. No color change was evident upon mixing at room temperature or even when the solution was boiled for a few minutes.

Acknowledgment. We are indebted to the National Aniline Division, Allied Chemical and Dye Corporation for gifts of the acetylenedicarboxylic acid monopotassium salt used in most of the present work.

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(24) J. Buraczewski and L. Marchlewski, *Ber.*, **34**, 4009 (1901).

(25) B. B. Corson *et al.*, *Org. Syntheses*, **Coll. Vol. I**, 244 (1941).

[CONTRIBUTION FROM WALKER LABORATORY, RENSSELAER POLYTECHNIC INSTITUTE]

Cyclopropyl Analogs of Hexestrol and Diethylstilbestrol[1,2]

JAMES G. BENNETT, JR.,[3] AND STANLEY C. BUNCE

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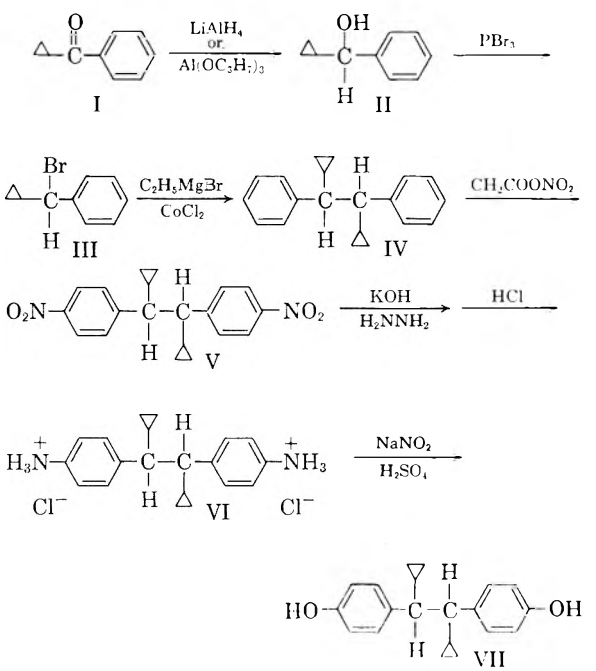
1,2-Dicyclopropyl-1,2-di-*p*-hydroxyphenylethane and 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene, which are cyclopropyl analogs of hexestrol and of the dimethyl ether of diethylstilbestrol, have been prepared.

The purpose of this research was to investigate synthetic routes for the preparation of several cyclopropyl compounds which are structurally related to hexestrol, diethylstilbestrol, and estradiol, namely, 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane (VII), 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethylene (XI), and 1,1′-di-*p*-hydroxyphenylbicyclopropyl.

The interest in these compounds lies in their possible estrogenic activity and possible action in relation to tumor initiation or cancer chemotherapy.

1,2-Dicyclopropyl-1,2-di-p-hydroxyphenylethane (VII) was successfully synthesized by the sequence of reactions illustrated in 1.1% over-all yield from γ-butyrolactone.

Cyclopropyl phenyl ketone (I), prepared from γ-butyrolactone by the method of Close,[4] was reduced to cyclopropylphenylcarbinol (II) by means of aluminum isopropoxide in 94% yield and also by means of lithium aluminum hydride[4] in 75% aver-



(1) Abstracted from the Ph.D. thesis of James G. Bennett, Jr., Rensselaer Polytechnic Institute, 1959.

(2) Presented before the Division of Organic Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

(3) Present address: Research Division, Parke, Davis & Co., Detroit, Mich.

(4) W. J. Close, *J. Am. Chem. Soc.*, **79**, 1455 (1957).

age yield. In several cases the hydride reduction led to the formation of cyclopropylphenylcarbinyl ether in yields up to 76%. Conversion of the carbinol to cyclopropylphenylcarbinyl bromide (III) in 84% average yield was accomplished using phosphorus tribromide at −15° without significant rearrangement. Cyclopropylphenylcarbinyl bromide was also prepared by reduction of cyclopropyl phenyl ketone to cyclopropylphenylmethane in 84% yield followed by bromination with *N*-bromosuccinimide in 31% yield (42% corrected for recovered hydrocarbon).

The preparation of cyclopropylphenylmethyllithium would permit several possible synthetic routes to dicyclopropyldiphenylethane derivatives. That two attempts to form the organolithium derivative from cyclopropylphenylmethane and *n*-butyllithium were unsuccessful was indicated by the recovery, in one case after carbonation and in another after attempted coupling using iodine, of 80 and 89% of the cyclopropylphenylmethane.

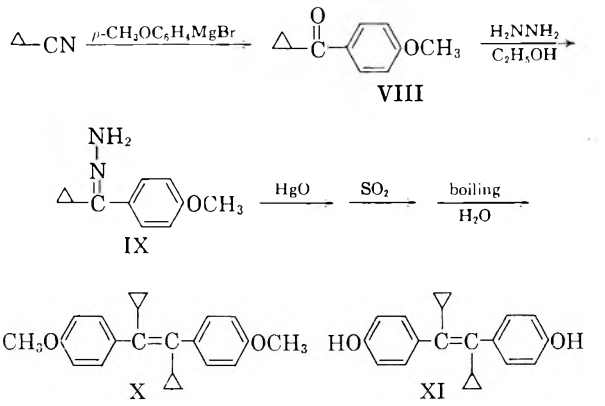
An attempt to prepare the sodium derivative of cyclopropylphenylmethane using *n*-amylsodium and to condense it with cyclopropyl phenyl ketone also gave cyclopropylphenylmethane (73% recovered) as the only identifiable product.

Nitration of cyclopropyl phenyl ketone using a mixture of sulfuric and nitric acids led to cyclopropyl *m*-nitrophenyl ketone in 35% yield.

The nitration of cyclopropylphenylmethane with sulfuric and nitric acids at 4° was unsuccessful; cyclopropylphenylmethane was found to polymerize in the presence of cold sulfuric acid. The reaction of the hydrocarbon with acetyl nitrate at 0° produced a crude material whose infrared spectrum indicated the presence of a nitro group, but attempted distillation led to sudden decomposition.

Cyclopropylphenylcarbinyl bromide was coupled using ethylmagnesium bromide and anhydrous cobaltous chloride to 1,2-dicyclopropyl-1,2-diphenylethane (IV) in 33% yield, following a modified coupling procedure of Wilds and McCormack.[5] Treatment of 1,2-dicyclopropyl-1,2-diphenylethane with acetyl nitrate gave a 22% yield of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane (V), which was reduced using hydrazine hydrate in diethylene glycol to 1,2-dicyclopropyl-1,2-di-*p*-aminophenylethane and isolated as the dihydrochloride (VI) in 95% average yield. Diazotization using 5% sulfuric acid and sodium nitrite followed by treatment with boiling water gave 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane (VII) in 19% yield.

1,2-Dicyclopropyl-1,2-di-p-anisylethylene (X) was prepared by the sequence of reactions shown below in 0.5% over-all yield from 1-bromo-3-chloropropane. No successful method of demethylation was devised.



Cyclopropyl phenyl ketone was selected as a model compound to investigate the hydrazone oxidation and coupling[6,7] since it was more readily prepared. Cyclopropyl phenyl ketone was converted to its hydrazone by treatment with excess hydrazine in absolute ethanol in 94% average yield. The hydrazone was oxidized using freshly prepared mercuric oxide to obtain cyclopropylphenyldiazomethane which was not isolated but treated in solution with anhydrous sulfur dioxide to yield a sulfone according to the procedure of Staudinger and Pfennenger.[6] The sulfone was not isolated but immediately decomposed with boiling water to obtain 1,2-dicyclopropyl-1,2-diphenylethylene in an average yield of 39%.

p-Methoxyacetophenone was selected as a model compound containing *p*-methoxy substituents to undergo this series of reactions with the intent to find reaction conditions suitable to give the highest yield of 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene. The hydrazone of *p*-methoxyacetophenone was prepared in 87% yield; attempts to prepare 1,2-dimethyl-1,2-di-*p*-anisylethylene from this hydrazone[8] led to the isolation of the azine of *p*-methoxyacetophenone in 0.5–16% yield and to the olefin, only in one case, in 2.0% yield.

These reactions were then applied to cyclopropyl *p*-anisyl ketone (VIII), obtained from the reaction of cyclopropanecarbonitrile and *p*-anisylmagnesium bromide in 71% average yield. Upon attempting to prepare the hydrazone of cyclopropyl *p*-anisyl ketone a liquid was obtained from which no solid material could be isolated. Partial crystallization of a subsequent preparation of the hydrazone permitted the isolation of small amounts of the pure hydrazone (IX) and also of the azine of cyclopropyl *p*-anisyl ketone. Distillation of the crude liquid hydrazone led only to the isolation of the azine. Oki and Urushibara[8] have reported difficulty in obtaining the pure hydrazone of *p*-methoxybutyrophenone. When the crude

(5) A. L. Wilds and W. B. McCormack, *J. Org. Chem.*, **14**, 45 (1949).

(6) H. Staudinger and F. P. Pfenninger, *Ber.*, **49**, 1941 (1916).

(7) L. I. Smith and K. L. Howard, *Org. Syntheses*, **Coll. Vol. III**, 351 (1955).

(8) M. Oki and Y. Urushibara, *Bull. Chem. Soc. Japan*, **25**, 109 (1952).

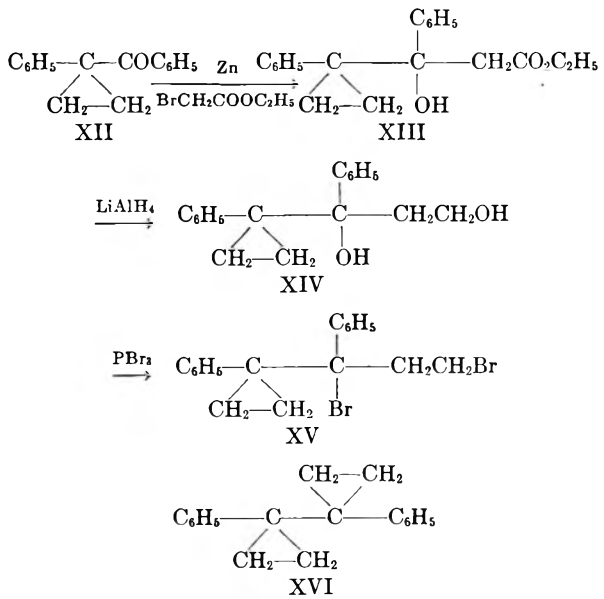
liquid hydrazone was treated with mercuric oxide followed by sulfur dioxide and boiling water, 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene (X) was obtained in yields from 2 to 4%.

Difficulties were encountered in attempting to demethylate 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene by heating with potassium hydroxide in ethanol. Due to the lack of sufficient material further demethylations were not attempted.

Attempts to prepare 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethylene from 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane were unsuccessful. The reaction of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane with 2 mol. of *N*-bromosuccinimide followed by treatment with sodium iodide in acetone led to a 60% recovery of starting material. The use of 1 mol. of *N*-bromosuccinimide followed by alcoholic potassium hydroxide led to a 97% recovery of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane. Fisher-Hirschfelder molecular models show the possibility of sufficient steric hindrance to prevent attack by the succinimide free radical.

The reduction of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane with hydrazine and potassium hydroxide did not parallel the reaction of 4,4′-dinitrobibenzyl to form 4,4′-diaminostilbene[9]; the saturated diamine was isolated in 66% yield.

The synthesis of *1,1′-di-p-hydroxyphenylbicyclopropyl* (the di-*p*-hydroxy derivative of XVI) was attempted following the route studied by Phelan[10] and Ward[11] as shown in the accompanying chart.



1-Phenylcyclopropyl phenyl ketone (XII), underwent a Reformatsky reaction with zinc and ethyl bromoacetate to yield ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate (XIII) in 25% yield or a 58% yield based upon unrecovered ketone. Reduction of the ester to 1-phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol (XIV) in 90% average yield was accomplished using lithium aluminum hydride. Reaction of the diol with phosphorus tribromide in ether gave a material from which a compound, m.p. 75.3–75.7°, was isolated in low yield. This compound, tentatively assigned the structure of 1,3-dibromo-1-phenyl-1-(1-phenylcyclopropyl)propane (XV), gave a positive test with alcoholic silver nitrate. From the reaction of the diol with phosphorus tribromide in methylene chloride a compound was obtained, m.p. 145.3–145.9°, which gave a negative test with alcoholic silver nitrate and also analyzed correctly for the dibromide. Both compounds contain a cyclopropane ring and give similar infrared and ultraviolet spectra. The structure of the second compound, which appears not to be isomorphous with the first, is not known. Attempts to close the second cyclopropane ring using crude dibromide with zinc dust and *n*-propyl alcohol led to the isolation of a small amount of liquid material believed to be impure 1,1′-diphenylbicyclopropyl (XVI). Attempted nitration gave no identifiable product.

The structures for all of the compounds presented are verified by infrared data obtained using a Perkin-Elmer Model 21 double-beam recording infrared spectrometer equipped with a sodium chloride prism. The carbon-hydrogen region was further investigated using a Perkin-Elmer Model 12B single-beam recording infrared spectrometer equipped with a lithium fluoride prism. Every cyclopropyl compound synthesized during this research shows a band in the region of 3072–3096 cm.$^{-1}$ and one in the region of 2996–3033 cm.$^{-1}$ confirming the work of Wiberley and Bunce.[12] An additional report on the infrared spectra of these cyclopropane derivatives is planned.

Samples of 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane, 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene, and the azine of cyclopropyl *p*-anisyl ketone have been sent to the Cancer Chemotherapy National Service Center to be tested for endocrine activity and antitumor properties.

EXPERIMENTAL[13]

Cyclopropylphenylcarbinol (II) *by Meerwein-Ponndorf-Verley reduction.* Cyclopropanecarbonitrile was obtained in

(9) Huang-Minlon, *J. Am. Chem. Soc.*, **70**, 2802 (1948).

(10) R. R. Phelan, B.S. thesis, Rensselaer Polytechnic Institute, 1953.

(11) V. E. Ward, B.S. thesis, Rensselaer Polytechnic Institute, 1955.

(12) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

(13) Boiling points are uncorrected; all reduced pressure distillations were conducted using a Vigreux column unless otherwise specified. Melting points, unless otherwise noted, were obtained by the capillary method with a thermometer calibrated with reference compounds [S. C. Bunce, *Anal. Chem.*, **25**, 825 (1953)]. Elemental analyses, unless otherwise noted, were performed by Drs. G. Weiler and F. B. Strauss, 164 Banbury Road, Oxford, England.

37% over-all yield from 1-bromo-3-chloropropane by the *Organic Syntheses* procedures,[14,15] and converted in 98% yield to cyclopropyl phenyl ketone,[16,17] b.p. 128–133° at 25 mm., n_D^{20} 1.5562 by the procedure of Henze and Gayler.[18] The method of Close[4] afforded a 74% yield from γ-chlorobutyryl chloride which was prepared in 86% yield from γ-butyrolactone; this preparation of cyclopropyl phenyl ketone was shorter and the product was apparently more pure, b.p. 121–124° at 16 mm., n_D^{21} 1.5530 (lit. n_D^{20} 1.5525,[18] n_D^{25} 1.5514[17]). The 2,4-dinitrophenylhydrazone melted at 211.5–212.0° (lit. m.p. 211–213°[17]).

Aluminum isopropoxide,[19] 675 g. (3.38 mol.) and 494 g. (3.38 mol.) of cyclopropyl phenyl ketone in 3 l. of dry isopropyl alcohol, b.p. 82–83°, were placed in a flask equipped with a stirrer and a 270-mm. vacuum-jacketed, silvered column packed with glass helices. Acetone, b.p. 62–80°, was removed slowly until the distillate gave a negative test with 2,4-dinitrophenylhydrazine solution. The isopropyl alcohol was removed under vacuum and the residue was stirred with 3 l. of dilute hydrochloric acid and then extracted with ether. The extract was neutralized with saturated sodium bicarbonate, dried over potassium carbonate, concentrated, and distilled twice yielding 471 g. (94%) of cyclopropylphenylcarbinol, b.p. 80–84° at 0.4 mm., n_D^{20} 1.5330 (lit. b.p. 121° at 12 mm., n_D^{25} 1.5390[4]).

Cyclopropylphenylcarbinol (II) *and cyclopropylphenylcarbinyl ether by lithium aluminum hydride reduction.* Cyclopropylphenylcarbinol, b.p. 96–97° at 2.0 mm., n_D^{20} 1.5411, d_4^{20} 1.0443, MRD 44.49 (calcd., using 0.45 exaltation for cyclopropyl,[20] 44.56), was prepared from cyclopropyl phenyl ketone in 90% yield by the procedure of Close.[4] In several cases the use of lithium aluminum hydride led to the formation of cyclopropylphenylcarbinyl ether. For example, 5.0 g. (0.13 mol.) of lithium aluminum hydride and 50.0 g. (0.34 mol.) of cyclopropyl phenyl ketone were refluxed for 2 hr. and the mixture was hydrolyzed, the ether layer separated, neutralized with saturated sodium bicarbonate, and dried over potassium carbonate. The ether was removed and the residue distilled to yield 35.9 g. (76%) of cyclopropylphenylcarbinyl ether, b.p. 175–181° at 4.0 mm. A portion was redistilled, b.p. 135.9–136.5° at 0.45 mm., to constant refractive index, n_D^{23} 1.5535.

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.96. Found: C, 86.43, 86.61; H, 8.20, 8.07.

Cyclopropylphenylcarbinyl bromide (III) *from cyclopropylphenylcarbinol.* Phosphorus tribromide, 352.0 g. (1.3 mol.) (Eastman), was cooled to −15° and 148.1 g. (1.0 mol.) of cyclopropylphenylcarbinol was added during 30 min. at −15°. After stirring for 15 min. at −15°, the mixture was poured over ice and extracted with ether. The ether layer was separated, washed with saturated sodium bicarbonate and saturated sodium chloride, and dried over potassium carbonate. The ether was removed and the residue distilled to yield 186.5 g. (88%) of cyclopropylphenylcarbinyl bromide, b.p. 85–87° at 0.3 mm., n_D^{20} 1.5872. An analytical sample, b.p. 73.5–74.0° at 0.1 mm., n_D^{20} 1.5882, did not react with dilute potassium permanganate.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 56.89; H, 5.25; Br, 37.86. Found: C, 57.18, 56.90; H, 5.24, 5.43; Br, 37.5, 37.2.

Cyclopropylphenylcarbinyl bromide from cyclopropylphenylmethane. Cyclopropylphenylmethane, 26.4 g. (0.20 mol.), obtained from cyclopropyl phenyl ketone in 84% yield,[4] was refluxed with 35.6 g. (0.20 mol.) of dried *N*-bromosuccinimide (Halogen Chemicals Inc.) in 400 ml. of carbon tetrachloride, b.p. 76–78°, with a trace of benzoyl peroxide. After 4 hr. the mixture was filtered, washed with warm water and saturated sodium bicarbonate, and dried over potassium carbonate. The carbon tetrachloride was removed under vacuum and the residue distilled, yielding 6.6 g. (25%) of recovered cyclopropylphenylmethane, b.p. 45–46° at 0.4 mm., n_D^{20} 1.5224, and 13.1 g. (31% or a 41% corrected yield) of cyclopropylphenylcarbinyl bromide, b.p. 90–92° at 0.5 mm., n_D^{20} 1.5850.

Cyclopropyl m-nitrophenyl ketone. Cyclopropyl phenyl ketone, 48.3 g. (0.33 mol.), was added during 30 min. to 90 ml. of sulfuric acid and 90 ml. of nitric acid at 0 to −10°. Following 2 hr. of stirring at 0°, the mixture was poured over ice, extracted with ether, and the ether extract dried over potassium carbonate and concentrated to a residue which partly crystallized. The crystals were collected and recrystallized from alcohol, giving 22.1 g. (35%) of cyclopropyl *m*-nitrophenyl ketone, which after four recrystallizations melted at 70.8–71.1°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.72; H, 4.82.

Cyclopropyl *m*-nitrophenyl ketone, oxidized according to the procedure of Markees and Burger[21] using hydrobromic acid followed by potassium permanganate, gave *m*-nitrobenzoic acid, m.p. 143–146° uncorr., which did not depress the m.p. of an authentic sample, m.p. 144–145° uncorr.

Attempted preparation of cyclopropylphenylacetic acid. n-Butyllithium was prepared from 3.2 g. (0.46 mol.) of lithium metal and 27.4 g. (0.20 mol.) of *n*-butyl bromide, b.p. 100–101°. Cyclopropylphenylmethane, 25.1 g. (0.19 mol.), in 100 ml. of ether was added over a 30-min. period and the solution refluxed for 90 min. The mixture was poured over crushed Dry Ice, water was added, and the ether layer was separated, washed with water until neutral, and dried. Removal of the ether and distillation of the residue gave 20.0 g. (80% recovery) of cyclopropylphenylmethane, b.p. 52–55° at 2.0 mm., $n_D^{22.5}$ 1.5072.

Attempted preparation of 1,2-dicyclopropyl-1,2-diphenylethane. n-Butyllithium was prepared from 6.4 g. (0.91 mol.) of lithium metal and 57.6 g. (0.42 mol.) of *n*-butyl bromide, b.p. 100–101°. Cyclopropylphenylmethane, 46.3 g. (0.35 mol.) was added and the solution was refluxed for 2 hr. Iodine, 44.4 g. (0.175 mol.), in 750 ml. of anhydrous ether was added over 45 min. and the solution was refluxed for 2¼ hr. Water was added and the ether layer was washed with 10% sodium thiosulfate solution and twice with water, and dried. After the ether was removed, the residue gave 41.4 g. (89% recovery) of cyclopropylphenylmethane, b.p. 42–43° at 0.7 mm.

Attempted preparation of 1,2-dicyclopropyl-1,2-diphenylethanol. A sodium dispersion was prepared from 11.5 g. (0.50 mol.) of metallic sodium and 500 ml. of *n*-butyl ether, b.p. 142–143°, with high speed stirring under nitrogen. *n*-Amyl chloride, 26.6 g. (0.25 mol.), b.p. 106–107°, in 125 ml. of *n*-butyl ether was added over a 50-min. period at 0°, followed by stirring at 0° for 1 hr. A solution of 23.4 g. (0.18 mol.) of cyclopropylphenylmethane in 150 ml. of *n*-butyl ether was added at 0° during 40 min., followed by heating at 60° for 30 min. After cooling to 0°, 14.6 g. (0.10 mol.) of cyclopropyl phenyl ketone in 100 ml. of *n*-butyl ether was added slowly and the mixture was allowed to stir for 2 hr. while warming to room temperature. The mixture was poured over crushed ice and steam-distilled. The distillate, after 2 hr. of steam-distilling, was salted out with potassium carbonate, extracted with ether, dried, and distilled to remove both ethers. The residue was distilled giving 17.1 g. (73% recovery) of cyclopropylphenylmethane, b.p. 70° at

(14) C. F. H. Allen, *Org. Syntheses*, Coll. Voll. I, 156 (1941).

(15) M. J. Schlatter, *Org. Syntheses*, Coll. Voll. III, 223 (1955).

(16) A. Haller and E. Benoist, *Ann. chim.* (Paris), IX, **17**, 25 (1922).

(17) R. P. Mariella and R. R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952).

(18) H. R. Henze and C. W. Gayler, *J. Am. Chem. Soc.*, **74**, 3615 (1952).

(19) We are indebted to the Harshaw Chemical Co. for gifts of this material.

(20) V. A. Slabey, *J. Am. Chem. Soc.*, **76**, 3603 (1954).

(21) D. G. Markees and A. Burger, *J. Am. Chem. Soc.*, **71**, 2031 (1949).

10 mm. and 26.1 g. of unidentified material, b.p. 113° at 10 mm. The distillate obtained by steam-distilling for 4 additional hr. was salted out, extracted, dried, and concentrated to 4.6 g. of a red liquid whose infrared spectrum showed a strong hydroxyl band at 3546 cm.$^{-1}$ and a strong carbonyl band at 1681 cm.$^{-1}$ After standing for 1 yr. a small quantity of cubic crystals had appeared. The residue from the steam distillation was extracted, dried, and concentrated to 4.8 g. of a red liquid whose infrared spectrum showed a weak hydroxyl band at 3623 cm.$^{-1}$ and a moderate carbonyl band at 1698 cm.$^{-1}$

1,2-Dicyclopropyl-1,2-diphenylethane (IV). The coupling procedure of Wilds and McCormack[5] was modified with respect to order of addition. Ethylmagnesium bromide was prepared in a flask with a bottom stopcock from 43.5 g. (1.79 mol.) of magnesium and 193.5 g. (1.76 mol.) of bromoethane, b.p. 38–39°, and filtered through glass wool into an ether solution containing 217.8 g. (1.03 mol.) of cyclopropylphenylcarbinyl bromide and 10.2 g. (0.08 mol.) of anhydrous cobaltous chloride, over a 90-min. period. A vigorous evolution of gas was noted which stopped immediately when the addition was completed; thereafter the mixture was stirred for 15 min., cooled, and poured over ice and hydrochloric acid. The ether layer was separated, washed with water and saturated sodium bicarbonate, and dried over potassium carbonate. The ether was removed and the remaining oil distilled at 1.2 mm. yielding 54.7 g. (42%) of solid 1,2-dicyclopropyl-1,2-diphenylethane boiling at 132–135°. Recrystallization from alcohol gave 47.8 g. (37%) melting at 72.2–72.8°.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.22, 91.36; H, 8.23, 8.47.

1,2-Dicyclopropyl-1,2-di-p-nitrophenylethane (V). The method of nitration is that of Markees and Burger.[21] Acetic anhydride, 15 ml., b.p. 138°, 8 ml. of glacial acetic acid, and 9 ml. of nitric acid (*d.* 1.5) were cooled to −20° and 8.9 g. (0.03 mol.) of 1,2-cyclopropyl-1,2-diphenylethane was added over a 15-min. period at −10°. After stirring at 0° for 1 hr. the mixture was poured over ice, the solid collected and recrystallized twice from an alcohol–ethyl acetate mixture yielding 3.1 g. (26%) of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane melting at 199.8–200.6°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.16; H, 5.72; N, 7.95. Found: C, 68.14, 67.97; H, 5.88, 5.78; N, 8.14, 8.08.

1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane was oxidized[21] to *p*-nitrobenzoic acid, isolated by sublimation, m.p. 242–245° uncorr., which did not depress the m.p. of an authentic sample.

1,2-Dicyclopropyl-1,2-di-p-aminophenylethane dihydrochloride (VI). The procedure for the reduction is that of Huang-Minlon.[22] 1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 2.0 g. (0.006 mol.), 100 ml. of diethylene glycol, and 20 ml. of hydrazine hydrate were heated at 140° for 30 min. and at 204° for 3 hr. The cooled solution was poured into water, extracted with ether, the extract dried over potassium carbonate, and saturated with gaseous hydrogen chloride precipitating a quantitative yield of diamine dihydrochloride, neut. equiv. 181.8, 182.1 (calcd. 182.7).

1,2-Dicyclopropyl-1,2-di-p-hydroxyphenylethane (VII). 1,2-Dicyclopropyl-1,2-di-*p*-aminophenylethane dihydrochloride, 13.4 g. (0.037 mol.), was dissolved in 250 ml. of 5% sulfuric acid and 5.2 g. of sodium nitrite in 30 ml. of water was added dropwise to the solution until a positive test for nitrous acid was obtained. After stirring at 3° for 20 min., the mixture was filtered and added dropwise to boiling water precipitating 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane. Recrystallization was best accomplished by using an alcohol-water mixture yielding 2.1 g. (19%), m.p. 190.3–191.0°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.76, 81.26; H, 7.33, 7.59.

Hydrazone of cyclopropyl phenyl ketone. Cyclopropyl phenyl ketone, 32.1 g. (0.22 mol.), 41.2 g. (1.28 mol.) of 95% hydrazine, and 150 ml. of absolute alcohol were refluxed for 19 hr. After cooling in a Dry Ice–acetone bath, the crude hydrazone was collected and recrystallized from absolute alcohol to give 34.6 g. (98%) of the hydrazone of cyclopropyl phenyl ketone melting at 64.8–65.6°.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.49. Found: C, 74.58; H, 7.48; N, 17.6.

1,2-Dicyclopropyl-1,2-diphenylethylene. The procedure is that of *Organic Syntheses*[7] and Staudinger and Pfenninger.[8] The hydrazone of cyclopropyl phenyl ketone, 16.0 g. (0.10 mol.), and 43.2 g. (0.20 mol.) of freshly prepared yellow mercuric oxide[23] in 500 ml. of *n*-hexane, b.p. 67–69°, were shaken for 20 hr. The cherry-red hexane solution was filtered and anhydrous sulfur dioxide passed in with dissipation of the color. Upon removal of the hexane a solid was obtained which was boiled with water for 2 hr., then extracted with ether. The extract was dried over potassium carbonate and the ether removed leaving fine needles which were recrystallized from alcohol using charcoal to yield 5.6 g. (43%) of 1,2-dicyclopropyl-1,2-diphenylethylene, m.p. 139.8–140.2°. An additional 1.1 g. (9%) was recovered from the mother liquors.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.23, 92.19; H, 7.94, 7.92.

Hydrazone of p-methoxyacetophenone. Using a procedure similar to that used for the preparation of the hydrazone of cyclopropyl phenyl ketone, there was obtained 94.3 g. (87%) of the hydrazone of *p*-methoxyacetophenone, m.p. 116.9–117.6° (lit. m.p. 118.5–120.0[8]), from 100.0 g. (0.663 mol.) of *p*-methoxyacetophenone and 160.0 g. (5.0 mol.) of 95% hydrazine.

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.17, 16.93.[24]

1,2-Dimethyl-1,2-di-p-anisylethylene; azine of p-methoxyacetophenone. The hydrazone of *p*-methoxyacetophenone, 12.0 g. (0.073 mol.), 32.4 g. (1.5 mol.) of mercuric oxide, and 23.0 g. (1.5 mol.) of anhydrous barium oxide in 200 ml. of low-boiling petroleum ether were treated as in the preparation of 1,2-dicyclopropyl-1,2-diphenylethylene. There was isolated 1.7 g. (16%) of yellow material, m.p. 199.3–199.7°, which was found by infrared and elemental analysis to be the azine of *p*-methoxyacetophenone.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.97; H, 6.79; N, 9.54.

There was also isolated 0.1 g. (2.0% corrected for isolated azine) of 1,2-dimethyl-1,2-di-*p*-anisylethylene, m.p. 127.3–128.1° (lit. m.p. 127–128°,[25] 131°,[26] and 140.5–142°[8]). Four other attempted preparations of the olefin led only to isolation of the azine; it was not ascertained whether the use of barium oxide in this instance led to the formation of the olefin.

Cyclopropyl p-anisyl ketone (VIII). The reaction of 87.2 g. (1.30 mol.) of cyclopropanecarbonitrile with the Grignard reagent prepared from 251.6 g. (1.34 mol.) of *p*-bromoanisole, b.p. 104–105° at 17 mm., gave 168.5 g. (73%) of solid cyclopropyl *p*-anisyl ketone, b.p. 101–104° at 0.05 mm., which, when recrystallized from petroleum ether (100–140°) melted at 40.3–40.8°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.98; H, 6.71.

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(22) Huang-Minlon, *J. Am. Chem. Soc.*, **70**, 2802 (1948).

(23) Obtained from the addition of 135.8 g. (0.5 mole) of mercuric chloride (Fisher) dissolved in 2 l. of water to 280.5 g. (5.0 moles) of potassium hydroxide dissolved in 1 l. of water. The product after washing twice with ethanol and drying was obtained in 93% yield.

(24) Analysis by Robert P. Yunick of this laboratory.

(25) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

(26) F. Wessely, A. Bauer, Ch. Chwala, I. Plaichinger, and R. Schonbeck, *Monatsh.*, **79**, 596 (1948); *Chem. Abstr.*, **43**, 6605 (1949).

It gave[27] a *2,4-dinitrophenylhydrazone*, m.p. 209.8–210.7°.

Azine and hydrazone (IX) *of cyclopropyl p-anisyl ketone.* Cyclopropyl *p*-anisyl ketone, 88.1 g. (0.50 mol.), and 64.1 g. (2.0 mol.) of 95% hydrazine in 150 ml. of absolute alcohol were refluxed for 24 hr., poured over ice, and extracted with ether. The extract was washed until neutral and dried over potassium carbonate. Upon removal of the ether there was obtained 88.8 g. of crude liquid hydrazone, which resisted attempts at crystallization from various solvents in a Dry Ice–acetone bath. Upon attempting to purify the hydrazone by distillation only a small fraction of liquid was distilled and the residue solidified; it was recrystallized three times from alcohol, and was found by infrared and elemental analysis to be the azine of cyclopropyl *p*-anisyl ketone, 11.1 g. (13%), m.p. 75.9–76.3°.

Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.22; H, 7.28; N, 7.74.

One preparation of the hydrazone using 1.10 mol. of ketone and 7.0 mol. of hydrazine partly crystallized upon standing and from it 39.0 g. of solid material was isolated by recrystallization from petroleum ether (100–140°). The first crop of crystals, after four recrystallizations, yielded the hydrazone of cyclopropyl *p*-anisyl ketone, m.p. 66.0–66.8°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.12; H, 7.28; N, 14.55.

It was later indicated that the remainder of the 39.0 g. isolated from petroleum ether was a mixture of hydrazone and unreacted ketone, while the mother liquors, which partly crystallized again after removal of the solvent, afforded no more pure hydrazone, but only small amounts of azine. It was attempted to convert the azine present in these residues to hydrazone by heating at 125° for 38 hr. with a seven-fold excess of hydrazine,[28] but when this solution was poured into ice water, extracted with ether, and dried over potassium carbonate an oil was again obtained.

1,2-Dicyclopropyl-1,2-di-p-anisylethylene (X). Following the same procedure as for the preparation of 1,2-dicyclopropyl-1,2-diphenylethylene, 65.4 g. (0.342 mol.) of crude liquid hydrazone of cyclopropyl *p*-anisyl ketone, in 600 ml. of *n*-hexane, b.p. 67.4–69.5°, and 216.6 g. (1.0 mol.) of mercuric oxide were shaken for 21 hr. The hexane was a very deep cherry-violet color which slowly faded as sulfur dioxide was passed into the solution. More heat and foaming were observed than with the hydrazone of cyclopropyl phenyl ketone. The hexane was removed leaving a black oil, water was added, and the solution was boiled for 3 hr., cooled, and extracted with ether. The ether solution was dried over potassium carbonate and the ether was removed leaving a deep red oil from which, after standing, a small amount of fine needles was separated. Recrystallization from alcohol yielded 1.1 g. (2.0%) of 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene which after two more recrystallizations melted at 175.5–175.9°.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.22, 82.20; H, 7.39, 7.54.

In one experiment, in which barium oxide was added, a 3% yield of the azine of cyclopropyl *p*-anisyl ketone and no olefin were isolated.

Attempts to decompose the addition compound by heating at 130°[6] led to a dark polymeric material from which no solid material could be isolated.

1,2-Dicyclopropyl-1,2-di-*p*-anisylethylene, 0.1 g. (0.0003 mol.), was placed in a Carius tube with 0.5 g. of potassium hydroxide and 3 ml. of absolute ethanol and sealed. The tube shattered after heating for 20 min. in a Carius furnace at 220°. A second tube also shattered.

Attempted preparation of 1,2-dicyclopropyl-1,2-di-p-nitrophenylethylene. 1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 3.0 g. (0.008 mol.), 200 ml. of distilled carbon tetrachloride, 100 ml. of glacial acetic acid, and a trace of benzoyl peroxide were mixed and 3.12 g. (0.017 mol.) of *N*-bromosuccinimide (Allied Chemical & Dye Corporation) was added and the solution was refluxed for 18 hr. The solvents were removed and a solution of sodium iodide in anhydrous acetone was added. The acetone turned a deep red with the precipitation of a yellow solid. After removal of the acetone, water was added, the solution extracted with ether, and the ether layer dried. Upon removal of the ether 1.8 g. (60%) of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane, m.p. 210–213° uncorr., was recovered.

1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 3.0 g. (0.008 mol.), was treated as before except that 1.52 g. (0.008 mol.) of *N*-bromosuccinimide was used. Upon removal of the solvents potassium hydroxide in absolute methanol was added. Dilution with water, filtration, and recrystallization afforded only 2.9 g. (97%) of recovered starting material.

Ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate (XIII). 1-Phenylcyclopropyl phenyl ketone (XII), 145.9 g. (88%), b.p. 150–156° at 2.5 mm., was prepared by the procedure of Bunce and Cloke[29] from 120.0 g. (0.76 mol.) of bromobenzene, b.p. 154–159°, 18.7 g. (0.77 mol.) of magnesium turnings, and 108.0 g. (0.75 mol.) of 1-phenylcyclopropanecarbonitrile.[30] A portion recrystallized twice from *n*-heptane and twice from alcohol melted at 72.6–72.9° (lit. m.p. 73.6–73.9°[29]). Its 2,4-dinitrophenylhydrazone[27] melted at 182.6–183.0° (lit. m.p. 184.8–185.3°[29]).

A solution of 750 ml. of anhydrous thiophene-free benzene containing 100.0 g. (0.60 mol.) of ethyl bromoacetate, b.p. 167–170°, and 72.8 g. (0.33 mol.) of 1-phenylcyclopropyl phenyl ketone was added to 42.5 g. (0.60 mol.) of 20-mesh zinc and a few crystals of iodine over a period of 4 hr. Following 17 hr. of refluxing, the reaction mixture was hydrolyzed using dilute sulfuric acid and the benzene layer was separated, neutralized with saturated sodium bicarbonate, and dried over sodium sulfate. The benzene was removed and the residue distilled to yield 40.4 g. of unreacted ketone boiling at 145–170° at 1.4 mm. and 39.5 g. (47% or 94% corrected yield) of ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate, b.p. 167–168° at 0.09 mm. A portion, recrystallized from petroleum ether (100–140°), melted at 48.2–48.8°. Ward[11] reported a m.p. of 40–41°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.25; H, 7.02.[31]

The above procedure was found to give the highest yield of several variants of the Reformatsky reaction which were investigated.

1-Phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol (XIV). Lithium aluminum hydride, 9.8 g. (0.258 mol.), was ground under an atmosphere of nitrogen and added to 500 ml. of anhydrous ether. Following 2 hr. of refluxing, 39.5 g. (0.127 mol.) of ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)-propionate dissolved in 500 ml. of absolute ether was added over a period of 3 hr. After refluxing for 21 hr. the reaction mixture was hydrolyzed with water followed by dilute sulfuric acid. The ether layer was separated, neutralized with saturated sodium bicarbonate, and dried over magnesium sulfate. After removal of the ether, the diol crystallized upon standing. It was found to be insoluble in petroleum ether at 50° and was washed free of contaminants. The white granular solid, 32.5 g. (96%), melted at 71.2–71.8°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.80; H, 7.61.[31]

1,3-Dibromo-1-phenyl-1-(1-phenylcyclopropyl)propane (XV). *A. Using phosphorus tribromide in ether.* Phosphorus

(27) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Edition, John Wiley & Sons, New York, N. Y., 1956, p. 219.

(28) L. Vargha and E. Kovacs, *Ber.*, **75**, 794 (1942).

(29) S. C. Bunce and J. B. Cloke, *J. Am. Chem. Soc.*, **76**, 2244 (1954).

(30) E. C. Knowles and J. B. Cloke, *J. Am. Chem. Soc.*, **54**, 2028 (1932).

(31) Analysis by George H. Potter of this laboratory.

tribromide, 34.6 g. (0.13 mol.) (Eastman), was added to 200 ml. of absolute ether and cooled to −12°. 1-Phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol, 23.8 g. (0.09 mol.), in 125 ml. of anhydrous ether was added over a period of 2 hr. at −5 to 0°. Following stirring for 48 hr. the solution was poured into ice water, the ether layer was separated and neutralized with saturated sodium bicarbonate and dried over sodium sulfate. Upon removal of the ether under vacuum there remained 16.1 g. of dark, partly crystalline product. Attempted recrystallization from absolute methanol yielded 0.7 g. of fine needles, m.p. 141.8–143.8°, which gave a negative test with alcoholic silver nitrate; the methanol-soluble portion after many treatments with charcoal, in acetone solution, yielded a brown solid. A sample of this material, after six recrystallizations from absolute alcohol, melted at 75.3–75.7° and gave a positive test with alcoholic silver nitrate.

Anal. Calcd. for $C_{18}H_{18}Br_2$: C, 54.84; H, 4.60; Br, 40.55. Found: C, 54.66; H, 4.43; Br, 40.5.

B. Using phosphorus tribromide in methylene chloride. A solution of 5 g. (0.019 mol.) of diol in 25 ml. of methylene chloride was cooled to −12°, and 5.4 g. (0.02 mol.) of phosphorus tribromide was added during 10 min., maintaining the temperature below 10°. After standing for 10 days, the mixture was poured over ice and the methylene chloride layer was separated, neutralized, and dried. Removal of the solvent under vacuum gave 7.3 g. of an oil which solidified rapidly. Recrystallization from absolute alcohol using charcoal yielded 1.7 g. (23%) of material, m.p. 69.7–71.0°, with an additional 2.2 g. (30%) isolated from the mother liquors. Subsequent work with this material showed it to be impure, containing some of the higher melting dibromide, m.p. 145.7–146.1°.

One experiment using 5.0 g. (0.019 mol.) of diol and 10.8 g. (0.04 mol.) of phosphorus tribromide was allowed to stand for 1 week. On removal of the methylene chloride, 3.0 g. of an oil was obtained which solidified upon the addition of absolute methanol. Recrystallization from methanol yielded a dibromide, m.p. 144.3–144.9°, which gave a negative test with alcoholic silver nitrate and whose mixed melting point with the higher melting dibromide previously obtained showed no depression.

Anal. Calcd. for $C_{18}H_{18}Br_2$: C, 54.84; H, 4.60. Found: C, 54.88, 55.19; H, 4.90, 5.22.

1,1′-Diphenylbicyclopropyl (XVI). The cyclization procedure is that of Bartleson, Burk, and Lankelma.[32] *n*-Propyl alcohol (100 ml.) and 13.08 g. (0.2 mol.) of zinc dust were cooled to −5° and the crude product from the reaction of 32.5 g. (0.12 mol.) of diol with phosphorus tribromide in ether was added in 90 min. at −3° to −5°. After stirring for 3 days, water was added, the alcohol distilled from the reaction mixture, and the mixture extracted with ether. The ether was washed with saturated sodium bicarbonate and dried over sodium sulfate. Upon removal of the ether, the residue was distilled at 0.1 mm.; 3.5 g. of material distilled between 124–130° and a large amount of tar remained in the distilling flask. The distilled material gave a negative test for halogens using the sodium fusion method. Its infrared spectrum agreed qualitatively with that expected for 1,1′-diphenylbicyclopropyl; it could not be induced to crystallize upon long standing.

Treatment of 2.0 g. of crude 1,1′-diphenylbicyclopropyl with a mixture of 10 ml. of acetic anhydride, 7 ml. of glacial acetic acid, and 7 ml. of nitric acid (*d* 1.5) at −15° gave a small amount of material which could not be recrystallized satisfactorily.

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TROY, N. Y.

(32) J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, **68**, 2513 (1946).

[CONTRIBUTION NO. 1566 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

20-Methylpregnane and Derivatives[1,2]

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20-Methylpregnane and several of its significant derivatives have been prepared by the Wittig reaction and by other methods.

In calculating the contributions of side chains to the optical rotations of sterols,[4] the molecular rotations of the respective sterols are generally compared with those of corresponding derivatives of pregnane. Pregnane, however, is not an ideal reference compound for such purposes. It has its C-17 attached to a β-oriented, secondary C-20 atom, while in the natural sterols C-17 is joined to β-oriented, tertiary C-20 atom. 20-Methylpregnane and its derivatives would therefore be more suitable reference compounds. At the beginning of this investigation, however, surprisingly little was known about this series of compounds or of others with relatively short alkyl side chains.

A number of derivatives of 20-methylpregnane have now been prepared by several methods. In one approach, 3β-acetoxydinor-5-cholenic acid (I), which possesses the desired carbon skeleton, was reduced to the known diol (IIa). This was converted

(1) The material presented in this paper constitutes part of a dissertation submitted by John P. Dusza in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1958.

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(4) W. M. Stokes and W. Bergmann, *J. Org. Chem.*, 16, 1817 (1951).

*Deceased.

to 20-methyl-5-pregnen-3β-ol (IIIa) by reductive cleavage of the monotosylate (IIb). A selective, direct monotosylation of the primary alcohol function of IIa was unsuccessful. The desired derivative was obtained only by selective hydrolysis of the ditosylate (IIc) with a dilute aqueous solution of sulfuric acid in acetone. This method had previously been used in the preparation of 3β,17-diol-17-monotosylates.[5] The monotosylate (IIb) was then reduced with lithium aluminum hydride in boiling dioxane. Some diol,[6] IIa, was obtained along with the desired product, IIIa.[7]

Hydrogenation of 20-methyl-5-pregnen-3β-ol (IIIa) smoothly afforded the stanol (IVa) which has become the reference compound of this series. It was oxidized with a chromic anhydride-pyridine complex to the stanone (V) which was reduced to 20-methyl-5α-pregnane (VI). Treatment of IIIa with thionyl chloride gave the 3-chloro-derivative (VII) which was reduced with sodium in amyl alcohol to 20-methyl-5-pregnene (VIII). Oxidation of IIIa with chromic anhydride gave the ketone, (IX).

In another series of experiments 5-pregnen-20-on-3β-ol (Xa) was converted by way of its tetrahydropyranyl ether (Xc) into XIa by means of the Wittig reaction. A preparation of this dienol by a very similar procedure has since been reported.[8] We have also obtained this compound by the dehydrotosylation of IIb with boiling collidine. Attempts to reduce selectively XIa to IIIa were unsuccessful. Even under mild conditions the hydrogenation proceeded rapidly, and only the stanol (IVa) was obtained. 20-Methyl-5,20-pregnadien-3β-ol (XIa) resisted all attempts to isomerize the exocyclic bone to give the known 20-methyl-5,17-pregnadien-3β-ol. Thus treatment of the acetate (XIc) with anhydrous hydrogen chloride in chloroform, a typical isomerization procedure for terminal double bonds in terpenes,[9] afforded a chloride which was reconverted to the starting material on treatment with base. The dienol (XIa) also did not react with maleic anhydride to give a 2-substituted succinic acid.[10] It appears therefore that the 20,22-double bond offers considerable resistance to rearrangement into the 17, 20-position. Oxidation of XIa with chromic anhydride leads to the methylene derivative of progesterone (XII) which had previously been prepared by a dehydrotosylation reaction.[11]

20-Methyl-5α-pregnan-3β-ol (IVa) was also prepared from the readily available 16-dehydropregnenolone acetate (XIIIb). The latter was converted by way of the pyranyl ether (XIIIc)[12] to the methylene derivative (XIVc) from which 20-methyl-5,16,20-pregnatrien-3β-ol (XIVa) was obtained. Since this work was completed a preparation of the acetate (XIVb) by way of the Wittig reaction has been reported.[8] The formulation of the trienol as XIV may be questioned. It is known that the Wittig reaction with α,β-unsaturated ketones may entail 1,4-rather than 1,2-additions.[13] In the present case therefore, structure XVI may not *a priori* be excluded. On the contrary a 1,4- addition might also be expected because of the particular susceptibility of 16-dehydropregnenolone (XIII) to base attack at C-16.[14] The problem was easily solved in favor of structure XIVa by the catalytic reduction of the trienol. It afforded 20-methyl- (IVa) rather than 16-methyl-5α-pregnan-3β-ol. Partial reduction of the trienol (XIVa) with sodium in ethanol gave a new pregnadienol. Its spectrum lacked absorption characteristics of a conjugated diene and of a terminal methylene group. Since its physical properties are different from those of 20-methyl-5,17-pregnadien-3β-ol, the new compound must be 20-methyl-5,16-pregnadien-3β-ol (XVa).

TABLE I

MOLECULAR ROTATIONS OF DERIVATIVES OF 20-METHYLPREGNANE

Compound	M_D
20-Methyl-5α-pregnane (VI)	+27
20-Methyl-5α-pregnan-3β-ol (IVa)	+30
20-Methyl-5α-pregnan-3β-ol acetate (IVb)	−7
20-Methyl-5α-pregan-3-one (V)	+96
20-Methyl-5-pregnene (VIII)	−270
20-Methyl-5-pregnen-3β-ol (IIIa)	−208
20-Methyl-5-pregnen-3β-ol acetate (IIIb)	−248
20-Methyl-5,16-pregnadien-3β-ol (XVa)	−185
20-Methyl-5,16-pregnadien-3β-ol acetate (XVb)	−232
20-Methyl-4-pregnen-3-one (IX)	+355

(5) M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **222**, 447 (1956).

(6) This anomalous cleavage of the tosyl group to the alcohol is not without parallel in the steroid literature. Thus the reduction of cholestan-3β-ol tosylate gave both cholestane and cholestan-3β-ol and that of cholestan-6α-ol tosylate gave both cholestane (38%) and cholestan-6α-ol (57%) [P. Karrer, H. Asmis, K. N. Sareen, and R. Schwyzer, *Helv. Chim. Acta*, **34**, 1022 (1951); **35**, 427 (1952)]. Under similar conditions moradiol 28-monotosylate, a primary tosylate, afforded only the diol [D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951)].

(7) The new compound is not identical with a "20-methyl-5-pregnen-3β-ol" mentioned in the older literature. The assignment of structure IIIa to this compound is contraindicated by the strongly positive rotation of 69°, and has already been questioned [*Elseviers Encyclopaedia of Organic Chemistry*, Elsevier Publishing Company, New York, Vol. **14**, p. 1600s].

(8) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(9) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); J. S. E. Holker, A. D. G. Powell, A. Robertson, J. J. H. Simes, R. S. Wright, and R. M. Gascoque, *J. Chem. Soc.*, 2422 (1953).

(10) R. T. Arnold and J. S. Showell, *J. Am. Chem. Soc.*, **79**, 419 (1957).

(11) C. Meystre and K. Miescher, *Helv. Chim. Acta*, **32**, 1758 (1949).

(12) W. Bergmann and J. P. Dusza, *J. Org. Chem.*, **23**, 459 (1958).

(13) H. H. Inhoffen, K. Bruchner, D. K. Domagk, and H. Erdmann, *Ber.*, **88**, 1415 (1955).

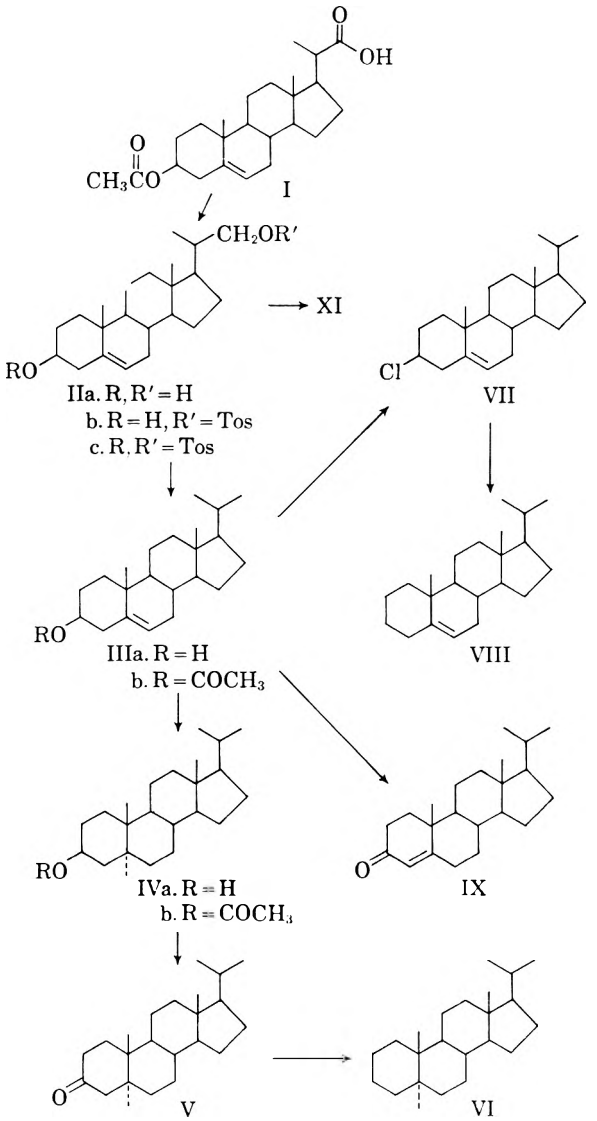
(14) D. K. Fukushima and T. G. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

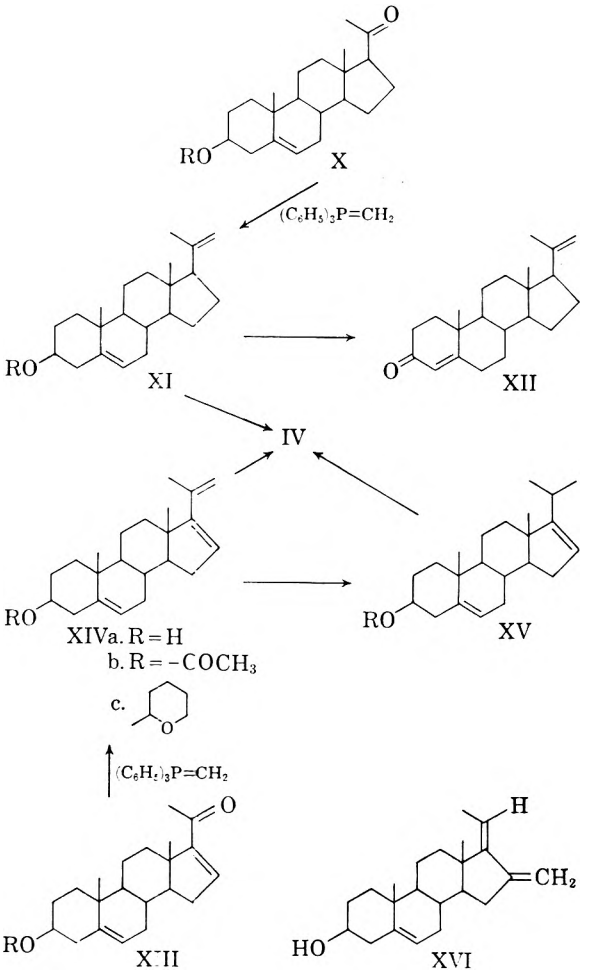
Catalytic hydrogenation of this dienol gave the expected stanol (IVa). Table I lists the molecular rotations of the new compounds which may be used as references.

EXPERIMENTAL

Dinor-5-cholene-3β,22-diol (IIa). A solution of 3β-acetoxydinor-5-cholenic acid (I) (6.0 g.) in dry tetrahydrofuran[15] (50 ml.) was added dropwise to a suspension of lithium aluminum hydride (2.2 g.) in tetrahydrofuran.[15] The solution was then stirred vigorously and refluxed for 5 hr. After cooling, ethyl formate was added to decompose the excess hydride, and the mixture poured into 2*N* sulfuric acid (500 ml.). The precipitated diol was collected and recrystallized several times from methanol; long needles, m.p. 204–206° (rep.[16] 202–206°); $[\alpha]_D^{25}$ −47.0° (c 0.35 in $CHCl_3$). The material was probably the hemihydrate.

The diacetate, prepared in the usual manner, was recrystallized from dilute methanol; needles, m.p. 128–129° (rep.[16] 127–129°); $[\alpha]_D^{25}$ −51.6° (c 1.30 in $CHCl_3$).





Dinor-5-cholene-3β,22-diol 22-tosylate (IIb). *p*-Toluenesulfonyl chloride (6.4 g.) was added to a solution of dinor-5-cholene-3β,22-diol (IIa) (2.0 g.) in pyridine (50 ml.) at a rate which did not let the temperature of the mixture exceed 20° (ice bath). The mixture was allowed to stand at room temperature for 24 hr. when it was poured into ice water (100 ml.) and kept at 5° for another 24 hr. The supernatant liquid was then decanted, and the sticky precipitate dissolved in ether. The ether extract was washed with cold 2*N* hydrochloric acid and then thoroughly with water. Evaporation of the dried extract left a glassy residue. It was dissolved in alcohol-free acetone (200 ml.) to which was added water (60 ml.) and 10 drops of concentrated sulfuric acid. The solution was then refluxed for 4 hr., diluted with water (40 ml.), and concentrated until it became turbid. The monotosylate (IIb) obtained on cooling was recrystallized twice from dilute acetone; 1.82 g.; m.p. 115–118°; $[\alpha]_D^{28}$ −37.2° (c 1.00, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{42}O_4S$: C, 71.56; H, 8.69. Found: C, 71.23; H, 8.72.

20-Methyl-5-pregnen-3β-ol (IIIa). Lithium aluminum hydride (500 mg.) was added to a solution of the tosylate (IIb) (1.01 g.) in dry dioxane (150 ml.).[17] The mixture was refluxed for 4 hr., and the excess hydride was decomposed with ethyl acetate and hydrochloric acid. The solution was then poured into water and extracted with ether. The ether extract was washed with water, dried and evaporated to dryness. The amorphous residue was taken up in benzene and chromatographed over neutral aluminum oxide (II–III). Elution with benzene–ether (5:1) gave the product which was crystallized from dilute methanol; yield: 0.59

(15) The solvent had been stored over sodium hydroxide pellets and distilled from lithium aluminum hydride.

(16) A. V. McIntosh, Jr., E. M. Meinzer, and R. H. Levin, *J. Am. Chem. Soc.*, **70**, 2955 (1948); H. L. Herzog, C. C. Payne, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 5324 (1955).

(17) The solvent had been passed over active aluminum oxide and distilled over lithium aluminum hydride.

g.; m.p. 131–133° (hydrate). After drying *in vacuo*, m.p. 136–137°; $[\alpha]_D^{25}$ −65.8° (c 1.30 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{36}O$: C, 83.45; H, 11.47. Found: C, 83.35; H, 11.52.

Elution with benzene-ether (1:1) gave some dinor-5-cholen-3β,22-diol (IIa), m.p. 203–205°.

The *acetate* (IIIb) was prepared by refluxing the alcohol (IIIa) with acetatic anhydride. It was recrystallized several times from methanol; large plates, m.p. 121–121.5°; $[\alpha]_D^{26}$ −69.2° (c 1.37 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.65; H, 10.67.

20-Methyl-5α-pregnan-3β-ol (IVa). Platinum oxide (35 mg.) was added to a solution of 20-methyl-5-pregnen-3β-ol (IIIa) (75 mg.) in acetic acid (30 ml.) and ethyl acetate (30 ml.). The solution was shaken for 2 hr. under hydrogen at 14 lb. pressure. The catalyst was filtered, the solvent removed *in vacuo*, and the residue recrystallized twice from methanol. The stanol melted at 145–146°; $[\alpha]_D^{25}$ +9.3° (c 1.31 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{38}O$: C, 82.95; H, 12.03. Found: C, 82.98; H, 11.96.

The *acetate* formed long needles, m.p. 122–123°; $[\alpha]_D^{25}$ −1.9° (c 1.31 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 80.29; H, 11.30.

20-Methyl-5α-pregnan-3-one (V). A solution of 20-methyl-5α-pregnan-3β-ol (IVa) (110 mg.) in pyridine (3 ml.) was added to a suspension of chromic anhydride complex[18] prepared from chromic anhydride (0.1 g.) and pyridine (5 ml.). The solution was allowed to stand for 17 hr. and was then poured into dilute hydrochloric acid and extracted with ether. The extract was washed with sodium carbonate solution and water, dried, and evaporated to dryness. The residue was dissolved in hexane and chromatographed on neutral alumina (VI). The material eluted with benzene-hexane (1:1) was recrystallized from dilute methanol. The ketone (87 mg.) melted at 144–145°; $[\alpha]_D^{25}$ +30.2° (c 1.18 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.48; H, 11.53.

20-Methyl-5α-pregnane (VI). A solution of 20-methyl-5α-pregnan-3-one (V) (100 mg.) in acetic acid (10 ml.) was refluxed with amalgamated zinc (3.5 g.). Over a 7-hr. period a solution of acetic acid (5 ml.), concentrated hydrochloric acid (20 ml.), and xylene (0.5 ml.) was added. The reaction mixture was refluxed during this time and an additional 30 min. After cooling, the solution was poured into water, extracted with ether, and the extract washed with 2*N* sodium hydroxide, water, and dried. The residue obtained upon evaporation of the ether was taken up in hexane and passed through neutral alumina (I). The hexane eluate was evaporated, and the residue crystallized twice from methanol and then sublimed. The hydrocarbon melted at 111–112°; $[\alpha]_D^{25}$ +8.90° (c 1.53 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{38}$: C, 87.34; H, 12.66. Found: C, 87.12; H, 12.69.

20-Methyl-4-pregnen-3-one (IX). To a solution of 20-methyl-5-pregnen-3β-ol (IIIa) (120 mg.) in alcohol-free acetone (30 ml.) was added 0.18 ml. of a standard chromic anhydride–sulfuric acid solution[19] (2.67 g. of chromic anhydride, 2.3 ml. of concentrated sulfuric acid, total volume brought to 10 ml. with water). This mixture was swirled for 5 min. until the characteristic light green precipitate was formed. The mixture was diluted with water and immediately extracted with ether. The residue obtained upon evaporation of the ether was refluxed with 2% alcoholic potassium hydroxide solution (25 ml.) for 10 min. and most of the methanol was then removed *in vacuo*. Water was added to the reaction mixture which was then extracted with ether. Evaporation of the ether gave a brown viscous oil which was chromatographed on neutral alumina (II). The fraction eluted with hexane-benzene (1:1) was crystallized from methanol-water (5:1) to give 30 mg. of long needles of the enone, m.p. 143–144°; $[\alpha]_D^{27}$ +113° (c 0.41 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}$: C, 84.01; H, 10.90. Found: C, 84.17; H, 11.08.

3β-Chloro-20-methyl-5-pregnene (VII). To a solution of 20-methyl-5-pregnen-3β-ol (IIIa) (0.8 g.) in dry benzene (25 ml.) was added 1.0 ml. of thionyl chloride. The mixture was allowed to stand at room temperature for 30 min. and then kept for 90 min. at 50–60°. The benzene and excess thionyl chloride was removed at reduced pressure and the residue taken up in hexane. The hexane solution was passed through a neutral alumina (VI) column. The solvent was evaporated and the residue crystallized from methanol; long needles; (0.78 g.) m.p. 147.5–148°; $[\alpha]_D$ −52.4° (c 1.30 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{35}Cl$: C, 78.88; H, 10.53. Found: C, 78.78; H, 10.63.

20-Methyl-5-pregnene (VIII). 3β-Chloro-20-methyl-5-pregnene (VII) (0.56 g.) was refluxed with 20 ml. of distilled isoamyl alcohol. To the refluxing solution were added small cubes of sodium. The addition of sodium was continued until the color of the solution had changed from yellow to colorless. This required approximately 1 g. of sodium and covered a period of 90 min.[20] Water was added, the mixture extracted with ether, and the extract thoroughly washed with water and dried. The residue was recrystallized three times from methanol-ether; very long needles (0.25 g.); m.p. 104.5–105°; $[\alpha]_D^{26}$ −89.7° (c 1.27 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{36}$: C, 87.92; H, 12.08. Found: C, 88.03; H, 12.17.

5-Pregnen-20-one-3β-(2'-tetrahydropyranyl)-ether (Xc). 5-Pregnen-20-one-3β-ol (Xa) (2 g.) 2-methoxytetrahydropyran (15 ml.) and Doxex-50 (2 g.) (H form, dried at 70° for 24 hr.) were heated on an oil bath at 95° for 10 hr. The resin was filtered and the excess 2-methoxytetrahydropyran was evaporated *in vacuo*. The slightly yellow, crystalline residue was dissolved in hexane and chromatographed on neutral alumina (VI) (60 g.). The hexane eluate was evaporated, and the residue crystallized from methanol; yield 1.81 g., m.p. 126–128°; $[\alpha]_D^{25}$ +16.5° (c 1.45 in $CHCl_3$), rep.[21] m.p. 129–131°, $[\alpha]_D^{25}$ +17.7°.

20-Methyl-5,20-pregnadiene-3β-(2'-tetrahydropyranyl)-ether (XIb). This compound was prepared from 5-pregnen-20-one-3β (2'-tetrahydropyranyl)-ether (Xc) (2.44 g.) and triphenylphosphonium methylene, obtained from 2.16 g. of triphenylphosphonium bromide, by the Wittig reaction, using the procedures previously described.[12] The ether thus obtained (2.01 g.) showed a great tendency to gel. Thus, crystallization from ethanol always gave a gel which slowly turned into crystalline material, a process which was somewhat hastened by successive warming and cooling of the solution. The crystalline ether melted at 110–112°; $[\alpha]_D^{24}$ −39.6° (c 1.25 in $CHCl_3$).

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(20) This reduction could not be carried out with lithium aluminum hydride in boiling tetrahydrofuran. Similar conditions were used by H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956) to reduce 3β-chloro-1-cholestene to 1-cholestene. In this case, however, the chlorine atom was in the more reactive allylic position. In contrast M. Gut and M. Vskokovic [133rd Meeting, ACS, San Francisco, Calif., April 1958, Abstract of Papers, p. 99N] reduced the sulfite function in bis(3β-chloro-androst-5-en-17β-yl) sulfite with lithium aluminum hydride selectively to 3β-chloroandrost-5-en-17-ol without touching the homoallylic chlorine.

(21) A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.55; H, 10.66.

20-Methyl-5,20-pregnadien-3β-ol (XIa). To a solution of 20-methyl-5,20-pregnadien-3β-(2¹-tetrahydropyranyl)-ether (2 g.) in hexane (100 ml.) was added 100 ml. of methanol containing 5 drops of concentrated hydrochloric acid. After standing at room temperature for 1 hr. the solution was evaporated to dryness and the residue crystallized from methanol-water (5:1); 1.23 g., m.p. 120–125°. An analytical sample after drying *in vacuo* exhibited the following properties: m.p. 133.5–134°; $[\alpha]_D^{25}$ −66.4° (c 0.55 in $CHCl_3$); rep.[8] m.p. 133–134°; $[\alpha]_D$ −59°.

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 84.23; H, 11.08.

The acetate (Xc) was recrystallized from methanol; long needles of m.p. 128.5–129°; $[\alpha]_D^{27}$ −72° (c 1.62 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.55; H, 10.45.

20-Methyl-5,20-pregnadien-3β-ol (Xa) *by dehydrotosylation.* Dinor-5-cholene-3β,22-diol 22-tolsylate (IIb) (0.7 g.) was refluxed with 10 ml. of dry, freshly distilled collidine for 3 hr. After cooling, the mixture was extracted with ether and the extract washed with dilute hydrochloric acid and dried. The residue obtained upon evaporation of the ether was taken up in hexane and chromatographed on neutral alumina (II). The material eluted with benzene-ether was crystallized several times from methanol to give 50 mg. of a product of m.p. 115–117°. It was somewhat impure 20-methyl-5,20-pregnadien-3β-ol. Its infrared spectrum was nearly identical to that of the pure product mentioned above.

20-Methyl-4,20-pregnadien-3-one (XII). This compound was prepared by the oxidation of 20-methyl-5,20-pregnadien-3β-ol (XIa) (0.2 g.) with a standard chromic anhydride–sulfuric acid solution according to the procedure outlined in the preparation of 20-methyl-4-pregnen-3-one (IX). The crude ketone was chromatographed on neutral alumina (III). The material eluted with hexane-benzene (9:1) was crystallized from methanol-water (5:1). It gave 97 mg. of long needles, m.p. 152–154°; $[\alpha]_D^{27}$ +112° (c 1.35 in $CHCl_3$); lit.[12] m.p. 155–160°, $[\alpha]_D^{23}$ +105°.

Hydrogenation of 20-methyl-5,20-pregnadiene-3β-ol (XIa). 20-Methyl-5,20-pregnadien-3β-ol (0.4 g.) was dissolved in 150 ml. of absolute ethanol and was hydrogenated using a 5% palladium-on-carbon catalyst (0.2 g.) under 14 lb. pressure of hydrogen for 1 hr. After filtration of the catalyst the solvent was evaporated to dryness and the residue crystallized from methanol-water (5:1). There was obtained 0.29 g. of 20-methyl-5α-pregnan-3β-ol, m.p. 144–145°. This was identical to the material previously prepared from the hydrogenation of 20-methyl-5-pregnen-3β-ol (IIIa).

5,16-Pregnadien-20-one-3β (2¹-tetrahydropyranyl)-ether (XIIIc). 5,16-Pregnadiene-20-one-3β-ol, (XIIIa) (5 g.), 2-methoxytetrahydropyran (50 ml.), and Dowex-50 (3 g.) (H-form dried at 70° for 24 hr.) were heated at 90° for 6 hr. with stirring and under nitrogen with exclusion of moisture. The resin was filtered and the excess 2-methoxytetrahydropyran removed under reduced pressure. The crystalline residue was taken up in hexane and passed through a neutral alumina (VI) column. The hexane eluate was evaporated to dryness and the residue crystallized from ether to give 4.2 g. of pyranyl ether, m.p. 165–167°. The mother liquor was evaporated and the residue crystallized from a minimum amount of ether to give 1.2 g. of additional product, m.p. 163–165°; $[\alpha]_D^{27}$ +49.7° (c 0.95 in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61. Found: C, 78.50; H, 9.66.

20-Methyl-5,16,20-pregnatriene-3β-(2¹-tetrahydropyranyl)-ether (XIV). This compound (1.5 g.) was prepared from the pyranyl ether (XIIIc) (2.2 g.) and triphenylphosphonium methylene by the procedure previously described.[12] It crystallizes from acetone in large plates, m.p. 155–156°; $[\alpha]_D^{27}$ −56.0° (c 0.82 in $CHCl_3$). λ_{max} 239 mμ (ε 16,500); shoulder 234 mμ (ε 15,600); inflection 247 mμ (ε 11,200); λ_{max} 6.17, 6.35, 11.41, 11.55, 12.43, and 12.56μ.

Anal. Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.95; H, 10.27.

20-Methyl-5,16-20-pregnatrien-3β-ol (XIVa). A solution of 20-methyl-5,16,20-pregnatriene-3β-(2¹-tetrahydropyranyl)-ether (XIVb) (0.26 g.) in hexane (25 ml.) was added to a solution of two drops of concentrated hydrochloric acid in methanol (25 ml.). The solution was allowed to stand at room temperature for 1 hr. with occasional stirring. The unhomogeneous mixture was evaporated to dryness *in vacuo* and the residue crystallized from methanol-water (5:1) to give the sterol (0.165 g.) of m.p. 149–161° dec. The infrared spectrum showed this material to be strongly hydrated. After subsequent recrystallizations from methanol the melting point was constant at 162–164°, $[\alpha]_D^{27}$ −69.0° (c 1.39 in $CHCl_3$). λ_{max} 239 mμ (ε 15,600); λ_{max} 2.95, 3.32, 5.67, 6.00, 6.12, 6.35, 11.38, 12.42, and 12.53μ.

Anal. Calcd. for $C_{29}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.55; H, 10.32.

The acetate was recrystallized from methanol; very long needles, m.p. 125–125.5°; $[\alpha]_D^{27}$ −75.3° (c 1.17 in $CHCl_3$); λ_{max} 239 mμ (ε 16,700); rep. m.p.[8] 124.5–126°, $[\alpha]_D$ −76°; λ_{max} 239 mμ (log ε: 4.21).

Hydrogenation of 20-methyl-5,16,20-pregnatrien-3β-ol (XIVa). Catalytic hydrogenation of XIVa in glacial acetic acid with a platinum oxide catalyst gave 20-methyl-5α-pregnan-3β-ol (IVa), m.p. 145–146°. The infrared spectra of this compound and of an authentic sample were identical.

20-Methyl-5,16-pregnadien-3β-ol (XVa). A solution of 20-methyl-5,16,20-pregnatriene-3β-ol (XIVa) (0.53 g.) in absolute ethanol (75 ml.) was refluxed vigorously. Cubes of sodium metal were added over a 90-min. period. After approximately 7 g. had been added, the solution was refluxed an additional 0.5 hr. It was then poured into water, extracted with ether, and the extract washed with a saturated salt solution until neutral and dried.

The ether was evaporated and the residue crystallized three times from methanol-water (5:1). The dienol (0.17 g.) melted at 130–132°; $[\alpha]_D^{27}$ −58.6° (*c* 1.40); λ_{max} 3.05, 6.00, 7.30, 7.37 (sh), and 12.43μ.

Anal. Calcd. for $C_{29}H_{34}O$: C, 84.01; H, 10.90. Found: C, 84.20; H, 11.17.

The acetate, (XVb), was recrystallized from methanol; m.p. 136–138°, $[\alpha]_D^{27}$ −65.5° (*c* 1.87 in $CHCl_3$). λ_{max} 5.75, 6.00, 8.06, and 12.53μ.

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.85; H, 10.18.

Hydrogenation of 20-methyl-5,16-pregnadien-3β-ol (XVa). Hydrogenation of XVa in glacial acetic acid with a platinum oxide catalyst under 14 lb. pressure gave 20-methyl-5α-pregnan-3β-ol (IVa); short needles, m.p. 145–146°. This was identical in all respects with the previously prepared reference compound.

NEW HAVEN, CONN.

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

Aluminum Chloride-Catalyzed Opening of the Steroidal Sapogenin Spiroketal System[1]

GEORGE R. PETTIT AND WILLIAM J. BOWYER

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Several representative steroidal sapogenins have been conveniently converted to the corresponding dihydrosapogenins employing the lithium aluminum hydride–aluminum chloride reagent. Dihydro derivatives of 11α-hydroxytigogenin, markogenin, and three previously described dihydrosapogenins were prepared by the new procedure. Lithium aluminum hydride reduction of tomatidine, in the presence of aluminum chloride, provided both isomers of dihydrotomatidine.

In 1939 Marker and Rohrmann reported the catalytic hydrogenation of sarsasapogenin (5β, Ia) to dihydrosarsasapogenin (5β, IIa).[2] Catalytic hydrogenation of steroidal sapogenins to dihydrosapogenins, using similar conditions,[3] has been described numerous times subsequent to Marker's discovery. Recently, the hydrogenation procedure has been carried out in the presence of perchloric acid.[4] Doukas and Fontaine[5] have employed an ethereal lithium aluminum hydride solution saturated with anhydrous hydrogen chloride or hydrogen bromide to achieve reduction. However, lithium aluminum hydride, either alone[5,6] or in the presence of hydrogen sulfide, sulfur dioxide, or *p*-toluenesulfonic acid is ineffective.[5]

The elegant mechanism proposed by Woodward, Sondheimer, and Mazur[7] to account for the acid-catalyzed interconversion of normal and isosteroidal sapogenins, involves rupture of the spiroketal system and eventual generation of a potential aldehyde at C-26 (*e.g.*, A).[8] In view of these experiments, current work in this laboratory and the novel lithium aluminum hydride–aluminum chloride reduction of acetals and ketals described by Eliel and Rerick[9] it appeared possible to generate an intermediate such as C or D by treating a steroidal sapogenin with ethereal aluminum chloride or boron trifluoride. Concomitant metal hydride reduction might then lead to a dihydrosapogenin.[10] A variety of steroidal sapogenins were, in fact, found to be converted in good yield to dihydro derivatives employing an ethereal mixture of lithium aluminum hydride and aluminum chloride.[9,11]

Addition of tigogenin acetate (Ib) to a cool mixture of the lithium aluminum hydride–aluminum chloride reagent in ether and recovery of the product after a 3 hr. reaction period afforded a 92.5% yield of dihydrotigogenin (IIb). Acetylation of the reaction product (IIb) gave a diacetate (IIc) which was identical with an authentic sample of tigogenin diacetate (IIc).[3a]

In order to verify the course of the reduction, two additional dihydrosapogenins of known composition were prepared. Diosgenin (IIIa) and desoxytigogenin (Id) were readily reduced to dihydrodiosgenin[5] (IVa) and dihydrodesoxytigogenin[12] (IId) respectively. Raney nickel desulfurization of tigogenin 3-ethylenethioketal (Ic)

(1) This investigation was supported in part by Research Grant CY-4074, from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 846 (1939). Hydrogenation in acetic acid or in acidified ethanol solution followed by saponification of the oily product gave crystalline dihydrosarsasapogenin. However, hydrogenation did not take place in a neutral medium. The unusual reactivity of the steroidal sapogenin side chain in acid media prompted Marker and Rohrmann to propose the presently accepted spiroketal system.

(3) See for example: (a) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, *J. Am. Chem. Soc.*, 69, 2167 (1947); (b) I. Scheer, R. B. Kostic, and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 641 (1955); (c) M. E. Wall, S. Serota, and C. R. Eddy, *J. Am. Chem. Soc.*, **77**, 1230 (1955); (d) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(4) R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 2645 (1958).

(5) H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **75**, 5355 (1953). This procedure presents the obvious advantages of preserving nuclear unsaturation and eliminating a subsequent saponification step.

(6) The following references are cited in support of this observation: C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951); J. Romo, H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951); R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 4654 (1951); J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 5375 (1951); C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 422 (1952); C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952); H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 3318 (1952); R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, 76, 4013 (1954).

(7) R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, 80, 6693 (1958).

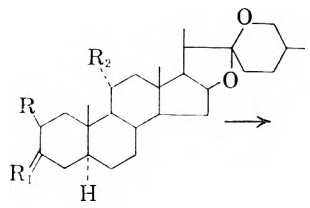
(8) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959), have provided additional experimental evidence in support of this hypothesis.

(9) E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958). We are grateful to these investigators for informing us of their experimental procedure prior to publication.

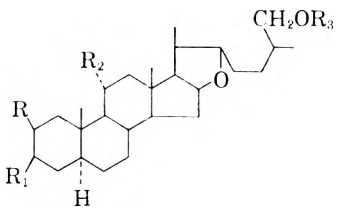
(10) The course of the reduction employing boron trifluoride etherate will be the subject of a subsequent communication.

(11) R. F. Nystrom, *J. Am. Chem. Soc.*, **81**, 610 (1959).

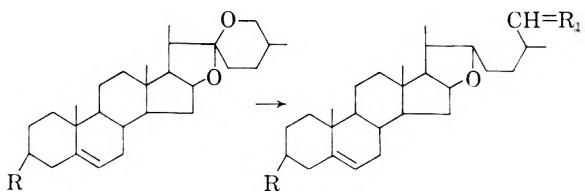
(12) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 1516 (1939).



Ia. R = R_2 = H; R_1 = OH (H)
b. R = R_2 = H; R_1 = $OCOCH_3$ (H)
c. R = R_2 = H; R_1 = 
d. R = R_2 = H; R_1 = H_2
e. R = OH; R_1 = OH (H); R_2 = H
f. R = H; R_1 = OH (H); R_2 = OH
g. R = R_2 = H; R_1 = O



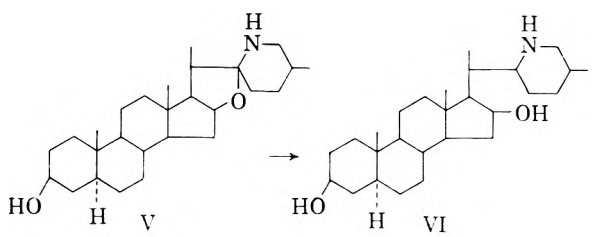
IIa. R = R_2 = R_3 = H; R_1 = OH
b. R = R_2 = R_3 = H; R_1 = OH
c. R = R_2 = H; R_1 = $OCOCH_3$; R_3 = $COCH_3$
d. R = R_1 = R_2 = R_3 = H
e. R = R_1 = OH; R_2 = R_3 = H
f. R = R_3 = H; R_1 = R_2 = OH



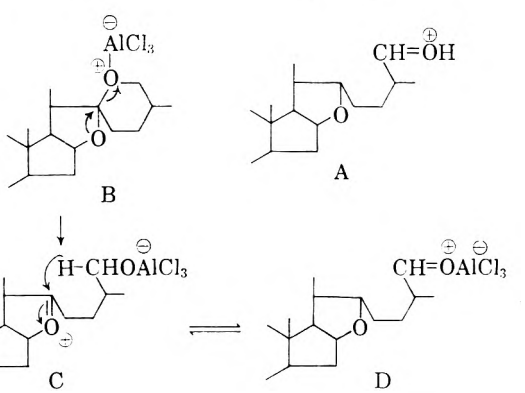
IIIa. R = OH
b. R = $OCOCH_3$

IVa. R = OH, R_1 = OH (H)

b. R = $OCOCH_3$, R_1 = 



V VI



B A C D

provided a convenient source of desoxytigogenin (Id).

Lithium aluminum hydride–aluminum chloride reduction of markogenin (Ie → IIe) and 11α-hydroxytigogenin (If → IIf) gave, in each case, a previously unreported dihydro derivative. Similar reduction of the steroidal alkaloid tomatidine (V) afforded a preponderant amount of the higher melting (229–230°) isomer of dihydrotomatidine[13,14] (VI), accompanied by a smaller quantity of the isomer melting at 193–195°.

When a solution of diosgenin acetate (IIIb) in ethereal aluminum chloride was allowed to react with ethanedithiol, 3β-acetoxy-5-furostene 26-ethylenethioketal (IVb) was formed in high yield. Implication of a mechanistic pathway such as B → D in the aluminum chloride catalyzed lithium aluminum hydride reduction of the spiroketal moiety receives some support from the result of this experiment.[15]

EXPERIMENTAL[16]

The preparation of dihydrotigogenin (IIb) illustrates the general procedure employed to effect reduction in each of the subsequent examples.

Dihydrotigogenin (IIb). Anhydrous aluminum chloride (6.4 g.), in 50 ml. of dry ether, was added to a cool (ice bath) mixture of lithium aluminum hydride (0.45 g.) and dry ether (50 ml.). An ether (75 ml.) solution of tigogenin (0.50 g.) was then added, with stirring, over a 15-min. period. Stirring was continued an additional 45 min. at ice bath temperature followed by a 2 hr. period at reflux. After cooling, the mixture was treated cautiously with water and dilute hydrochloric acid. The resulting aqueous phase and suspended product was extracted with ether (5 × 100 ml.) and the combined ethereal extract washed with dilute sodium bicarbonate solution, dried (sodium sulfate), and concen-

(13) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956). An authentic specimen of VII was generously provided by Dr. Sato.

(14) It may be of some mechanistic importance that the yield of this isomer is reduced to *ca.* 10% when lithium aluminum hydride reduction of V is carried out in the absence of aluminum chloride.[13]

(15) Alternatively, reduction might simply take place at the stage illustrated by intermediate C. However, the possibility of a completely different initial mechanism being operative in the reduction reaction cannot be overlooked. Additional experimental evidence will be necessary before this point can be satisfactorily resolved.

(16) Melting points were observed on the Fisher-Johns apparatus unless otherwise noted, and are uncorrected. The microanalyses were provided by Dr. A. Bernhardt, Mülheim, Germany, and the optical rotation (chloroform solution) measurements by Drs. Wieler and Strauss, Oxford, England.

trated to a cream colored crystalline product; yield 0.42 g., m.p. 153–159°. Recrystallization from acetone gave colorless crystals of dihydrotigogenin melting at 165–166°, $[\alpha]_D^{16}$ 0.0°.[5,12]

The diacetate (acetic anhydride–pyridine, 1 hr. at 90–95°) melted at 115° and was identical (mixed melting point and infrared comparison) with an authentic specimen (m.p. 116–117°) of dihydrotigogenin diacetate (IIc).[5,17]

Desoxytigogenin (Id). In one experiment, a solution of tigogenone (Ig, 0.14 g.)[18] in ethanedithiol (3 ml.) was treated with 1 drop of 70–72% perchloric acid. Colorless crystals began to separate within several minutes. However, the reaction was allowed to proceed for 3 hr. at 25° before dilution with ether and 2*N* sodium hydroxide. The ethereal solution was washed successively with 2*N* sodium hydroxide and water before removing the dry (sodium sulfate) solvent *in vacuo*. Chromatography of the pale yellow colored crystalline residue, in 4:1 petroleum ether–benzene on 10 g. of Merck activated alumina, followed by elution with the same solvent, gave 0.15 g. of colorless product melting at 299–302°. Two recrystallizations from chloroform–ethyl acetate afforded a pure sample of tigogenin 3-ethylenethioketal (Ic) as needles, m.p. 307–309°,[19] $[\alpha]_D^{16}$ −67.7°.

Anal. Calcd. for $C_{29}H_{46}O_2S_2$: C, 70.97; H, 9.44; S, 13.07; mol. wt. 490.8. Found: C, 70.62; H, 9.70; S, 13.15; mol. wt. (Rast), 465.

Desulfurization of the ethylenethioketal Ic (0.027 g.) with W-4 Raney nickel[20] (0.5 ml.) was carried out in ethanol (30 ml.) employing a 4-hr. reflux period. The solvent was removed after filtering the hot reaction mixture through Celite. The crystalline residue recrystallized from ethanol as colorless plates (0.011 g.), m.p. 174–175°. Mixed melting point determination with an authentic sample (m.p. 174–175°) of desoxytigogenin (Id)[18] was undepressed.

Dihydroxydesoxytigogenin (IId). Conversion of desoxytigogenin (Id, 0.72 g.) to the *dihydro* derivative IId was readily accomplished. The crude oily product was chromatographed in petroleum ether on 10 g. of Merck acid washed alumina. Elution with petroleum ether–benzene (1:1) afforded 0.70 g. of pale yellow oil which crystallized upon trituration with acetone. Recrystallization from acetone gave colorless needles, m.p. 92–93°, $[\alpha]_D^{16}$ 0.0°.[12]

Dihydrodiosgenin (IVa). Reduction of diosgenin (IIIa, (0.50 g.) led to dihydrodiosgenin (0.45 g.). A sample recrystallized from acetone as colorless needles, m.p. 167–168°, $[\alpha]_D^{16}$ −28.9° (*cf.* ref. 5). The product gave a straw coloration with tetranitromethane. A mixed melting point with dihydrotigogenin (IIb) was 160–164°, while comparison infrared spectra (potassium bromide) were distinctly different.

Diosgenin acetate (IIIb, 0.50 g.) afforded 0.45 g. of dihydrodiosgenin melting at 163–165°. Recrystallization from acetone gave colorless needles, m.p. 165–167°.

Dihydromarkogenin (IIe). A 0.28 g. sample of markogenin[17] provided 0.25 g. of dihydromarkogenin which crystallized as colorless needles from acetone, m.p. 179–180°, $[\alpha]_D^{16}$ 0.0°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.58; H, 10.61.

11α-Hydroxydihydrotigogenin (IIf). Almost quantitative conversion of 11α-hydroxytigogenin (If, 0.15 g.)[21] to the dihydro compound (IIf) was realized; yield 0.14 g. Recrystallization from acetone gave colorless rosettes of needles, m.p. 176–177°, $[\alpha]_D^{16}$ −13.0°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.74; H, 10.71.

Dihydrotomatidine (VI). Lithium aluminum hydride–aluminum chloride reduction of tomatidine (V, 0.50 g.) was carried out as previously described (*cf.* IIb). In this case, the reaction mixture was diluted with sodium hydroxide solution. Ether extraction and recovery of product in the usual manner afforded 0.35 g. of cream colored solid, m.p. 226–228°. Recrystallization from methanol-water gave colorless plates (0.20 g.) melting at 229–230°. Concentration of the mother liquors afforded the lower melting isomer (0.09 g.) as cream colored crystals, m.p. 193–195°. The isomer melting at 229–230° was found to be identical (mixture melting point determination and infrared comparison) with an authentic sample of the higher melting (230–233°) isomer of dihydrotomatidine.[13]

3β-Acetoxy-5-furostene 26-ethylenethioketal (IVb). A mixture of diosgenin acetate (IIIa, 0.5 g.), ethanedithiol (1 g., 0.9 ml.) and aluminum chloride (2 g.) in ether (5 ml.) was allowed to stand at room temperature over a 3-hr. period. Following dilution with benzene, the reaction mixture was washed successively with 2*N* sodium hydroxide and water. The residue obtained after removing the dry (sodium sulfate) solvent *in vacuo* was chromatographed in 1:1 petroleum ether–benzene on Merck activated alumina. Elution with the same solvent gave an oil which crystallized as needles from acetone; yield 0.38 g., m.p. 140°. The product was identified by mixed melting point determination and infrared comparison with an authentic sample of 3β-acetoxy-5-furostene 26-ethylenethioketal (m.p. 140–142°).[8]

ORONO, ME.

(17) This sample was kindly provided by Dr. M. E. Wall.

(18) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **78**, 1747 (1956).

(19) Capillary tube melting point.

(20) A. A. Pavlic and H. Adkins, *J. Am Chem. Soc.*, **68**, 1471 (1946).

(21) A sample of this compound was generously provided by Dr. Carl Djerassi.

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

Amino Derivatives of Kojic Acid

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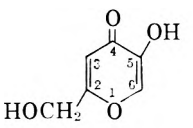
An investigation of the physiological properties of new compounds from kojic acid, 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one has led to the synthesis of several amino derivatives which have not previously been reported. Secondary as well as tertiary aminomethyl groups were introduced into position 6 of kojic acid by use of the Mannich reaction. Factors which influence this reaction, as it applied to kojic acid, were also studied.

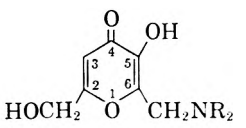
Our work on kojic acid derivatives is an extension of the program here to prepare a large number of aminophenols and aminobisphenols of various types, with the ultimate view of evaluating them as

potential chemotherapeutic agents.[1-3] Some interesting physiological properties of kojic acid have already been observed, including a definite, but weak, bacteriostatic activity, a synergistic activity when used with insecticides, cardiotoxic and cardiotonic activity, and the ability to kill human leucocytes *in vitro*.[4] As an enzyme inhibitor kojic acid has been found to decrease the activity of D amino acid oxidase in rate bearing growing transplanted tumors.[5] We would expect that the physiological properties of kojic acid should be considerably modified by the introduction of amino groups.

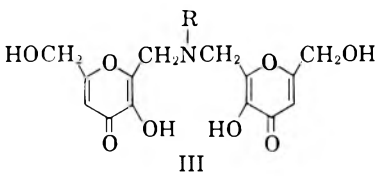
Because of its phenol-like properties kojic acid (I) should provide at least one hydrogen atom in the 6 position which can be replaced by Mannich[6] groups such as $-CH_2NHR$ and $-CH_2NR_2$ (II). The only previously reported compounds of this general type were those of Woods[7] and also Barchielli.[8] The latter prepared two derivatives which are structurally somewhat similar to Mannich bases by reaction of kojic acid with Schiff bases



I



II



III

such as benzalaniline and *p*-methylbenzalaniline. Woods[7] has reported four di-Mannich derivatives obtained in an acid medium from kojic acid, formaldehyde, and aromatic amines. He suggests that two Mannich groups entered positions 3 and 6 of the kojic acid ring in each of his compounds, although the molar ratio of reactants used in each case (1:1) would seem to favor a mono-Mannich derivative instead of a di-Mannich product. Inasmuch as there has been some difficulty in separating and obtaining pure products from the reaction mixture by the use of Woods' method, we are excluding the group of aromatic primary amines from this discussion and they will be reported later when sufficient data are available.

The present group of amine derivatives of kojic acid (II and III) was obtained by reaction of kojic acid with formaldehyde and strongly basic amines at room temperature. The reaction proceeded very rapidly and the derivatives could be isolated from the reaction mixture in good yield within thirty minutes. Using primary and secondary aliphatic amines, as well as some heterocyclic secondary amines, it was found that only one position of the kojic acid ring (position No. 6) was substituted by a Mannich group ($-CH_2NR_2$), even when an excess of amine and formaldehyde was employed (see Table 1). In the case of the primary amines tried, both hydrogens attached to the nitrogen were replaced by kojic acid rings (at the 6 position in the latter, see formula III above). For secondary amines, products corresponding to the structure in II above were obtained.

The method of Meadow and Reid[9] and also that used by Woods[10] led to the formation of resinous materials of indefinite composition when kojic acid was heated with formaldehyde and strongly basic amines such as dimethylamine, morpholine, or piperidine. In view of the sensitivity of the pyranone ring to basic reagents[11] it is understandable that the Mannich reaction involving kojic acid and amines more basic than the aromatic amines has not been described. Although ring cleavage, by hydroxide ion is reversed by the action of acids, such ring cleavage in the presence of amines could be expected to lead to any of several side reaction products, such as open chain amine derivatives, pyridones and polymers. Thus kojic acid although capable of entering into some of the substitution reactions typical of a phenol, is not as stable under these conditions as a true phenol. The success of this study depends on the possibility of kojic acid taking part in the Mannich reaction under conditions which will not produce extensive ring cleavage. The surprising observation that kojic acid reacts rapidly with morpholine and other strongly basic amines in the presence of formaldehyde at room temperature led us to the preparation and study of a large number of other similar derivatives using such exceedingly mild conditions.

We were able to isolate only products which contained a single Mannich group in the 6 position. Attempts to force a second group presumably in the 3 position failed. The supposition or conclusion that the Mannich group entered the 6 position of kojic acid is based on the following reasons: First in the nuclear substitution derivatives at present reported in the literature[12] the entering group is believed to enter the 6 position, *ortho* to the enolic hydroxyl group although no very definite

(1) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **76**, 3479 (1954).

(2) C. J. Korpics and J. R. Meadow, *Trans. Kentucky Acad. Sci.*, 16 (3): 66–71 (1955).

(3) G. O'Brien and J. R. Meadow, *Trans. Kentucky Acad. Sci.*, 19 (1–2): 1–5 (1958).

(4) A. Beelik, *Advances in Carbohydrate Chemistry*, **11**, 145 (1956).

(5) J. P. Greenstein, *Biochem. of Cancer*, 2nd ed., Academic Press, N. Y., 541 (1954).

(6) C. Mannich and W. Krosche, *Arch. Pharm.*, **250**, 647 (1912).

(7) L. L. Woods, *J. Am. Chem. Soc.*, **68**, 2744 (1946).

(8) R. Barchielli, *Ann. chim. appl.*, **30**, 473 (1940).

(9) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **76**, 3479 (1954).

(10) L. L. Woods, *J. Am. Chem. Soc.*, **68**, 2744 (1946).

(11) L. F. Cavalieri, *Chem. Revs.*, **41**, 525 (1947).

(12) A. Beelik, *Advances in Carbohydrate Chemistry*, **11**, 145 (1956).

TABLE I

MANNICH DERIVATIVES OF KOJIC ACID WITH ALIPHATIC AND HETEROCYCLIC AMINES

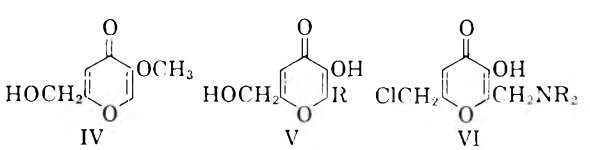
Mannich Derivative (Amine Used)	Formula	Melting Point, °C[a]	Nitrogen Analysis, %		Neutralization Equivalent	
			Calcd.	Found	Calcd.	Found
Dimethylamine[b]	$C_9H_{13}NO_4HCl$	185–186	5.94	6.06		
Diethylamine[b]	$C_{11}H_{17}NO_4HCl$	157–158	5.31	5.23		
Laurylamine	$C_{26}H_{39}NO_3$	61	2.90	2.89	484	490
Stearylamine	$C_{32}H_{51}NO_3$	72–73	2.42	2.44	578	585
Pyrrolidine[b]	$C_{11}H_{15}NO_4HCl$	168–169	5.35	5.34		
Morpholine	$C_{11}H_{15}NO_5$	156	5.81	5.70	241	241
Piperidine	$C_{12}H_{17}NO_4$	166–168	5.85	5.80	239	239
N-Methylpiperazine	$C_{12}H_{18}N_2O_4$	192	11.02	10.61	127	129
1,2,3,4-Tetrahydroquinoline	$C_{16}H_{17}NO_4$	138–139	4.87	4.74	287	280

[a] Some decomposition was apparent when all derivatives were melted on the heating block. [b] Isolated as the hydrochloride salt, washed with acetone, and recrystallized from alcohol.

evidence for this orientation has yet been presented; and secondly some indirect evidence based on our experimental work here.

Alexander and Underhill[13] have shown that an electrophilic substitution is involved in the preparation of Mannich derivatives of ethylmalonic acid. It is probable that an electrophilic substitution reaction is also involved in the preparation of Mannich derivatives of phenols and possibly those of kojic acid. The failure of 6-hydroxymethylkojic acid to enter into the Mannich reaction indicates that 6-hydroxymethylkojic acid is not an intermediate in the reaction and lends support to the idea that the Mannich reaction with kojic acid involves electrophilic substitution of the kojic acid ring. Of the two open nuclear positions of kojic acid, positions 3 and 6, only position 6 is under the activating influence of the enolic hydroxyl group of kojic acid, and only position 6 would be deactivated by the conversion of the hydroxyl group to an ether group. Position 3 is *meta* to the hydroxyl group and should be only slightly affected. With this in mind, we have carried out the following experiments.

Methyl kojate (IV) failed to undergo the Mannich reaction using both acidic and basic conditions. A similar situation exists in the phenol series; anisole has not been converted into a Mannich derivative.



The other open position of kojic acid the 3 position, is *meta* with respect to the enolic hydroxyl group, but *ortho* to a keto group. Any activity of the 3 position should arise as a result of the influence of this keto group. Since the keto group should be unaffected by the formation of methyl kojate, it is unlikely that the activity of the 3 position would be altered by forming methyl kojate. The observed lack of reactivity of methyl kojate can be explained only if it is assumed that the 6 position is the reactive position of kojic acid. Second, four mono-substituted nuclear derivatives of kojic acid (V) failed to form a Mannich derivative. The derivatives in question (V) were 6-bromokojic acid, 6-bromochlorokojic acid or 2-chloromethyl-5-hydroxy-6-bromo-4*H*-pyran-4-one, 6-hydroxymethylkojic acid, and 6,6′-methylene-bis-kojic acid. These compounds have been previously reported in the literature, and are presumed to be derivatives in which the 6 position of kojic acid has been substituted. The failure of these four mono-substituted derivatives of kojic acid to yield Mannich derivatives, may be considered an indication that the position ordinarily substituted in the Mannich reaction is blocked in these derivatives. It may be concluded that the position on the kojic acid molecule which is substituted in other nuclear substitution reactions is also substituted in the Mannich reaction.

Chlorokojic acid or 2-chloromethyl-5-hydroxy-4-*H*-pyran-4-one which contains a chloromethyl group instead of hydroxymethyl group in the 2 position reacted in the usual way to form a mono-Mannich derivative (VI). Both the 3 and 6 positions remain unsubstituted in chlorokojic acid, and the enolic hydroxyl is free. It was anticipated that alkylation of the amine by the chloromethyl group might produce a serious side reaction. However, the reactivity of the chlorine atom of chlorokojic acid was sufficiently low to permit the formation of Mannich derivatives (VI) in the usual way with several amines tried. Additional Mannich compounds are listed in Table II.

The results of this work indicate very strongly that the pronounced reactivity of kojic acid in the Mannich reaction is due to the presence of a free enolic hydroxyl group. The enhanced reactivity

(13) E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949).

TABLE II

MANNICH DERIVATIVES FROM SUBSTITUTED KOJIC ACID COMPOUNDS

Substituted Kojic Acid Used as Starting Material	Mannich Group Introduced in Position No. 6	Formula	Melting Point, °C.	Nitrogen Analysis, %		Neutralization Equivalent	
				Calcd.	Found	Calcd.	Found
Chlorokojic acid[a]	Morpholinomethyl	$C_{11}H_{14}ClNO_4$	140–141	5.39	5.44	260	258
Chlorokojic acid[a]	Piperidinomethyl	$C_{12}H_{16}ClNO_3$	138–139	5.43	5.41	258	257
7-*O*-Acetylkojic acid[b]	Morpholinomethyl	$C_{13}H_{17}NO_6$	120–121	4.96	5.03	283	285

[a] Prepared by reaction of kojic acid with thionyl chloride in $CHCl_3$ by a modification of the method described by Kipnis, Soloway, and Ornfelt.[22] [b] Obtained by aminolysis of 2,7-di-*O*-acetylkojic acid. The latter was prepared by the method of Maurer.[23]

of kojic acid compared to phenol is probably due to the larger anion concentration of kojic acid since kojic acid is somewhat more acidic than phenol. In addition, it appears that only one position in the kojic acid ring is sensitive to substitution by a so-called Mannich group.

EXPERIMENTAL

All melting points were taken with a Fisher-Johns apparatus, and are uncorrected. Neutralization equivalents were determined with standard perchloric acid in glacial acetic acid solution according to the method of Seaman and Allen.[14] The Kjeldahl analyses for nitrogen were determined by a modification of the method of McKenzie and Wallace,[15] with 0.025*N* sulfamic acid as the titrant. Results for the derivatives are summarized in Table I. A typical preparation procedure may be described as follows.

Morpholinomethyl derivative of kojic acid. Three and one-half grams (0.04 mol.) of freshly distilled morpholine was mixed with 3.2 g. (0.04 mol.) of 37% aqueous formaldehyde and 40 ml. of 95% ethyl alcohol. The mixture was allowed to stand 15 min., after which 4.3 g. (0.03 mol.) of kojic acid was added. The flask was stoppered and shaken vigorously for 15 min., during which time a tan crystalline solid began to form. After standing 1 hr. at room temperature the reaction mixture was chilled and then filtered. Washing with two small portions (15 ml. each) of cold 95% ethyl alcohol gave about 6.5 g. (88% yield) of nearly white leaflets, melting at 156° with decomposition. In this case recrystallization from hot alcohol failed to change the melting point; furthermore, it was observed that prolonged heating to dissolve the compound caused some decomposition to take place which resulted in a slight loss of recovered product. This and other Mannich derivatives of kojic acid were appreciably soluble in cold water.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27. Found: C, 55.06; H, 6.00. (See Table I for additional analytical data.)

Piperidinomethyl derivative of chlorokojic acid. Chlorokojic acid, m.p. 165–166° (see note a, Table II) reacted rapidly with both morpholine and piperidine in a manner similar to kojic acid. Two and six-tenths grams (0.03 mol.) of freshly distilled piperidine and 3.0 g. (0.036 mol.) of 37% aqueous formaldehyde were mixed with 40 ml. of 95% ethanol and allowed to stand for about 15 min. Chlorokojic acid, 4.8 g. (0.03 mol.), was then added slowly to the mixture and shaking or stirring was continued for another 15 min. After standing at room temperature for at least 1 hr., the product was then chilled until crystallization was complete and filtered. The crystals were washed two or three times with small portions of cold 95% ethanol, then with 20 ml. of ether, after which the product was dried rapidly by suction. A yield of 6.4 g. (82% of theory) of faintly pink, crystalline powder, m.p. 138–139° (dec.), was obtained. (Analytical data are found in Table II.) It was possible to recrystallize the product from 95% ethanol, but the loss due to decomposition was high (as much as 50 to 60% when the alcohol was heated to boiling for any length of time).

Methyl kojate and the Mannich reaction. Methyl kojate (IV) was prepared by the method of Campbell, Ackerman, and Campbell.[16] It failed to form a Mannich derivative with morpholine under basic conditions used previously. Also, it failed to react under acidic conditions with hydrochloric acid present. Other substituted kojic acid compounds which failed to undergo the Mannich reaction were the following: 6-bromokojic acid, prepared by a modification of Yabuta's method[17]; 6-bromochlorokojic acid, obtained by bromination of chlorokojic acid[18] with *N*-bromosuccinimide according to Woods[19]; 6-hydroxymethylkojic acid, prepared by the method of Woods[20]; and 6,6′-methylene-bis-kojic acid, obtained by the method of Barham and Reed.[21]

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LEXINGTON, KY.

(14) W. Seaman and E. Allen, *Anal. Chem.*, **23**, 592 (1951).

(15) H. A. McKenzie and H. S. Wallace, *Australian J. Chem.*, **7**, 55 (1954).

(16) K. N. Campell, J. K. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950).

(17) T. Yabuta, *J. Chem. Soc. Japan*, **37**, 1185, 1234 (1916).

(18) F. Kipnis, H. Soloway, and J. Ornfelt, *J. Am. Chem. Soc.*, **70**, 4264 (1948).

(19) L. L. Woods, *J. Am. Chem. Soc.*, **74**, 1107 (1952).

(20) L. L. Woods, *J. Am. Chem. Soc.*, **72**, 4322 (1950).

(21) H. N. Barham and G. N. Reed, *J. Am. Chem. Soc.*, **60**, 1541 (1938).

(22) F. Kipnis, H. Soloway, and J. Ornfelt, *J. Am. Chem. Soc.*, **70**, 4264 (1948).

(23) K. Maurer, *Ber.*, **63**, 25 (1930).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

New Synthetic Approach to the Berberine Alkaloids

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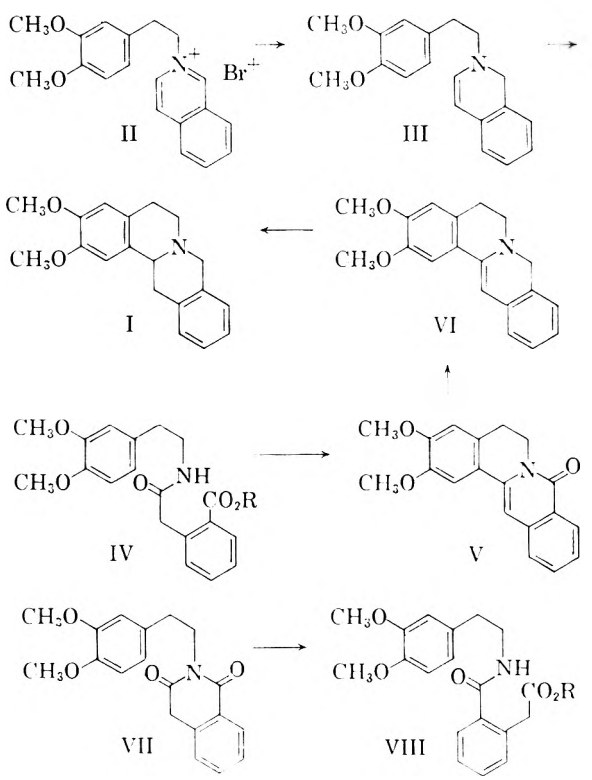
2-[2-(3,4-Dimethoxyphenyl)ethyl]isoquinolinium bromide has been reduced with lithium aluminum hydride to the dihydroisoquinoline, which on acid treatment affords 2,3-dimethoxyberbine. The same berbine derivative has been prepared by the classical berberine alkaloid synthesis, from homoveratryl amine and homophthalic anhydride.

Although a number of synthetic routes to the berberine alkaloids have been thoroughly investigated,[1] all of those using readily available starting materials fail to give rise to the naturally occurring compounds without multistep reaction sequences.[2] With the recent elucidation of the course of the reductive cyclization of indolylethylisoquinolinium salts to dehydroyohimbanes[3] a new synthetic approach *via* substituted β-phenylethylisoquinolinium salts appeared feasible. The goal chosen for our synthetic efforts was 2,3-dimethoxyberbine (I) to be obtained from 2-[2-(3,4-dimethoxyphenyl)ethyl]isoquinolinium bromide (II) on treatment with lithium aluminum hydride followed by acid.

The salt (II) was prepared from 3,4-dimethoxyphenylethyl alcohol,[4] followed by treatment with phosphorus tribromide, and heating of the crude bromide with isoquinoline, the method used for the preparation of the parent phenylethylisoquinolinium salt.[5] Reduction of the salt with lithium aluminum hydride in ether gave 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2-dihydroisoquinoline (III), as an unstable oil, which gave the desired 2,3-dimethoxyberbine (I) as the hydrochloride on heating with hydrochloric acid. Although the yield on this conversion is low (18% for the two steps), from a standpoint of steps involved this appears to be the shortest and most general synthetic approach to the berberine alkaloids yet devised.

For comparison with the sample of I prepared by reductive cyclization we attempted to prepare this compound from 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline by the method used for the preparation of berbine.[6] Although there were no difficulties encountered in the preparation of 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline,[7] we were unable to repeat the reduction of this compound with zinc and sulfuric acid.[8] We finally obtained the tetrahydroisoquinoline by catalytic hydrogenation of the dihydro compound; however all attempts to convert it to I met with failure.



The route which ultimately led to the dimethoxyberbine derivative was a modification of that employed in the classical total synthesis of the berbine alkaloids.[9]

(1) T. A. Henry, *The Plant Alkaloids*, Blakiston, Philadelphia, Pa., 1949, pp. 334–336.

(2) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958), have recently investigated what appears to be a very promising "short" synthesis of these alkaloids.

(3) J. W. Huffman, *J. Am. Chem. Soc.*, **80**, 5193 (1958).

(4) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 4252 (1956) have prepared this compound from veratryl lithium and ethylene oxide, and also lithium aluminum hydride reduction of 3,4-dimethoxyphenylacetic acid. Although the yields on the reduction are low (in our hands 30%), the commercial availability and relatively low cost of this acid make this the method of choice for the preparation of modest quantities of this alcohol.

(5) J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **68**, 868 (1946).

(6) (a) W. Leithe, *Chem. Ber.*, **62**, 2343 (1930). (b) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 2783 (1948).

(7) G. Tsatsas, *Ann. pharm. franc.*, **10**, 61 (1952); *Chem. Abstr.*, **46**, 11208 (1952).

(8) R. A. Robinson, *J. Org. Chem.*, 16, 1911 (1951).

(9) (a) R. D. Haworth, W. H. Perkin, and H. S. Pink, *J. Chem. Soc.*, **127**, 1709 (1925). (b) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, *J. Chem. Soc.*, 549 (1927). (c) J. B. Koepfli and W. H. Perkin, *J. Chem. Soc.*, 2989 (1928).

Homoveratrylamine with homophthalic anhydride in boiling benzene afforded the amido acid (IV. R = H) which was converted by diazomethane to the methyl ester (IV. R = CH_3). In an effort to obtain the acid (III) in greater yield, an attempt was made to accomplish the hydrolysis of the homophthalimide, obtained from homoveratryl amine and homophthalic anhydride (VII). Although hydrolyses of this type have been reported to occur exclusively at the benzamide side of the imide ring,[9,10] the only solid product obtainable by this reaction in our hands was an acid isomeric with IV (R = H), undoubtedly the amido acid (VIII. R = H). The hydrolysis product gave an ester (VIII. R = CH_3) isomeric with, but not identical to IV (R = CH_3).

The assignment of structures IV and VIII is based on the following observations:

The acid IV (R = H) showed infrared absorption bands in the carbonyl region at 5.86 μ and 6.00 μ, while its isomer (VIII. R = OH) had bands at 5.74 μ and 6.17 μ.[11] The methyl ester of IV has carbonyl bands at 5.82 μ (benzoate ester), and 6.00 μ. A secondary argument favoring our assignment of structures is the observation that homophthalic anhydride has been shown to react preferentially at the aliphatic carbonyl group with alcohols and under Friedel-Crafts conditions.[12]

Amido ester (IV. R = CH_3) with phosphorus oxychloride in toluene afforded 2,3-dimethoxy-5,6-dihydro-8-oxo-8*H*-dibenzo[*a*,*g*]quinolizine (V). V was reduced with lithium aluminum hydride to the corresponding dihydroisoquinoline, (VI), which was treated directly with sodium borohydride[3] to give I identical to that obtained *via* reductive cyclization.

EXPERIMENTAL[13]

2-[2-(3,4-Dimethoxyphenyl)ethyl]isoquinolinium bromide. To a solution of 1.50 g. of 2-(3,4-dimethoxyphenyl)ethyl alcohol in 90 ml. of dry ether at 0° was added 1.5 g. of phosphorus tribromide. The reaction mixture was allowed to stand 24 hr. at room temperature, washed with water, 5% sodium bicarbonate, dried and the solvent removed at room temperature and reduced pressure, leaving 1.20 g. of yellow oil. The crude bromide was mixed with 0.75 g. of isoquinoline and heated 2 hr. on the steam bath, during which time the reaction mixture set to a crystalline mass. Recrystallization from ethanol–ethyl acetate gave 1.1 g. (36%) of pale yellow crystals m.p. 209–210°. The compound was crystallized for analysis from ethanol–ethyl acetate, and had m.p. 210–211°.

Anal. Calcd. for $C_{19}H_{20}BrNO_2$: C, 61.11; H, 3.74; N, 5.38. Found: C, 61.53; H, 3.86; N, 5.33.

2-Carboxy-N-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide. To a solution of 4.0 g. of homoveratryl amine[14] in 100 ml. of benzene was added 3.2 g. of homophthalic anhydride, and the mixture heated under reflux 2 hr. On cooling the product separated as fine white needles, which were collected, and washed with two small portions of benzene. Recrystallization from cyclohexane–ethyl acetate gave 4.82 g. (67%) of material, m.p. 142–144°. Several recrystallizations from the same solvent pair gave an analytical sample, m.p. 148–149°.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.57; H, 6.32; N, 4.32.

2-Carbomethoxy-N-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide. To a solution of 2.0 g. of the homophthalamic acid dissolved in 100 ml. of a chloroform-methanol mixture was added 100 ml. of an ethereal diazomethane solution, prepared from 3.3 g. of nitrosomethylurea. Following the rapid evolution of nitrogen the solution was allowed to stand 3 hr. at room temperature, and then concentrated to dryness at reduced pressure, leaving a pale yellow oil. Trituration with cyclohexane afforded a white solid, which on recrystallization from a cyclohexane–ethyl acetate mixture gave 1.84 g. (88%) of fluffy white needles, m.p. 100–102°. Additional recrystallizations from the same solvent pair gave an analytical sample m.p. 102–103°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.84; H, 6.75; N, 4.35.

2,3-Dimethoxy-5,6-dihydro-8-oxo-8H-dibenzo-[a,g]-quinolizine. To a solution of 1.0 g. of the above amido ester in 20 ml. of toluene was added 20 ml. of phosphorus oxychloride, and the mixture was heated under reflux for 2 hr. After cooling, ice water was added and the aqueous layer drawn off, and shaken with ether. After washing with water, drying and removal of the solvent *in vacuo* a small amount of dark colored oil was obtained which could not be induced to crystallize. The acidic aqueous phase was made basic with 10% aqueous sodium carbonate, and extracted with five portions of ether. The ethereal extracts were washed with water, dried, and the solvent removed at reduced pressure leaving a pale yellow solid. Recrystallization from ethyl acetate gave 0.34 g. (40%) of small yellow crystals, m.p. 187–189°. Several recrystallizations from ethyl acetate gave material m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.24 H, 5.35; N, 4.67.

2,3-Dimethoxyberbine. a. To a suspension of 0.2 g. of lithium aluminum hydride in 20 ml. of boiling dry tetrahydrofuran was added slowly a solution of 0.1 g. of the dibenzooxoquinolizine in 5 ml. of tetrahydrofuran. The reaction was heated under reflux 2 hr., cooled with an ice bath and a solution of ethyl acetate in moist ether added slowly to decompose the excess hydride. Following the addition of several drops of water the aluminum salts were removed by filtration through a sintered glass funnel. After washing the precipitate thoroughly with tetrahydrofuran, the filtrate was concentrated to dryness at the water pump, leaving a pale yellow glass. This was dissolved in 4 ml. of methanol, treated with 0.1 g. of sodium borohydride and heated at reflux 30 min. After cooling and dilution with water the solution was first made acidic with 10% hydro-

(10) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

(11) We have no rational explanation for this abnormally high amide band. *N*-homoveratryl benzamide [H. J. Harwood and T. B. Johnson, *J. Am. Chem. Soc.*, 56, 468 (1934)] shows normal amide absorption at 6.00 μ.

(12) N. P. Buu-Hoi, *Compt. rend.*, 209, 562 (1932); *Bull. soc. chim.*, 11, 338 (1944). That the reactions of homophthalic anhydride with amines is not completely selective is evidenced by the isolation of a small amount of acid (VIII) from the saponification of impure IV (R = CH_3). In view of the known hydrolysis rates of aliphatic *versus* aromatic esters (J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956, p. 274). It is surprising that the earlier workers (Refs. 9 and 10) obtained acids similar to (IV) in hydrolyses of homophthalimides.

(13) All melting points were determined on a Fischer-Johns block, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer, using chloroform as a solvent. Analyses were carried out by Galbraith Analytical Laboratories, Knoxville, Tenn.

(14) We would like to thank Dr. S. F. Kern of Eli Lilly and Company for a generous sample of homoveratryl amine.

chloric acid and then basic with 10% sodium carbonate. Extraction with chloroform, drying, and removal of the solvent *in vacuo* gave a viscous pale yellow oil. This oil was boiled with several 10-ml. portions of hexane, which were combined and concentrated to a small volume, however no solid could be obtained. Removal of the hexane and treatment of the oily residue with concentrated hydrochloric acid afforded 0.021 g. (25%) of the base hydrochloride, m.p. 236–238 (dec.). Recrystallization from ethanol–ethyl acetate gave material m.p. 237–239 (dec.).

Anal. Calcd. for $C_{19}H_{21}NO_5$·HCl: C, 68.76; H, 6.68; N, 4.22. Found: C, 68.67; H, 6.89; N, 4.31.

b. To a stirred suspension of 0.4 g. of lithium aluminum hydride in 50 ml. of dry ether was added slowly 0.46 g. of 2-[2-(3,4-dimethoxyphenyl)ethyl]isoquinolinium bromide, and the mixture was stirred at room temperature overnight. The excess reducing agent was decomposed with ethyl acetate, and finally water and 10% sodium carbonate were added. The aqueous layer was drawn off and extracted with two portions of ether. The ethereal extracts were combined, dried, and the solvent removed at reduced pressure and room temperature giving 0.28 g. (77%) of crude dihydroisoquinoline as a red oil. This oil was taken up in 50 ml. of concentrated hydrochloric acid and heated on the steam bath 4 hr., with an additional 5 ml. of acid being added hourly. The pale yellow solution was concentrated to a small volume and on cooling deposited 0.071 g. (18% based on bromide, 23% on crude reduction product) of white powder, m.p. 225–235 (dec.). Recrystallization from ethanol–ethyl acetate gave a white powder m.p. 236–238 (dec.), undepressed on mixture with material prepared in part *a*. The infrared spectra of the free base from this material and from material in part *a*. were identical.

N-[2-(3,4-dimethoxyphenyl)ethyl]homophthalimide. A mixture of 0.8 g. of homophthalic anhydride and 1.0 g. of homoveratrylamine were heated at 180° for 2 hr. On cooling the molten mass solidified, and was recrystallized from chloroform-methanol to give 0.8 g. (45%) of small needles m.p. 145–147°. The analytical sample was crystallized from the same solvent pair and had m.p. 147–148°.

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.31. Found: C, 70.26; H, 5.86; N, 4.28.

2-[N-(2-[3,4-dimethoxyphenyl]ethyl)carboxamido]phenylacetic acid. a. To 12 ml. of 2*N* sodium hydroxide was added 0.6 g. of the homophthalimide, and the mixture was heated at 100° for 12 hr. Addition of water, treatment with charcoal, filtration and acidification gave 0.43 g. of white slightly gummy solid, m.p. 146–153°. Recrystallization from ethyl acetate–cyclohexane afforded 0.13 g. of small white needles, m.p. 159–162°. No additional solid material could be obtained from the mother liquors. The analytical sample, m.p. 162–163°, was obtained by several recrystallizations from ethyl acetate–cyclohexane.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.33; H, 6.13; N, 4.15.

b. A suspension of 50 mg. of crude 2-carbomethoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide in 1 ml. of 10% sodium hydroxide was heated on the steam bath 30 min. Acidification with dilute hydrochloric acid gave a small amount of solid, which on crystallization from ethyl acetate gave a few crystals of material m.p. 160–161°, undepressed with material from part *a*. above.

2-Carbomethoxymethyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-benzamide. To a solution of 0.08 g. of the substituted phenylacetic acid in 10 ml. of chloroform was added 10 ml. of an ethereal solution of diazomethane prepared from 0.15 g. of nitrosomethyl urea. After standing 3 hr. at room temperature, the solvent was removed *in vacuo*, leaving a colorless oil, which on crystallization from cyclohexane–ethyl acetate afforded 0.05 g. (60%) of small white needles, m.p. 92–93°, unchanged on additional recrystallizations. A mixed melting point with the other homophthalamic ester was 79–90°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.67; H, 6.75.

1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. A solution of 2.2 g. of 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline in 25 ml. of ethanol was added to 0.1 g. of prehydrogenated platinum oxide in 25 ml. of ethanol and hydrogenated at atmospheric pressure until the uptake of hydrogen ceased, when 1.32 mol. had been absorbed. The catalyst was filtered off, and the filtrate evaporated at reduced pressure leaving a brown oil. Treatment of 0.1 g. of this oil with ethanolic picric acid gave a gummy picrate which after several recrystallizations had m.p. 100–102°, resolidifying at about 120° followed by melting at 160–165°. The remainder of the oil was dissolved in benzene and chromatographed on 75 g. of Merck alumina. Elution with benzene-chloroform mixtures gave several fractions of pale yellow oils whose picrates behaved as above. These fractions were combined to give 1.40 g. (61%) of the desired product. The picrate after several recrystallizations from ethanol had m.p. 102–104°, resolidification, m.p. 163–165°.

Anal. Calcd. for $C_{24}H_{24}N_4O_9$: C, 56.25; H, 4.72; N, 10.93. Found: C, 56.34; H, 4.54; N, 10.87.

ATLANTA, GA.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY AND THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. XLIX. Synthesis of 29-Isofucosterol[1,2]

JOHN P. DUSZA[3]

Received July 2, 1959

The attempted synthesis of fucosterol by the Wittig reaction has led to an isomer. It has been deduced from its infrared spectrum and the mechanism of its formation that the isomer differs from the natural product in the orientation around the 24,28-double bond, which is *trans* in the former and *cis* in the latter. The new isomer has accordingly been named 29-isofucosterol.

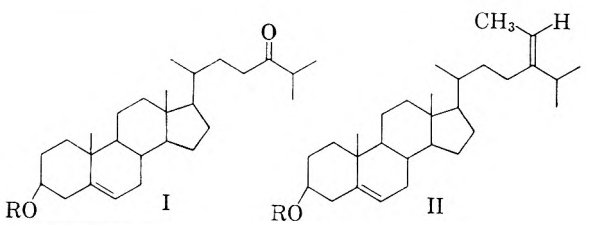
Fucosterol is the typical sterol of the brown algae. Its structure has been established by careful ozonolysis of the sterol to acetaldehyde[4] and 24-ketocholesterol.[5,6] More recently a synthesis of fucosterol has also been reported.[7] Neither the degradative nor synthetic procedures, however, have as yet permitted the assignment of a configuration to the 24,28-double bond of fucosterol.

In connection with studies on the synthesis of natural sterols now in progress in this laboratory, an attempt was made several years ago to prepare fucosterol by means of the Wittig reaction. This reaction has been used with conspicuous success in the synthesis of other sterols.[8] 24-Ketocholesterol (Ia) was converted to its pyranyl ether (Ic) by the previously reported transpyranylation reaction.[9] When this ether was reacted with triphenylphosphonium ethylidene[10] the 24-ethylidene derivative (IIc) was obtained in a rather low yield (20%). Neither changes in reaction times nor temperatures improved the yields, and in all instances more than one half of the starting material was recovered. Removal of the protective group afforded the sterol (IIa) which melted slightly but significantly higher than fucosterol which had been obtained from *Fucus vesiculosus*. (Table I). Even more pronounced was the difference between the melting points of the acetates. Both acetates readily form tetrabromides differing in melting points which revert to the original acetates upon debromination with zinc in acetic acid.

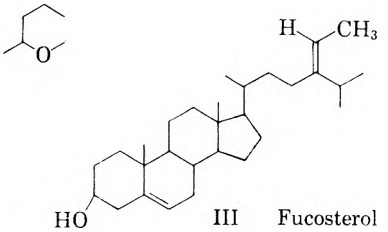
TABLE I

COMPARISON OF FUCOSTEROL AND 29-ISOFUCOSTEROL

	Fucosterol[11]		29-Isofucosterol	
	M.P.	$[\alpha]_D°$	M.P.	$[\alpha]_D°$
Sterol	124	−38.4	128–129	−41.8
Acetate	118–119	−43.8	130.5–131	−41.9
Acetate-tetrabromide	133 (dec.)		138–141 (dec.)	



Ia. R = H
Ib. R = $COCH_3$
Ic. R =



When ozonized, the new sterol affords acetaldehyde as the volatile fragment, demonstrating the presence of the 24,28-double bond (IIa). The difference between the new sterol and fucosterol must therefore rest in the arrangement of groups around this double bond, and the new sterol may be re-

(1) The material presented in this paper constitutes part of a dissertation submitted by the author in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1958.

(2) The investigation was in part supported by a research grant, Nonr 253(00), from the Office of Naval Research.

(3) F. W. Heyl Fellow 1957–1958. Present address: Organic Chemical Research Division, American Cyanamid Company, Pearl River, New York.

(4) H. B. MacPhillamy, *J. Am. Chem. Soc.*, 64, 1732 (1942).

(5) D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.*, 2881 (1950).

(6) W. Bergmann and M. Klosty, *J. Am. Chem. Soc.*, 73, 2935 (1951).

(7) R. Hayatsu, *Pharm. Bull. (Tokyo)*, 5, 452 (1957). This synthesis involves the reaction of ethylmagnesium bromide with 24-ketocholesterol and the dehydration of the ensuing alcohol with phosphorus oxychloride in pyridine. It is surprising that the dehydration is sufficiently selective to afford fucosterol in a yield of at least 36%.

(8) See for example the recent review by U. Schöllkopf, *Angew. Chem.*, 71, 260 (1959).

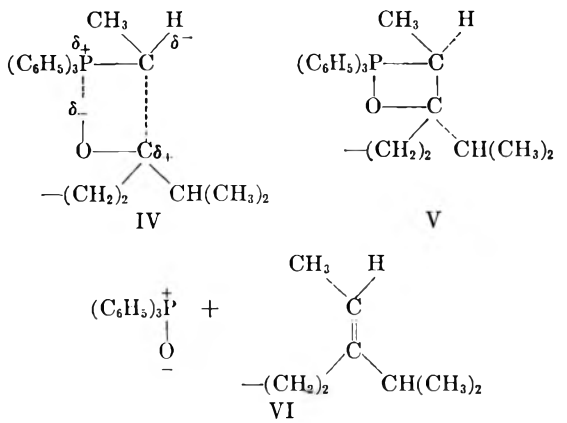
(9) W. Bergmann and J. P. Dusza, *Ann.*, 603, 36 (1957); *J. Org. Chem.*, 28, 459 (1958).

(10) G. Wittig and D. Wittenberg, *Ann.*, 606, 1 (1957); K. Matsiu, *Yûki Gôsei Kagaku Kyôkaishi*, 8, 211 (1950).

(11) I. M. Heilbron, R. F. Phipers, and H. R. Wright, *Nature*, 133, 419 (1934); *J. Chem. Soc.*, 1572 (1934).

garded as a 29-isofucosterol. The geometry of the 24,28-double bond of fucosterol appears to be unknown. It has in fact never been mentioned, not even in connection with the recent synthesis.[7,12]

Consideration of the mechanism of the Wittig reaction between 24-ketocholesterol and triphenylphosphonium ethylidene suggests that the *trans*-isomer (IIa) be formed predominantly. The geometry of the intermediates is illustrated by structures IV–VI. Structure IV shows the most favorable arrangement for the transition state in which the methyl group is located *trans* to the isopropyl group which is bulkier in the immediate vicinity than the $(CH_2)_2$-group leading to the ring system. The same geometry should be favored in the four-membered state (V). With the collapse of the intermediate (V), 29-isofucosterol will be formed with the methyl and isopropyl groups in *trans*-arrangement (IIa).



More direct evidence for the assignment of the configurations II and III may be derived from the infrared spectra of the respective sterols. They are virtually identical except for a shift in the wave length of a peak in the 12 micron region (Fig. I). Absorption in this region is associated with unsaturation; it is absent in the tetrabromides. Both sterols show the twin peaks near 11.9μ and 12.5μ attributed to the 5,6-double bond. Each sterol exhibits an additional peak between these two. Absorption in this region may arise from the out-of-plane bending frequency of a hydrogen atom on a trisubstituted ethylene[13] such as the 24,28-double bond of the sterols in question. The peak for this deformation in the synthetic material occurs at longer wavelength (12.30μ) than in the natural product (12.14μ). One would expect the *cis*-arrangement of groups (III) to give maximum interference between the methyl and the isopropyl groups, to impair the bending mode of the hydrogen

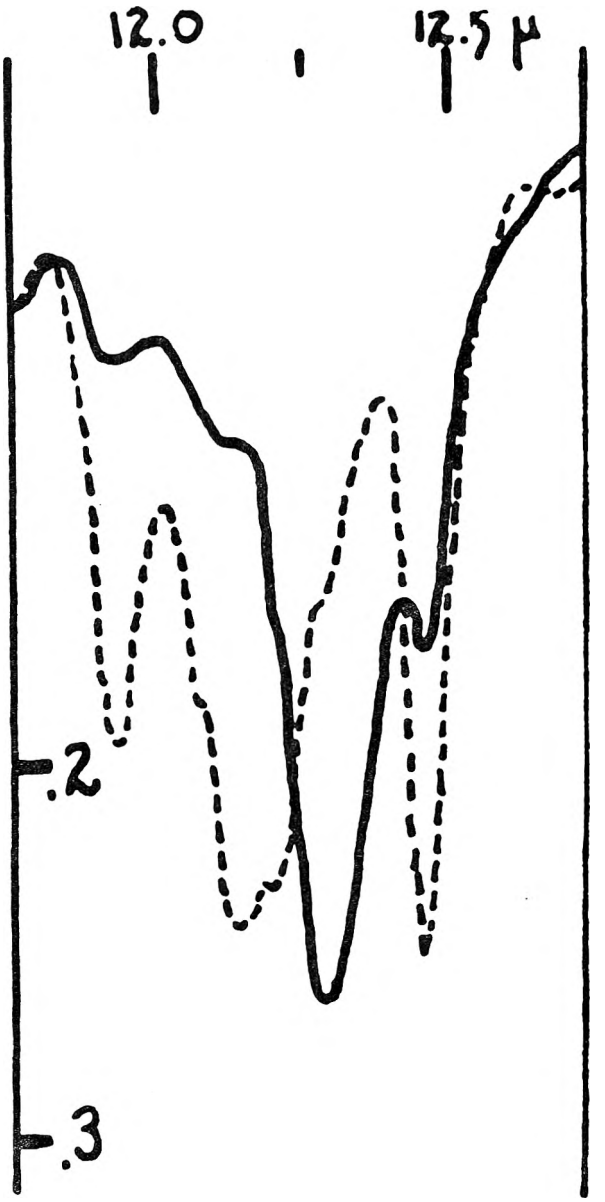


Fig. 1. Infrared spectra in KBr of the acetates of 29-isofucosterol (———) and fucosterol (– – – –) in the 12-micron region

atom at C-28 and to move the band to shorter wavelength. On the basis of such considerations structure III should be assigned to the natural product, fucosterol, and structure II to 29-isofucosterol.

These considerations derive support from the infrared spectra of pairs of simple olefins which have been published in the American Petroleum Institute Series. Here the *cis*-isomers show the deformation in question at the lower wave lengths. This is best illustrated by the 3,4-dimethyl-2-pentenes which are analogous to the sidechains of fucosterol (III) and 29-isofucosterol (II). The *cis*-isomer (VIII) exhibits the peak at 12.18μ,[14] and

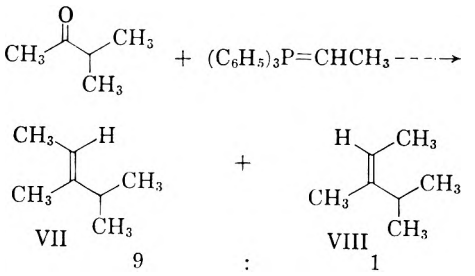
(12) More recently, however, attention has been called to the problem by Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, 80, 6296 (1958) in connection with the structure of citrostadienol which also carries a 24,28-double bond.

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1954, p. 51–52.

(14) Infrared Spectral Data, American Petroleum Institute Research Project 44, Serial Number 1796.

the *trans*-isomer (VII) at 12.39μ.[15] As the analogous peak is at the lower wavelength in the fucosterol spectrum, 12.14μ with a shoulder at 12.18μ, we may conclude that the natural product is the *cis*-isomer (III), and that the synthetic 29-isofucosterol with a peak at 12.30μ is the *trans*-isomer (II).

For comparative studies, the Wittig reaction between methyl isopropyl ketone and triphenylphosphonium ethylidene was also investigated. The olefin obtained was a mixture of 3,4-dimethyl-2-pentenes, the infrared spectrum of which showed strong peak at 12.33μ with a shoulder at 12.18μ. Gas chromatography of the mixture indicated an approximate 9:1 ratio of *trans*- (VII) to *cis*-isomer- (VIII).



EXPERIMENTAL

All melting points were taken in open capillary tubes in a Hershberg apparatus equipped with Anschütz thermometers. Optical rotations were determined with a polarimeter having a Rudolph photoelectric attachment on samples in a 1-dm. tube. Samples were dissolved in chloroform with the concentration given in each case. The infrared spectra were determined on a Perkin-Elmer Model 21 Recording Spectrophotometer as potassium bromide pellets or as otherwise stated. All values were corrected against an atmosphere spectrum.

24-Ketocholesteryl-3β-(2′-tetrahydropyranyl)-ether (Ic). To a suspension of 6.00 g. of 24-ketocholesterol in 50 ml. of 2-methoxytetrahydropyran[16] was added 2.0 g. of Dowex-50 (dried at 70° for 24 hr.). This was stirred and kept at 90° for 7 hr. under a slow stream of nitrogen, the flask being capped with a calcium chloride tube. After cooling the resin was filtered and the excess solvent removed *in vacuo*. The residue was taken up in hexane and passed through a neutral alumina column. The eluate was evaporated to dryness and crystallized from acetone to give 5.70 g. of pyranyl ether, m.p. 115–121°. An additional 0.35 g. could be obtained on slight concentration of the mother liquor. The analytical sample melted at 131–132°, $[\alpha]_D^{26}$ −30.4° (*c*, 1.18); λ_{max} 5.86 and 8.99 μ.

Anal. Calcd. for $C_{32}H_{50}O_3$: C, 79.28; H, 10.81. Found: C, 79.10; H, 10.57.

No attempt was made to separate the optical isomers formed on preparation of this derivative.

29-Isofucosteryl-3β-(2′-tetrahydropyranyl)-ether (IIc). A suspension of 1.95 g. of triphenylethylphosphonium bromide[10] in 25 ml. of absolute ether (distilled from phenylmagnesium bromide) was stirred in a pressure flask (175 ml. capacity). To this was added 4.0 ml. of 1.3*N* butyllithium solution[17] with the characteristic development of the clear red-orange solution. After this solution had been stirred for 1 hr., 2.5 g. of 24-ketocholesteryl-3β-(2′-tetrahydropyranyl)-ether dissolved in 35 ml. of absolute ether was added followed by an additional 24 ml. of absolute ether which promoted the stirring of the precipitated material.

An additional hour of stirring at room temperature was provided and then the flask was sealed and placed in an oil bath which was heated to 65° and held there for 16 hr. After cooling, the excess reagent was decomposed with the addition of water and the mixture filtered. The ether was evaporated to dryness.

The residues from two identical reactions were combined and taken up in hexane. This was chromatographed on a Silicic acid-Celite 545 column (150 g.:75 g.). The pyranyl ether was eluted with benzene-hexane (3:1) and with benzene to give 1.02 g. of the ether, which was usually depyranylated directly without further purification. In one preparation the pyranyl ether was crystallized from ethanol to give a gel which slowly crystallized, m.p. 105–107°; $[\alpha]_D^{28}$ −18.9° (*c*, 0.90).

Anal. Calcd. for $C_{34}H_{56}O_2$: C, 82.20; H, 11.36. Found: C, 82.05; H, 11.25.

The column was stripped with ether. Upon evaporation of the solvent, 2.45 g. of starting material was recovered.

29-Isofucosterol (IIa). A solution of 1.02 g. of 29-isofucosteryl-3β-(2′-tetrahydropyranyl)-ether in 50 ml. of hexane was added to a solution of four drops of concentrated hydrochloric acid in 50 ml. of methanol and the two-phased system was allowed to stand at room temperature for 1 hr. with intermittent stirring. The solvents were removed *in vacuo* and the residue crystallized from methanol to give 0.79 g. of the sterol, m.p. 120–122°. After several crystallizations an analytical sample showed the following physical constants, m.p. 128–129°; $[\alpha]_D^{26}$ −41.8°[18] (*c*, 1.20); λ_{max}^{KBr} 11.91, 12.30 and 12.50 μ; $\lambda_{max}^{CS_2}$ 11.93, 12.27 and 12.50 μ.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.74; H, 11.81.

29-Isofucosteryl acetate (IIb). A solution of 610 mg. of the sterol in 15 ml. of acetic anhydride and 15 ml. of dry pyridine was kept overnight at room temperature. The acetylation mixture was poured into water and the crude acetate filtered. On crystallization from methanol there was obtained 0.55 g. of the acetate, m.p. 122–125°. After several more crystallizations and drying *in vacuo*, the acetate melted at 130.5–131°, $[\alpha]_D^{27}$ −41.9° (*c*, 1.51); λ_{max}^{KBr} 5.77, 8.02, 11.92, 12.30 and 12.47 μ; $\lambda_{max}^{CS_2}$ 5.76, 8.10, 11.92, 12.30 and 12.48 μ.

Anal. Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.23; H, 11.21.

29-Isofucosteryl acetate 5,6,24,28-tetrabromide. A sample of 29-isofucosteryl acetate, 110 mg., was dissolved in 1.0 ml. of absolute ether. To this solution was added 2.0 ml. of a 5% solution of bromine in glacial acetic acid (wt./wt.). A precipitate began forming immediately. The solution was refrigerated overnight and then filtered. After washing with acetic acid and methanol, there was obtained 80 mg. of the tetrabromide, m.p. 139–141° dec.; λ_{max} 5.75 and 8.09 μ. No absorption between 12.0 and 12.5 μ.

Anal. Calcd. for $C_{31}H_{50}O_2Br_4$: C, 48.08; H, 6.53. Found: C, 48.38; H, 6.50.

Debromination of 29-isofucosteryl acetate tetrabromide. The tetrabromide was suspended in 1.5 ml. of dry ether and 10

(15) Infrared Spectral Data, American Petroleum Institute Research Project 44, Serial Number 1904.

(16) R. Paul, *Bull. soc. chim. France*, [5], 1, 973 (1934); G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, 69, 2246 (1947).

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

(18) The molecular rotation contribution of the 24-ethylidene group in 29-isofucosterol [M_D(29-isofucosterol)-M_D(cholesterol)] is −22, or of the same magnitude and direction as the corresponding contribution of the 24-ethylidene group in fucosterol, −18 (D. H. R. Barton, *J. Chem. Soc.*, 813 (1945)). In contrast the contribution of the 24-ethylidene group of unknown configuration in citrostadienol has been reported as +90; see ref. 12.

drops of glacial acetic acid and 50 mg. of zinc dust was added. After 1 min. of stirring the tetrabromide dissolved. Occasional stirring was provided during an additional 15 min. period. Ether was added to the solution and this was decanted from the zinc. The ether solution was washed with water and dried. Crystallization of the residue left after evaporation of the ether gave 30 mg. of the acetate, m.p. 129–131°. An additional crystallization sharpened the melting point to 130.5–131°. The infrared spectrum of this material was identical in every minute detail to that of 29-isofucosteryl acetate. No change had occurred in the structure of the steryl acetate during the bromination and debromination steps.

Ozonolysis of 29-isofucosteryl acetate. A solution of 260 mg. of the acetate in 50 ml. of cold purified glacial acetic acid was subjected to a stream of ozone (6%) for 5 min. Zinc dust was added to decompose the ozonide. This was shaken and then filtered. The water from a gas scrubber (25 ml.) used in the ozonolysis train was added to the acetic acid solution and the material was distilled until approximately 25 ml. of distillate was collected.

The distillate was poured into a solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The derivative precipitated immediately. After filtration, the material was dissolved in chloroform and chromatographed on a column of Bentonite:Celite 545 (3:1).[19] The derivative was eluted with chloroform-ethanol (10:1). Crystallization from ethanol gave the 2,4-dinitrophenylhydrazone of acetaldehyde, m.p. 160–162°. This was identical to an authentic sample (mixed melting point, infrared spectrum, paper chromatogram).

Isolation of fucosterol from Fucus vesiculosus. The ether extract of the air-dried material was saponified to give the pure sterol after several crystallizations from methanol, m.p. 122–123°; λ_{max} 11.90, 12.17 and 12.50 μ. The sterol was acetylated to give the acetate. Crystallization from methanol gave the pure acetate, m.p. 119–120°; λ_{max} 5.77, 6.00, 8.02, 11.92, 12.14, 12.19 (sh) and 12.47 μ. Addition of bromine gave the acetate tetrabromide, m.p. 131–133° dec. Debromination with zinc and acetic acid gave back fucosteryl acetate.

Wittig reaction of methyl isopropyl ketone with triphenylphosphonium ethylidene. To a heavy slurry of 13.15 g. (35.4 mmol.) of triphenylethylphosphonium bromide in 15 ml. of absolute ether was added 25.9 ml. of 1.3*N* butyllithium solution (33.7 mmol.). The solution was stirred for 1 hr. to give a red solution with the suspended excess salt. The solution was cooled to 0° and 3.62 ml. of dry redistilled methyl isopropyl ketone (2.90 g., 33.7 mmol.) was added and the heavy precipitate stirred for 1 hr. The pressure flask was then capped and heated to 65° for 3 hr. in an oil bath.

After cooling, the flask was opened and a column attached and as much ether distilled (bath 70°) as possible. The pressure was reduced and the distillate collected in a Dry Ice-cooled receiver. This material was distilled and gave 0.45 g. of olefin with a considerable loss due to hold-up. The following physical constants were obtained after another vacuum distillation; b.p. 85–88° (microdetermination); n_D^{28} 1.4163; λ_{max}^{neat} 6.00, 7.25, 7.30, 7.37, 12.18–12.27 (sh) and 12.33μ; reported for 3,4-dimethyl-2-pentene (*cis* or *trans* not specified) b.p. 86.2–86.4°, n_D^{25} 1.4052[20]; b.p. 85–89°, n_D^{27} 1.4100[21]; b.p. 91°, n_D^{21} 1.4135[22]; b.p. 87°, n_D^{21} 1.404.[23]

Gas chromatography of a sample of the olefin in a four meter column and operated at 85° showed an isomer ratio of 9:1.

Acknowledgment. The author is indebted to Professor Werner Bergmann for his advice, encouragement and suggestions during the course of this work.

NEW HAVEN, CONN.

(19) J. W. White, *Anal. Chem.*, 20, 725 (1948); J. A. Elvidge and M. Whalley, *Chem. and Ind.* (London), 589 (1955).

(20) F. J. Soday and C. E. Boord, *J. Am. Chem. Soc.*, 55, 3293 (1933).

(21) I. N. Narsarov, *Ber.*, 70, 617 (1937).

(22) A. Guillemonat, *Ann. Chim.*, 11, 143 (1939).

(23) Selective Values of Properties of Hydrocarbons, National Bureau of Standards, Circular 0461, November 1947, Washington, p. 49.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

Steroidal Aldosterone Blockers. III[1,2]

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The syntheses and biological activities of several new steroidal 17-spirolactones are presented. Oxygenation of position 11 in the steroid nucleus produces some increase of aldosterone blocking activity and this activity is further enhanced by the additional introduction of 9-α-fluoro substituent.

Earlier articles[1] in this series reported on a number of steroidal 17-spirolactones bearing modifications in the lactone and 3-oxo-4-ene systems; nuclear unsaturation and acylthio substituents were also introduced. This article reports on a number of oxygenated steroidal 17-spirolactones and related derivatives. The basic structures subjected to modification in this work were those of 3-(3-oxo-17β-hydroxy-4-androsten-17-α-yl)propanoic acid lactone (Ia) and its 19-nor analog (Ib).

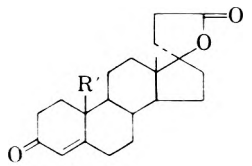
Monohydroxy derivatives of Ia and Ib were prepared both by adrenal perfusion[3] and by fermentation with a species of *Rhizopus*. Perfusion has been shown to give predominantly 11β-hydroxylation.[4] The products of perfusion, IIa and IIb, were oxi-

(1) Paper II, J. A. Cella and R. C. Tweit, *J. Org. Chem.*, 24, 1109 (1959).

(2) Presented in part before the Division of Medicinal Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

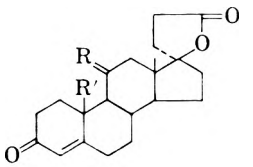
(3) These perfusions were carried out at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., by Mr. Austin Fish.

dized to the corresponding ketones, IId and IIa, which showed hypsochromic shifts in ultraviolet absorption maxima when compared to the hydroxy compounds. This is a characteristic effect of a ketone at C-11 on the absorption of the 3-keto-4-ene system.[5] The compounds IIf and IIc, obtained from fermentation of Ia and Ib with a species of *Rhizopus*, were oxidized to yield the identical ketones obtained by oxidizing IIe and IIb. The ultraviolet absorption spectra of IIc and IIf showed no significant changes on standing at room temperature in 0.1*N* methanolic potassium hydroxide twenty four hours, indicating that the hydroxyl groups could not be in the C-2, C-6, or C-7 positions.[6] On the basis of the foregoing evidence, we have assigned the 11β- and the 11α-hydroxyl structures to the perfusion and fermentation products respectively.



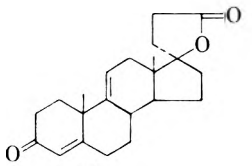
I

a. R′ = CH_3
b. R′ = H

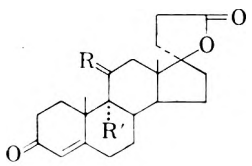


II

a. R = O, R′ = H
b. R =  , R′ = H
c. R =  , R′ = H
d. R = O, R′ = CH_3
e. R =  , R′ = CH_3
f. R =  , R′ = CH_3
g. R =  , R′ = CH_3



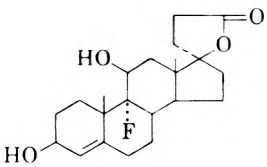
III



IV

a. R =  , R′ = Br
b. R =  , R′ = F
c. R = O, R′ = F

V



VI

The remarkable biological activities of the 9α-halo corticoids made it of interest to prepare 9α-fluoro-11β-hydroxy-17-spirolactone derivatives. The 9α-fluoro-11β-hydroxy derivative (IVb) was prepared from the 11α-hydroxyl compound (IIf) by the method of Fried and Sabo[7] involving conversion of the 11α-mesylate (IIg) to the 9(11)-ene (III). Hypobromous acid addition gave the 9,11-bromohydrin (IVa) which on treatment with potassium acetate in absolute ethanol gave the 9β,11β-epoxide (V). The fluorohydrin was then obtained by addition of hydrogen fluoride to this epoxy compound. In order to increase its solubility the 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) was reduced to the 3β-hydroxy-4-ene compound (VI) with sodium borohydride in methanol. Assignment of the 3β-configuration is based on the work of previous investigators[8,9] who have noted that the 3β-hydroxyl is the preferred product in the sodium borohydride reduction of Δ^4-cholestenone. It also appeared desirable to prepare the 9α-fluoro-11-keto compound (IVc) and this was accomplished by oxidation of IVb with pyridine–chromic acid complex.

The biological studies, reported in Table I, were conducted by Dr. C. M. Kagawa of these laboratories. It has been demonstrated that a definite and proportional relationship exits between the blocking effects of typical steroidal spirolactones when tested on rats treated with aldosterone and with desoxycorticosterone acetate (DOCA).[10] The more available DOCA was employed as the sodium retaining agent throughout this work.

TABLE I

DESOXYCORTICOSTERONE ACETATE BLOCKING POTENCIES

Compound	M.E.D.[a] Oral	M.E.D.[a] Subcutaneous
Ia	19.2	0.26
Ib	2.2	0.07
IIa	>0.6	<0.6
IIb	0.48	0.17
IIc		>2.4
IIe		1.1
IIf		>2.4
IIg		>1.2
III	>1.2	0.52
IVa		>1.2
IVb	>0.5	0.22
IVc	0.2	0.05
V		>1.2
VI	0.39	0.14

[a] M.E.D. is the medium effective dose (total mg./rat) which when used with 12 μg. of desoxycorticosterone acetate in adrenalectomized rats produces the same urinary sodium-potassium ratio as that which results from the use of 6 μg. of DOCA alone.

(4) O. Hechter, R. P. Jacobsen, R. Jeanloz, H. Levy, C. W. Marshall, G. Pincus, and V. Schenker, *J. Am. Chem. Soc.*, **71**, 3261 (1949) and *Arch. Biochem.*, **25**, 457 (1950).
(5) L. Dorfman, *Chem. Rev.*, **53**, 72 (1953).
(6) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1954).
(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).
(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).
(9) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).
(10) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1953).

An increase in oral activity is noted with introduction of the 11β-hydroxyl function. The most active compound is 3-(3,11-dioxo-9α-fluoro-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IVc).

EXPERIMENTAL

The microanalyses and optical determinations were carried out by Dr. Robert T. Dillon and his associates of these laboratories.

General procedures are reported for adrenal perfusion and microbiological oxidation techniques. Reference is made to them when they were used for specific preparations.

Melting points were determined on a Fisher-Johns block and are reported uncorrected. Ultraviolet spectra were determined in methanol. Optical rotations were measured in chloroform except as otherwise noted.

Procedure A: adrenal perfusion.[3] The perfusion medium is prepared by mixing 7 volumes of citrated whole beef blood with 5 volumes of "modified" (calcium chloride omitted) Tyrode Solution and subjecting the resultant mixture to the action of a stream of oxygen during a 2.5-hr. period. A solution of 1 g. of the steroid in 40 ml. of propylene glycol is added to 250 ml. of this medium and the mixture is then perfused at 36–37.5° through 8 beef adrenals (av. wt. 17.9 g. each) prepared according to the technique of Hechter and co-workers.[11] During the course of perfusion, oxygen is continuously bubbled through the medium. After approximately 3 hr., in the course of which 6 passes of the medium through the glands are completed, perfusion is stopped, and the perfusate is thrice extracted with isopropyl acetate. Solvent is removed from the combined extracts by evaporation under reduced pressure, and the residue is crystallized by appropriate means.

Procedure B: microbiological oxidation. A stainless steel fermentation tank of 40-l. capacity is charged with a nutrient medium containing 3.3% dextrose, 0.5% cotton seed flour, 0.3% corn steep liquor, and 0.2% silicone antifoam in tap water. Tank and medium are sterilized by heating to a temperature of 120° and then cooled to about 25°, whereupon the medium is inoculated with an aqueous suspension of spores from a culture of *Rhizopus sp.* A.T.C.C. 13429. The culture is maintained at about 25° for 24 to 48 hr., during which time a stream of sterile air is passed through it at the rate of about 0.3 l. of air per l. of culture per minute. The culture is stirred continuously by means of a vertically-mounted mechanical agitator in order to produce submerged growth. Sufficient steroid dissolved in a minimal quantity of acetone is then introduced to bring the concentration of steroid to 1 part per 3000 parts of medium. Agitation and aeration are continued for 12 to 16 hr., at the end of which time the resultant mixture is extracted with dichloromethane. The extract is dried over anhydrous sodium sulfate and stripped of solvent by distillation. The residual oil, on trituration with anhydrous ether, crystallizes.

3-(3-Oxo-11β,17β-dihydroxy-19-nor-4-androsten-17α-yl)-propanic acid lactone (IIb). According to procedure A, 1.0 g. of 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (Ib) was perfused through adrenal glands. The residual oil obtained was triturated with 50 ml. of benzene and the mixture filtered. The crude precipitate weighed 600 mg. and melted at 208–218°. A total of 401 mg. was recovered in two crops by recrystallization from 10 ml. of absolute ethanol. The analytical sample (1st crop) melted at 213–215° (solidified and remelted at 220–222°), and showed $[\alpha]_D$ +40° (diox.), $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 17,700).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.26; H, 8.17.

3-(3,11-Dioxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic lactone (IIa). A solution of IIb, 130 mg., in 5 ml. of acetone was treated with 0.17 ml. of a reagent containing 100 g. of chromic acid per 500 ml. of 6*N* sulfuric acid solution. The mixture was filtered and the filtrate evaporated to dryness. Recrystallization of the residue from methanol yielded 70 mg. of IIa, m.p. 234–237°, $[\alpha]_D$ +117° (diox.), $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,000).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.68; H, 7.83.

Similar oxidation of 100 mg. of IIc yielded 53 mg. of the identical ketone as demonstrated by mixed melting point and infrared spectra.

3-(3-Oxo-11α,17β-dihydroxy-19-nor-4-androsten-17α-yl)-propanoic acid lactone (IIc). Using Procedure B, 10 g. of 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (Ib) was hydroxylated. The crude crystalline product (500 mg.) was recrystallized several times from ethyl acetate to give a total of 377 mg. of product, m.p. 138–140° in several crops. An analytical sample showed m.p. 140–142°, $[\alpha]_D$ −66° (diox.), and $\lambda_{max}^{CH_3OH}$ 240.5 mμ (ε 17,000).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.87; H, 8.21.

3-(3-Oxo-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIe). One gram of 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (Ia) was oxidized according to Procedure A. The crude residue was chromatographed on 60 g. of silica gel. Elution with a solvent mixture of benzene–ethyl acetate (3:1) yielded 213 mg. of product. Upon recrystallization from ethyl acetate there was obtained in two crops, a total of 157 mg. of product, m.p. 205–208°, showing $[\alpha]_D$ +98° (diox.) and $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 16,250).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.66; H, 8.38.

3-(3,11-Dioxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IId). The hydroxyl compound IIe, 59 mg., was dissolved in 5 ml. of acetone and treated with 0.1 ml. of a reagent containing 100 g. of chromic acid per 500 ml. of 6*N* sulfuric acid solution. The mixture was filtered and the filtrate evaporated to dryness. Recrystallization of the residue from ethanol yielded 26 mg. of IId, m.p. 255–258°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 15,300).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.82; H, 8.03.

Similar oxidation of 100 mg. of IIf yielded 40 mg. of the identical ketone as demonstrated by mixed melting point and infrared spectra.

3-(3-Oxo-11α,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIf). According to procedure B, 10 g. of 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (Ia) was hydroxylated. The crude crystalline product was recrystallized successively from ethyl acetate and methanol to yield a total of 3.64 g. of product in several crops. The average melting point was 170–173°. The analytical sample melted at 173–174° and showed $[\alpha]_D$ +48.4° (diox.) and $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 15,900).

Anal. Calcd. for $C_{22}H_{30}O_4 \cdot {}^1/_2CH_3OH$: C, 72.29; H, 8.61. Found: C, 72.29; H, 8.52.

3-(3-Oxo-11α-mesyloxy-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (IIg). To a solution of 1.07 g. of 3-(3-oxo-11α,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IIf) in 4.2 ml. of chloroform and 1.0 ml. of pyridine was added at 0° with stirring over a 10 min. period 0.51 g. (1.5 mol. equiv.) of methanesulfonyl chloride dissolved in 1.0 ml. of chloroform. After 16 hr. of refrigeration the reaction mixture was diluted with 3 volumes of chloroform and washed successively with water, dilute aqueous sulfuric acid, water, dilute aqueous sodium bicarbonate, and finally water. After drying over sodium sulfate the chloroform solution was evaporated at temperatures less

(11) O. Hechter, R. P. Jacobsen, V. Schenker, H. Levy, R. W. Jeanloz, C. W. Marshall, and G. Pincus, *Endocrinology*, 52, 679 (1953).

than 25° to a sirupy residue and 30 ml. of absolute ethanol was added. Refrigeration for several hours produced a first crop of 670 mg. and concentration of the mother liquors produced an additional 130 mg., m.p. 157–163° (dec.).

Anal. Calcd. for $C_{23}H_{32}O_6S$: C, 63.27; H, 7.39. Found: C, 63.21; H, 7.15.

3-[3-Oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (III). To a solution of 1.85 g. of anhydrous sodium acetate in 16.6 ml. of glacial acetic acid heated in a Woods metal bath at a bath temperature of 112° was added over a 2 min. period 1.35 g. of 3-(3-oxo-11α-mesyloxy-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (IIg). The bath temperature was maintained at 112° for an additional 30 min. and the reaction mixture was intermittently stirred during this period. The reaction mixture was then promptly cooled to room temperature and diluted with 33 ml. of water. Refrigeration produced 500 mg. of crystalline product, m.p. 155.5–157°. An analytically pure sample was obtained by recrystallization from ethyl acetate, m.p. 157.5–158°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,000).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.66; H, 8.14.

3-(3-Oxo-9α-bromo-11β,17α-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVa). A reaction mixture composed of 10.35 g. of 3-[3-oxo-17β-hydroxy-4,9(11)-androstadien-17α-yl]propanoic acid lactone (III), 5.20 g. of *N*-bromoacetamide and 165 ml. of peroxide-free dioxane was stirred at room temperature and 16.5 ml. of 1*N* perchloric acid was added all at once. After stirring for an additional 10 min. 560 ml. of 2% aqueous sodium bisulfite was added and then the reaction mixture was cooled to 5°. The precipitate was collected on a funnel, washed with water, and air dried to yield 7.7 g. of crude product. An analytically pure sample was obtained by recrystallization from ethanol, m.p. 162–164°, $\lambda_{max}^{CH_3OH}$ 242.5 mμ (ε 16,300).

Anal. Calcd. for $C_{22}H_{29}BrO_4$: C, 60.41; H, 6.68. Found: C, 60.43, 60.41; H, 7.18, 6.94.

3-(3-Oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (V). A solution of 580 mg. of anhydrous potassium acetate in 5.85 ml. of absolute ethanol was heated to the boiling point and then the heat source was removed. A solution of 850 mg. of 3-(3-oxo-9α-bromo-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVa) in 2.75 ml. of peroxide-free dioxane was promptly added. The reaction mixture was brought rapidly to reflux, maintained there for 40 min., and then promptly cooled in an ice bath. Addition of 14.5 ml. of water and subsequent refrigeration for 2 hr. produced crystals which were recrystallized from acetone–hexane to yield 348 mg. of product. An analytically pure sample was obtained by recrystallization from methanol, m.p. 205–210°, $\lambda_{max}^{CH_3OH}$ 243 mμ (ε 14,500).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.70; H, 7.73.

3-(3-Oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVb). A solution of 29 mg. of 3-(3-oxo-9β,11β-oxido-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (V) in 2.75 ml. of redistilled chloroform was added dropwise to a cold (−50°) solution of 696 mg. of anhydrous hydrogen fluoride in 1.32 g. of redistilled tetrahydrofuran. The reaction mixture was held at 0° for 3.5 hr., diluted with four volumes of chloroform, and then washed successively with water, dilute aqueous sodium bicarbonate, and finally water. The chloroform solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to yield 6.5 mg., m.p. 276–278° (dec.), $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 16,100), $[\alpha]_D$ +168.4°.

Anal. Calcd. for $C_{22}H_{29}FO_4$: C, 70.19; H, 7.76. Found: 70.22; H, 7.68.

3-(3β,11β,17β-Trihydroxy-9α-fluoro-4-androsten-17α-yl)-propanoic acid lactone (VI). To a stirred suspension of 300 mg. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) in 35 ml. of methanol at 35° was added a solution of 250 mg. of sodium borohydride in 10 ml. of methanol. Stirring was continued for 35 min. when complete solution had been obtained and the reaction temperature was allowed to fall to room temperature. A solution of 4 ml. of glacial acetic acid in 15 ml. of water was slowly added and then the solution was evaporated *in vacuo* to one half of its original volume. Addition of 150 ml. of water was followed by concentrating again to one-half volume, producing a granular solid which was crystallized from aqueous ethanol to yield 200 mg. of VI, m.p. 143–146°, $[\alpha]_D$ +72.8°. Concentration of mother liquors produced an additional 50 mg. of product.

Anal. Calcd. for $C_{22}H_{31}FO_4$: C, 69.81; H, 8.26. Found: C, 69.51; H, 8.11.

3-(3,11-Dioxo-9α-fluoro-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (IVc). A solution of 200 mg. of 3-(3-oxo-9α-fluoro-11β,17β-dihydroxy-4-androsten-17α-yl)propanoic acid lactone (IVb) in 10 ml. of pyridine was added slowly with mixing to a pyridine–chromic acid complex prepared by adding 200 mg. of chromium trioxide slowly to 5 ml. of pyridine. During the addition of the steroid solution the reaction mixture was kept at 20° with external cooling and maintained at that temperature for 15 min. afterwards. After standing at room temperature overnight the reaction mixture was transferred slowly into a two-phase solvent mixture of 50 ml. of ethyl acetate and 25 ml. of water. The ethyl acetate layer was separated and combined with one ethyl acetate extract of the aqueous layer. The combined ethyl acetate extracts were washed successively with water, dilute hydrochloric acid, and water. After drying over sodium sulfate the solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from ethyl acetate–hexane to yield 71 mg., m.p. 238–239°, $[\alpha]_D$ +96°, infrared ($CHCl_3$), 5.62μ, 5.76μ, 5.97μ.

Anal. Calcd. for $C_{22}H_{27}FO_4$: C, 70.56; H, 7.27. Found: C, 70.36; H, 7.12.

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CHICAGO 80, ILL.

[CONTRIBUTION FROM THE LABORATORIOS DE INVESTIGACIÓN, E. R. SQUIBB AND SONS, ARGENTINA, S.A.]

Synthesis of 3-Hydroxy-4,5,6-trimethoxyaporphine (Pseudocorydine)

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The synthesis of 3-hydroxy-4,5,6-trimethoxyaporphine (IV) is described.

Only a few phenolic aporphines have been synthetized. In 1954 Hey and Lobo[1] reviewed the different attempts to prepare them. At that time only the phenolic, 6-hydroxy-3,4-dimethoxynoraporphine, had been prepared by total synthesis.[2] In their paper, Hey and Lobo described the synthesis of two nonnatural phenolic aporphines: 3-hydroxy-4-methoxy-5,6-methylendioxyaporphine (isobulbocapnine) and of 3-hydroxy-2-methoxy-5,6-methylendioxyaporphine.

Tomita and Kikkawa[3] were the first to describe the synthetic preparation of a natural diphenolic aporphine, 2,5-dihydroxy-3,6-dimethoxy-*N*-methylaporphine [(±)-laurifoline]. Soon thereafter the synthesis of 5-hydroxy-3,4,6-trimethoxyaporphine [(±) corydine] was reported by Hey and Palluel[4] and by Arumugam, Govindachari, Nagarajan, and Rao.[5]

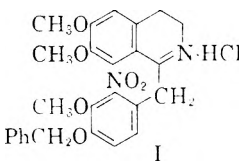
In this paper we describe the preparation of 3-hydroxy-4,5,6-trimethoxyaporphine (IV), a base isomeric with corydine and isocorydine, which we propose to name pseudocorydine.

In one of a series of papers on the synthesis of phenolic aporphines, Gulland and co-workers,[6] had already planned the synthesis of pseudocorydine, at a time when it was thought to be identical with corydine or isocorydine. They reported the preparation of some intermediates up to the stage of the dipicrolonate of base (III).

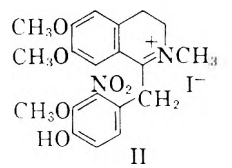
We have studied in detail the different steps of the synthesis. The hydrochloride of the dihydroisoquinoline (I) was prepared by the Bischler-Napieralski reaction from the corresponding amide; its methiodide (II) was reduced to the aminotetrahydroisoquinoline (III) which was isolated as the dipicrolonate. Application of the Pschorr reaction, using copper powder as catalyst, produced not only pseudocorydine (IV) but also, by substitution of the amino group by hydrogen, some pseudocodamine (V).[7]

Separation of the pseudocorydine from the pseudocodamine was done by column chromatography on alumina. The identification of the pseudocorydine is based on the ultraviolet spectrum which contains the two typical maxima of the aporphine alkaloids.

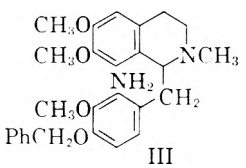
The formation of an aprophine and/or a benzylisoquinoline alkaloid when the Pschorr reaction is applied to the bases of type III, has already been



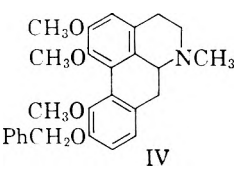
I



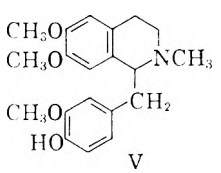
II



III



IV



V

described, but the conditions that favor one or the other product have not been worked out. While we obtained both types of bases using copper powder, a result similar to that described by Arumugam *et al.*[5] in the synthesis of corydine, Tomita and Kikkawa[3] found that this catalyst favored the exclusive production of the benzylisoquinoline alkaloid, coclanoline. Only when the reaction was carried out with zinc powder could they obtain the related aporphine base laurifoline. On the other hand, it is of interest that Hey and Lobo[1] and Hey and Palluel[4] have prepared aporphines by the Pschorr reaction, employing copper powder as catalyst.

EXPERIMENTAL

All the ultraviolet spectra were recorded in 96% ethanol. Melting points are uncorrected.

4-Benzyloxy-3-methoxy-2-nitro-phenylacetic acid. Ten grams of 4-hydroxy-3-methoxy-2-nitro-phenylacetic acid[8] were partially dissolved in 40 ml. of dioxane, 8.5 ml. of benzyl chloride and 5 g. of potassium carbonate were added, and the mixture was boiled for 1.5 hr. with agitation. One hundred ml. of water was then added and steam was passed

(1) D. H. Hey and L. C. Lobo, *J. Chem. Soc.*, 2246 (1954).

(2) H. Kondo and S. Ishiwata, *Ber.*, **64**, 1533 (1931).

(3) M. Tomita and T. Kikkawa, *Pharm. Bull. (Japan)*, **4**, 230 (1956).

(4) D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 2926 (1957).

(5) N. Arumugam, T. R. Govindachari, K. Nagarajan, and U. R. Rao, *Chem. Ber.*, **91**, 40 (1958).

(6) J. M. Gulland, K. I. Ross, and N. B. Smellie, *J. Chem. Soc.*, 2885 (1931).

(7) B. Frydman, R. Bendisch, and V. Deulofeu, *Tetrahedron*, **4**, 342 (1958).

(8) S. F. McDonald, *J. Chem. Soc.*, 885 (1948).

through the solution to eliminate dioxane and benzyl chloride. A heavy dark brown oil and a water phase remained. Upon storing at 0° the oil crystallized. The crystals of crude benzyl ester of 4-benzyloxy-5-methoxy-2-nitrophenylacetic acid were filtered and hydrolyzed by boiling for 30 min. in 20 ml. ethanol with 20 ml. 4*N* potassium hydroxide. The solution was acidified with 2*N* hydrochloric acid, whereupon light brown crystals separated. Recrystallized from ethanol-water, 1.2 g. of white needles was collected which, after drying at 100°, melted 144°.

The water filtrate from the ester was cooled thoroughly and acidified with 2*N* hydrochloric acid. There was produced a crystalline precipitate which, after filtering and recrystallizing from ethanol-water, yielded 8.5 g. of the dried acid, m.p. 144°. The total yield was 9.7 g. (55%). Gulland[9] gives m.p. 144°.

4-Benzyloxy-3-methoxy-2-nitrophenylacetyl chloride. Five grams of the acid was dissolved in 50 ml. chloroform, 20 ml. thionyl chloride was added, and the mixture was boiled for 1.5 hr. on a water bath. The excess chloroform and thionyl chloride were removed *in vacuo* and the red oil remaining was extracted five times with 100 ml. of boiling petroleum ether (66–72°) leaving an insoluble dark residue. The petroleum ether solution was diluted to 700 ml. and left at 5° whereupon the chloride crystallized as long white needles (3.9 g., 75%), m.p. 133–134°. The m.p. was not improved by further recrystallization.

Anal. Calcd. for $C_{16}H_{14}ClNO_5$: Cl, 11.56. Found: Cl, 11.11.

1-(4′-Benzyloxy-3′-methoxy-2′-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline methiodide (II). The necessary 4′-benzyloxy-3′-methoxy-2′-nitrophenyl-*N*-2-(3,4-dimethoxyphenyl)ethylacetamide, m.p. 112°, was prepared by the method of Gulland and co-workers,[6] using chloroform instead of benzene as solvent. It was cyclized to 1-(4′-benzyloxy-3′-methoxy-2′-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (I), m.p. 230–232°, in 85% yield, by a slight modification of the method of Gulland[6]; λ_{max} 276 mμ (log ε 3.85); 312 mμ (log ε 3.86).

The hydrochloride was transformed into the free base by treatment of its solution in ethanol with ammonia. The crystalline base melted 144–145°, decomposed easily, and was not analyzed (Gulland *et al.*[6] give m.p. 119°). By boiling 11.8 g. of the free base with 120 ml. methyl iodide and 20 ml. ethanol for 30 min., 14 g. of yellow long rectangular plates of the methiodide were obtained. M.p. 193–194°, unchanged by recrystallization. Gulland *et al.*[6] give 108° as the m.p. of the methiodide with decomposition at 200°.

Anal. Calcd. for $C_{26}H_{26}N_2O_6 \cdot ICH_3$: C, 52.70; H, 4.50; N, 4.63; I, 21.00. Found: C, 53.40; H, 4.63; N, 4.85; I, 21.15.

1-(4′-Benzyloxy-3′-methoxy-2′-nitrobenzyl)-N-methyltetrahydroisoquinoline hydriodide. Three grams of the former methiodide were dissolved in 180 ml. of absolute ethanol by heating, and the solution was allowed to cool at room temperature and reduced at atmospheric pressure employing 300 mg. platinum dioxide catalyst. During the reduction, white needles of the hydriodide precipitated. When the absorption of hydrogen was complete, the hydriodide was dissolved by heating, the catalyst filtered, and the yellow-green solution concentrated to 120 ml., whereupon crystallization started. After standing for 24 hr. at 5°, the crystals were filtered and recrystallized from absolute ethanol. White needles (2.4 g.), m.p. 162°, were obtained (yield: 81%).

Anal. Calcd. for $C_{27}H_{30}N_2O_6 \cdot HI$: C, 53.46; H, 4.14; N, 4.61; I, 20.92. Found: C, 53.75; H, 4.32; N, 4.53; I, 21.87.

The free nitro base was prepared by dissolving 410 mg. of the hydriodide in 10 ml. warm absolute ethanol and adding 2 ml. of concentrated ammonia. A precipitate was obtained which after cooling was filtered and recrystallized from absolute ethanol. The yield was 315 mg. (98%) of rectangular plates, m.p. 138°.

(9) J. M. Gulland, *J. Chem. Soc.*, 2872 (1931).

Anal. Calcd. for $C_{27}H_{30}N_2O_6$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.69; H, 6.22; N, 5.94.

1-(2′-Amino-4′-benzyloxy-3′-methoxybenzyl)-N-methyltetrahydroisoquinoline (III). The reduction of the nitro group was followed by ascending chromatography on Whatman paper No. 1, employing butyl alcohol:acetic-acid:water (80:3:17) as the mobile phase and Dragendorff's reagent for development. The nitro base, R_f 0.77, shows no fluorescence with ultraviolet light and gives an orange spot with the reagent. The amino base, R_f 0.48, shows a strong violet fluorescence and gives a red spot.

From the hydriodide. Two hundred milligrams of the hydriodide of the nitro base (II) was dissolved in 20 ml. methanol, and reduced for 7 hr. at 4 atm. pressure, employing 40 mg. of platinum oxide as catalyst. After filtering and evaporating the solvent, the residue was dissolved in water, and the solution was made alkaline with ammonia and extracted with ether. Evaporation of the ether gave an oily residue which showed a faint spot of the nitro base in the chromatogram. It was dissolved in ethanol and an excess of a solution of picrolonic acid in the same solvent was added. The dipicrolonate (250 mg., 78%), m.p. 208°, was obtained in the usual way. Gulland *et al.*[6] give m.p. 207°.

From the free nitro base. The same result was obtained by hydrogenation of the free nitro base. Five hundred milligrams was suspended in 140 ml. of water and dissolved by adding 0.1*N* sulfuric acid to *p*H 2, and hydrogenated at room pressure and temperature for 60 hr., employing 160 mg. of platinum dioxide as catalyst. After filtering the slightly yellow solution was made alkaline with diluted ammonia and extracted with ether. The dried ethereal extract was evaporated and the residue, dissolved in a small amount of warm absolute ethanol, was transformed into the picrolonate, m.p. 208°, 634 mg. (67.5%).

Benzyl-pseudocorydine hydriodide. The dipicrolonate (1.2 g.) was suspended in 6 ml. of cold methanol, 1.2 ml. of concentrated sulfuric acid dissolved in 6 ml. of cold methanol was added and the insoluble solid was well ground. The base dissolved and the insoluble picrolonic acid was filtered and washed with methanol. The mixed yellow methanolic solutions were cooled to 0° and 84 mg. of sodium nitrite, dissolved in 2.4 ml. of water, was slowly added. After standing overnight at 3–5°, 300 mg. of catalytic copper was added and a strong evolution of nitrogen took place. After 1 hr. at room temperature, with stirring, the suspension was boiled during 30 min., an equal volume of water was added and, when cool, the mixture was extracted twice with ether, and the extract discarded. The solution was then alkalinized with concentrated ammonia and again extracted with ether, until the extract gave a negative Mayer's reaction. The ether solution was well dried and evaporated to dryness and 386 mg. of a dark orange oil was obtained. It was dissolved in a few ml. of benzene and chromatographed by passage through a column of 18 g. of neutral aluminum oxide, activity III. The column was washed with 100 ml. of benzene and eluted with benzene–0.1% ethanol. Fractions of 50 ml. were collected. Fractions 7–12 gave a positive Mayer reaction and fraction 13 was negative. Benzene–1% ethanol was then employed and fractions 14–15 gave a positive reaction, while fraction 16 was again negative.

The oily residue from fractions 7 and 8, with a total weight of 128 mg., were pooled, dissolved in 2 ml. warm methanol, a small amount of acetic acid was added, and the solution was saturated with sodium iodide. Upon cooling, the hydriodide of benzylpseudocorydine crystallized. After recrystallization from methanol, 96 mg. of white prisms, m.p. 237° (dec.) was collected; λ_{max} 270 mμ (log ε 4.20), 299 mμ (log ε 3.77). No crystalline material could be obtained from the other fractions.

Anal. Calcd. for $C_{27}H_{29}NO_4 \cdot IH$: C, 57.97; H, 5.41; N, 2.50; I, 22.69. Found: C, 58.04; H, 5.40; N, 2.55; I, 23.02.

Pseudocodamine (V). Fractions 14 and 15 gave 89 mg. of a dark orange oil that was boiled for 45 min. with 15 ml. of 20% hydrochloric acid. After cooling, the solution was ex-

tracted with ether, alkalinized with ammonia and extracted again with ether until a negative Mayer's reaction was obtained. This last ether extract was well dried and a few drops of cyclohexane were added to the oily residue, whereupon it was caused to crystallize by scratching. The filtered crystals, recrystallized from cyclohexane, gave prisms, m.p. 130–131°, undepressed by pseudocodamine, m.p. 130–131°.[7] The picrate melted at 156–157°, and was identical with pseudocodamine picrate.

Pseudocorydine hydrochloride. One hundred milligrams of the former benzyl-pseudocorydine hydriodide was suspended in water, the solution covered with a layer of ethyl ether, made alkaline with saturated sodium hydrogen carbonate solution, and extracted with ether until a negative Mayer reaction was obtained. The ether extracts were dried and on evaporation gave 70 mg. of a brown oily residue. Fifteen ml. of 20% hydrochloric acid was added, and the solution was boiled for 1 hr. and evaporated to dryness, *in vacuo*. A crystalline brown residue was obtained, which was recrystallized by dissolving in ethanol and adding ether to turbidity. Thirty mg. (Vacuum) of white needles, m.p. 268–269° (sintering from 262°), was collected. λ_{max} 272 mμ (4.09); 302 mμ (3.70).

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot ClH$: C, 63.56; H, 6.40; N, 3.70; Cl, 9.38. Found: C, 63.43; H, 6.37; N, 3.77; Cl, 9.37.

Pseudocorydine (IV). The hydrochloride (50 mg.) was dissolved in water, covered with a layer of ethyl ether, made alkaline with diluted ammonia and extracted with ether until a negative Mayer reaction was obtained. The dried extracts on evaporation left a white grayish crystalline solid, very soluble in all organic solvents, excepting cyclohexane and petroleum ether. After several recrystallizations from cyclohexane, white long prisms were obtained, melting 184–185° in vacuum. λ_{max} 272 mμ (log ε 4.04), 302 mμ (log ε 3.66).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.51; H, 6.98; N, 4.07.

Pseudocorydine gives the same color reactions as isocorydine except with Fröhde's reagent which gives a dark purple color with pseudocorydine and a violet one with isocorydine.

Picrate. Prisms from ethanol m.p. 210–211°.

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot C_6H_3N_3O_7$: N, 9.82. Found: N, 9.52.

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Effects of Perfluoroalkyl Groups on Adjacent Functions

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The adjacency of a perfluoroalkyl group can affect the stability of intermediate reaction products in such an adverse way as to render impractical some conventional reactions. Aldehydes and ketones so fluorinated react with diazomethane to give the expected oxides, but these are cleaved by hydrogen to give secondary and tertiary alcohols, instead of primary and secondary alcohols. Pyrolysis of *N,N'*-di(trifluoroacetyl)hydrazine and *N*-benzenesulfonyl-*N'*-trifluoroacetylhydrazine did not give trifluoroacetaldehyde, but its pyrolysis products, carbon monoxide and fluoroform. Hydrogenolysis of the benzyl ester of *N*-heptafluoropropylcarbamic acid gave toluene with hydrogen fluoride and pentafluoropropionamide instead of heptafluoropropylamine.

The adjacency of a perfluoroalkyl group, besides modifying the polarity of a function, can affect the stability of a conventional reaction product in such a favorable way as to render practical certain reactions otherwise not useful, *e.g.*, the preparation of ketones in good yields from perfluorinated acids and Grignard reagents due to the stability of the intermediate.[2–4] This modifying action is not always an aid and may make impractical some convential reactions.

Most aldehydes and ketones react conventionally with diazomethane to give the next higher homologs, or mixtures of them, and substituted ethylene oxides.[5–7] When electron withdrawing groups are present in the alpha position, the oxide is the major or sole product.[8–10] When trifluoroacetaldehyde and trifluoroacetone were used, the reaction proceeded as expected to give the corresponding oxides, 1,2-epoxy-3,3,3-trifluoropropane (I) and 1,2-epoxy-2-methyl-3,3,3-trifluoropropane (II), respectively. On hydrogenation, unfluorinated oxides give primary and secondary alcohols.[11–13] In contrast, hydrogenation with Raney nickel of the fluorinated oxides gave 2-trifluoromethyl-2-propanol, and 1,1,1-

(1) Present address: Dept. of Chemistry, University of Hartford, Hartford, Conn.

(2) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2259 (1956).

(3) A. Sykes, J. C. Tatlow, and C. R. Thomas, *Chem. & Ind. (London)*, 630 (1955).

(4) R. H. Groth, *J. Org. Chem.*, **24**, 1709 (1959).

(5) H. Meyer, *Monatsch.*, **26**, 1300 (1905).

(6) H. Meerwein and W. Burneleit, *Ber.*, **61**, 1840 (1928).

(7) *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, 1948, pp. 518, 528.

(8) F. Arndt, B. Eistert, and W. Partale, *Ber.*, **62**, 1107 (1928).

(9) B. Eistert, *Tautomerie und Mesomerie*, Enke, Stuttgart, 1938.

(10) F. Arndt and B. Eistert, *Ber.*, **62**, 44 (1929).

(11) P. Weill and F. Kayser, *Bull. soc. chim. France*, (5) **3**, 841–844 (1936).

(12) M. F. Ushakov and B. M. Mikhailov, *J. Gen. Chem. (U.S.S.R.)*, **7**, 249–252 (1937).

(13) I. G. Farbenind, A.G., Brit. Patent **320,424**, July 17, 1928; *Brit. Abstr.*, **BII**, 182 (1930).

trifluoro-2-propanol. Reduction of II with lithium aluminum hydride gave the same tertiary alcohol. The central carbon atom of these oxides should by induction be more positive than the other carbon linked to the oxygen and hence preferentially reduced. Since in the final product it is the end carbon which appears reduced, it seems desirable to assume that a rearrangement takes place during the course of the reaction.

The McFadyen-Stevens aldehyde synthesis has been reported as useful and convenient in the case of aromatic aldehydes;[14-18] applications to aliphatic aldehydes have been unsuccessful except in the case of cyclopropylaldehyde[19] and it has been assumed that the difference was due to the presence of alpha hydrogen in the aliphatic compounds tested. In the present investigation, fluorinated compounds without alpha hydrogens were tested. *N*-benzenesulfonyl-*N'*-trifluoroacetylhydrazine and *N,N'*-di-(trifluoroacetyl)hydrazine were prepared by reaction of trifluoroacethydrazide hydrate with benzenesulfonyl chloride and trifluoroacetyl chloride, respectively. Pyrolysis, in the presence of carborundum or powdered glass, with or without sodium carbonate, in various high boiling media gave only fluoroform and carbon monoxide in both cases. Mass spectroscopic examination of the effluent gases indicated that the molar ratio of fluoroform to carbon monoxide was 1:1. These results seem to indicate that the aldehyde was formed as an intermediate, held tenaciously by the solvent and then decomposed by heating to its components fluoroform and carbon monoxide.

Syntheses of primary amines carrying fluorine on the same carbon atom as the amino group such as heptafluoropropylamine by the Hofmann hypohalite degradation of heptafluorobutyramide or the Schmidt-Curtius degradation of heptafluorobutyric acid azide have been reported as unsuccessful.[20,21] Husted[22] has found that the intermediate heptafluoropropylisocyanate is formed, and that its hydrolysis gives pentafluoropropionamide. It is also known that addition of ammonia to tetrafluoroethylene gives a triazine, 2,4,6-tridifluoromethyl-1,3,5-triazine, instead of 1,1,2,2-tetrafluoroethylamine.[23] On the basis of this, Stewart believed the $-CF_2NH_2$ group was not inherently unstable, but rather, sensitive to spontaneous loss of hydrogen fluoride and to extremely easy hydrolysis. The new method of approach tested here is the use of a benzyl urethane, a derivative known to give a primary amine, carbon dioxide, and toluene on hydrogenolysis.[24] This was to be tested in an anhydrous medium.

In the present investigation, the urethane prepared from benzyl alcohol and heptafluoropropylisocyanate was formed conventionally. On hydrogenolysis with Raney nickel or with palladized charcoal, it gave toluene and carbon dioxide as expected, but with hydrogen fluoride and pentafluoropropionamide instead of heptafluoropropylamine despite all efforts rigidly to exclude moisture. This practical failure is seen as a decomposition of the amino derivative by hydrogen fluoride loss, followed by passage to the lower amide in the presence of water.

EXPERIMENTAL

Reaction of trifluoroacetaldehyde with diazomethane. Polymeric trifluoroacetaldehyde (18 g., 0.184 mol.) was heated with a gas burner and the vapor of the monomer was passed into a solution of diazomethane (about 0.125 mol. prepared from 50 g. of *N*-methyl-*N*-nitrosourea) in 400 ml. of cyclohexane at 0°. The solution in a 1-l., 3-necked round bottom flask was stirred continuously and held under the refluxing of a Dry Ice condenser whose outlet led to a Dry Ice trap and eudiometer to follow the progress of the reaction. The diazomethane was decolorized by the excess of aldehyde after the reaction was allowed to reach room temperature. Fractionation of the solution gave the oxide (9.5 g., 0.097 mole, 53%) boiling at 38–46°. Fluoral hydrate (3 g., 0.026 mole, 14%) was also recovered. The identity of the oxide was established by infrared spectra showing no carbonyl and by comparison of its constants (b.p. 39–40°, n_D^{20} 1.3000) with known values (b.p. 39.1–39.3°, n_D^{20} 1.2997).[25]

Reaction of trifluoroacetone with diazomethane. Using a similar procedure, trifluoroacetone (25.5 g., 0.228 mol.) was distilled from an ampoule into a cyclohexane solution of diazomethane (about 0.125 mol. in 500 ml.) at 0°. Fractionation gave: trifluoroacetone (6.9 g., 0.061 mol., 26.8%) boiling 20–25°, a midcut (4.8 g., about 0.040 mol., about 17.5%), the oxide (10.7 g., 0.084 mol., 36.8%) boiling at 47–58°, and a tail cut boiling up to 80°. Refractionation of the oxide cut gave mostly material boiling at 50–52°, which gave a (−)2,4-DNPH test and an infrared spectra which was carbonyl-free and similar to that of other oxides.

Hydrogenation of I *with Raney nickel.* The oxide (6.5 g., 0.066 mol.) was dissolved in 50 ml. of dry ether and placed in a steel autoclave with 4 g. of Raney nickel and enough hydrogen to obtain a pressure of 5.3 atm. The autoclave, heated to 170°, was rocked mechanically for 15 hr. during which time the pressure fell asymptotically. Fractionation of the contents gave the alcohol (4.1 g., 0.043 mol., 65%) boiling at 65–70°. Infrared spectral comparison showed it to be 1,1,1-trifluoro-2-propanol. The 3,5-dinitrobenzoate derivative melted at 87°, mixed m.p. 87°.

(14) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936); 584 (1943).

(15) C. Harington and R. Rivers, *J. Chem. Soc.*, 1101 (1940).

(16) S. Natelson and S. Gottfried, *J. Am. Chem. Soc.*, **63**, 487 (1941).

(17) C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **65**, 482 (1943).

(18) H. Ungnade, *J. Am. Chem. Soc.*, **63**, 2091 (1941).

(19) J. D. Roberts, *J. Am. Chem. Soc.*, **73**, 2959 (1951).

(20) E. Gryszkiewicz-Trochimowski, A. Sporzcynski, and J. Wnuk, *Rec. trav. chim.*, **66**, 499 (1947).

(21) D. R. Husted and W. L. Kohlhase, *J. Am. Chem. Soc.*, **76**, 5141 (1954).

(22) A. H. Ahlbrecht and D. R. Husted, U. S. Patent **2,617,817** (1952).

(23) E. I. du Pont de Nemours & Co. and G. W. Rigby, Brit. Patent **607,103** (1948); *Chem. Abstr.*, **43**, 1444e (1949).

(24) A. L. Henne and J. J. Stewart, *J. Am. Chem. Soc.*, **74**, 1426 (1952).

(25) E. T. McBee and T. M. Burton, *J. Am. Chem. Soc.*, 74, 3022 (1952).

Hydrogenation of II *with Raney nickel and lithium aluminum hydride.* The oxide (9.2 g., 0.073 mol.) in 50 ml. of dry ether with 5 g. of Raney nickel was hydrogenated in the same way as in the previous case. Fractionation gave the tertiary alcohol as the main product (2.5 g , 0.02 mol., 27%) boiling at 70–82° in addition to a forecut (5 g.) consisting of alcohol and ether. The identity of the alcohol was ascertained by infrared spectra and physical constants of a purified sample of the 70–82° material (b.p. 82°, n_D^{25} 1.3370) compared to known values for the tertiary alcohol (b.p. 82°, n_D^{20} 1.3350[26]) and for the primary alcohol, 2-trifluoromethyl-1-propanol (b.p. 109°, n_D^{20} 1.3399[27]).

The oxide (6.7 g., 0.053 mol.) was added in 20 min. to a slurry of lithium aluminum hydride (2.3 g., 0.06 mol.) in 75 ml. of dry ether at 0°. The mixture, continuously stirred, was protected from moisture by a reflux condenser whose outlet led to a Dry Ice trap. After addition, the mixture was stirred for 1 hr. at 0°, warmed to room temperature for 15 min., and then cooled to 0° for decomposition with wet ether followed by 25 ml. of concentrated hydrochloric acid in 10 ml. of water. The ether layer and extracts of the aqueous layer were dried using Molecular Sieve 4A. Fractionation gave a forecut (2 g.) boiling in the range 40–78°, the main cut (3 g., 0.023 mol., 44%, n_D^{20} 1.3352) boiling 78–81° and a tail cut (1.4 g.). The tertiary alcohol was confirmed as before.

Preparation of trifluoroacethydrazide hydrate. Ethyl trifluoroacetate (106.5 g., 0.75 mol.) was refluxed for 3 hr. with 85% hydrazine hydrate (48.9 g., 0.825 mol.) in 150 ml. of 95% ethanol. After removal of the ethanol with a take-off condenser, a viscous liquid (96 g., 0.66 mol., 88%) remained which solidified on standing. Recrystallization from butanol gave crystals, m.p. 138–140°, identified as trifluoroacethydrazide hydrate by comparison of its infrared spectra with that of the unfluorinated analog.

Preparation of N-benzenesulfonyl-N'-trifluoroacetylhydrazine. Benzenesulfonyl chloride (48.6 g., 0.275 mol.) was added through an addition funnel to a solution of trifluoroacethydrazide hydrate (36.5 g., 0.25 mol.) in pyridine (198 g., 2.5 mol.) at 0°. During addition, the solution was continuously stirred and the 500-ml. 3-necked round bottom flask was equipped with a reflux condenser. After reaching room temperature, the stirring action was continued for an additional hour. The reaction mixture was then poured over 500 g. of ice and 30 ml. of concentrated hydrochloric acid. The yellow precipitate resulting was washed with 200 ml. of water and recrystallized from water-acid mixture to give a white product (58.3 g., 0.217 mol., 87%) melting at 212–213° which on sodium fusion gave positive tests for sulfide with lead acetate solution and for fluoride with cerous nitrate solution.

Preparation of N,N'-di(trifluoroacetyl)hydrazine. Trifluoroacetyl chloride (53 g., 0.40 mol.) was vaporized and led into a slurry of sodium phosphate, tribasic (49.5 g., 0.3 mol.) in 245 ml. of dry dioxane containing trifluoroacethydrazide hydrate (36.5 g., 0.25 mol.). This slurry was continuously stirred and protected from moisture by a Dry Ice reflux condenser whose outlet led to a Dry Ice trap. After addition at 0° was completed, the mixture was allowed to reach room temperature and then the stirring was maintained for an additional several hours. The white solid was filtered and extracted for 24 hr. with ethanol in a Soxhlet-type extractor. Removal of solvent from the filtrate and extracts gave an alcoholic residue (74 g.) which on sublimation gave a crystalline product (46.2 g., 0.206 mol., 82.6%) melting at 180–180.5°, and identified by infrared spectral comparison with the unfluorinated analog to be *N,N'*-di(trifluoroacetyl)hydrazine.

An attempted preparation by the method employed in the case of *N*-benzenesulfonyltrifluoroacetylhydrazine using pyridine gave a product (about 80–85%) which on sublimation gave crystals melting at 85° but which had a slight pyridine odor, enhanced by crushing the crystals. Infrared spectra showed it to be identical to *N,N'*-di(trifluoroacetyl)-hydrazine except for additional bands attributable to pyridine. Analysis indicated 2 mol. of pyridine per mole of compound.

Preparation using anhydrous hydrazine, trifluoroacetyl chloride, and sodium carbonate in ether was effected with a 70% yield of product.

Decomposition of N-benzenesulfonyltrifluoroacetylhydrazine. In a typical decomposition, *N*-benzenesulfonyltrifluoroacetylhydrazine (5.3 to 8 g., 0.02 to 0.03 mol.) and an equivalent amount of sodium carbonate in 50 to 100 ml. of solvent were placed in a 200-ml. 2-necked round bottom flask or 425-ml. steel autoclave with a few grams of carborundum or ground glass as surface catalyst. The mixture, continuously stirred in the flask or mechanically rocked in the autoclave, was heated to the boiling point of the mixture or to 200–220° in the autoclave. The effluent gases were led through a train which consisted of a water cooled condenser, a Dry Ice trap, a calcium chloride drying tube, an Ascarite tube, a Dry Ice trap, and an eudiometer. The effluent gases were passed through the train as formed in flask reactions; in autoclave reactions, gases were built up and then released slowly after the reaction was completed. The solvent was either decalin or ethylene glycol. No liquid products were isolated and no solids except small amounts of phenyl disulfide (m.p. and mixed m.p. 61°) in a run using ethylene glycol as the solvent, and starting material. Infrared spectra of the effluent gases from the last run in decalin showed the presence of carbon monoxide and fluoroform.

Decomposition of N,N'-di(trifluoroacetyl)hydrazine. These decompositions were carried out in the same manner as described above for autoclave reactions at 225°. For convenience an infrared gas cell, protected from moisture by Dry Ice traps, was inserted into the train. The effluent gas was found by infrared spectra to be rich in carbon monoxide and fluoroform. Mass spectra data indicated a 1:1 mole ratio of the two gases.

Similar results were obtained with or without base. Decalin, carbitol, and *o*-dichlorobenzene were used as solvents. In the case of carbitol, much ammonia was isolated (12 meq. found on titration in a run using 0.045 mol. of compound after some standing).

Preparation of benzyl ester of N-heptafluoropropylcarbamic acid. Heptafluoropropylisocyanate (32 g., 0.151 mol., prepared by reaction of heptafluorobutyryl chloride and sodium azide followed by heating) was vaporized by use of warm water into a solution of benzyl alcohol (16 g., 0.148 mol.) in 50 ml. of dry ether. The solution, continuously stirred in a 200-ml. 3-necked round bottom flask, was protected from moisture by a Dry Ice condenser whose outlet led to a Dry Ice trap. After addition in 1 hr., the solution was permitted to stand several days at room temperature. The solvent was then removed by aspiration and a low melting solid (46 g., 0.144 mol., 97%) was obtained. Recrystallization from 30–60° petroleum ether gave crystals melting at 34.5–35.5°, which were identified by infrared spectra as the urethane.

Vacuum distillation of the product of an earlier run gave a cloudy liquid distilling at 120°/10 mm. which contained some hydrogen fluoride. Considerable solid also formed which clogged the column. The liquid was identified by infrared spectra as the urethane. The solid melted at 97° and was identified as pentafluoropropionamide by infrared spectra; mixed m.p. with authentic sample, 97°. In addition, a polymeric glassy material, soluble in chloroform, remained as a residue. The amounts of amide, urethane, and polymer were roughly equal, *viz.* 7 g., 7 g., and 6 g. from a run made using 0.083 mol. each of isocyanate and alcohol in 40 ml. of carbon tetrachloride.

Stability of benzyl ester of N-heptafluoropropylcarbamic acid. (*a*) *Standing in solution.* Crude urethane on standing in

(26) F. Swarts, *Bull. soc. chim. Belges*, **38**, 99 (1929).

(27) M. W. Buxton, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 66 (1954).

TABLE I

NEW COMPOUNDS

Compound	M.P., °C.[a]	% C[b] Calcd.	% C[b] Found	% H[b] Calcd.	% H[b] Found	% N[b] Calcd.	% N[b] Found	% F[c] Calcd.	% F[c] Found
$CF_3(CH_3)C(O)CH_2$	[d]	—	—	—	—	—	—	45.3	44.1
$CF_3CONHNH_2 \cdot H_2O$	138–140	—	—	—	—	—	—	39.7	39.4
$CF_3CONHNHSO_2C_6H_5$	212–213	35.83	36.10	3.61	2.85	10.45	10.34	—	—
$CF_3CONHNHCOCF_3$	180–180.5	21.40	21.50	0.89	1.28	12.50	12.64	—	—
$CF_3CONHNHCOCF_3 \cdot 2C_5H_5N$	85	42.93	42.74	3.15	3.24	—	—	—	—
$C_3F_7NHCO_2CH_2C_6H_5$	34.5–35.5	41.37	41.45	2.51	2.65	4.43	4.39	—	—
$C_2H_5CONHCO_2CH_2C_6H_5$	95	—	—	—	—	—	—	32.87	32.63

[a] Temperatures uncorrected. [b] Analyses by Galbraith Laboratories. [c] Analyses by M. Renoll. [d] B.p. 50–52°, n_D^{20} 1.3146, d_4^{20} 1.203, M.R. 20.55, A.R. for F 1.24.

TABLE II

HYDROGENOLYSIS OF $C_3H_7NHCO_2CH_2C_6H_5$

Run	Urethane, g.	Pressure H_2, atm.	Catalyst	Temp., °C.	Time	Spectra Change
1	2.5	3.3	Pd/C[a]	25	48 hr.	Partial loss of 6.48-band
2	3.0	3.3	Pd/C[a]	25	6 days	Complete loss of 6.48-band
3	3.0	3.3	3 g. Ra-Ni	25	45 hr.	No change
4	3.0	9.3	Pd/C[a]	100	24 hr.	Complete loss of 6.48-band
5	3.0	11.0	3 g. Ra-Ni	125	24 hr.	Complete loss of 6.48-band

[a] The Pd/C consisted of 30 mg. $PdCl_2$ and 120 mg. C.

petroleum ether for several days without protection from moisture gave a crystalline material (5 to 15%) melting at 95°. The solvent gave a positive test for fluoride with cerous nitrate solution. The infrared spectra and analysis indicated the material to be the benzyl ester of *N*-pentafluoropropionylcarbamic acid. No change occurred in this material under hydrogenolysis conditions used later with unchanged urethane.

(*b*) *On standing exposed to air and moisture.* On prolonged standing (several months) in open air, a crystalline solid melting at 87° was obtained. Before recrystallization, a strongly acidic odor was detected. Infrared spectra showed this material to be benzyl carbamate, mixed m.p. with authentic sample, 87°.

(*c*) Under similar conditions as outlined in (*a*) and (*b*) as well as to heat, the methyl ester of *N*-heptafluoropropylcarbamic acid was found to be stable.

Hydrogenolysis of benzyl ester of N-heptafluoropropylcarbamic acid. In a typical run, the urethane (2 to 3 g., 0.006 to 0.009 mol.) in 30 to 40 ml. of dry ether was placed in either a 220-ml. glass bottle in the Parr hydrogenation apparatus or in a 425-ml. steel autoclave. A variety of catalysts, time, temperature, and hydrogen pressure were used. In all cases when reaction occurred, the infrared spectra showed a loss of the 6.48-band characteristic of the starting material (see Table II). Removal of the solvent in run 2 gave pentafluoropropionamide (1.4 g., 0.0085 mol.) identified as before. The solvent contained toluene, identified by odor and infrared spectra, and also gave a positive test for fluoride with cerous nitrate solution.

Under similar conditions, as outlined in Table II, the methyl ester of *N*-heptafluorobutylcarbamic acid was stable.

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COLUMBUS, OHIO

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & CO., INC.]

Addition of Mercuric Fluoride to Fluoroethylenes

C. G. KRESPAN

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A convenient new synthesis of polyfluoroethylmercurials has been found in the addition of mercuric fluoride to fluoroethylenes in the presence of a solvent. Volatile bis(polyfluoroethyl)mercury compounds are formed directly and in good conversion. Bis(1,2,2,2-tetrafluoroethyl)mercury and bis(2,2,2-trifluoroethyl)mercury have been characterized.

A basic mercury salt or the mercuric salt of a carboxylic acid will generally add to an olefin to form a monoalkylmercury salt containing a hydroxy, alkoxy, or acyloxy substituent in the alkyl group.[1] The structures of the products formed suggest polar intermediates, and mechanisms

(1) J. Chatt, *Chem. Rev.*, 48, 7 (1951).

involving both ionic addition and formation of a polarized complex in the transition state have been proposed.[1,2] Although salts containing the mercury-oxygen bond react with olefins, no similar addition of a salt containing the more stable, covalent mercury-chlorine bond has been found.[3] Fluorine, however, is more electronegative than oxygen and forms reactive ionic compounds with mercury. Thus such a substance as mercuric fluoride might add to fluoroethylenes to form fluoroethyl derivatives of mercury.

Such has now been found to be the case. Reactions of mercuric fluoride with three fluoroethylenes proceeded readily at 50–100° under autogenous pressures to give the corresponding bis(fluoroethyl)mercury compounds in conversions of 56–66%. Tetrafluoroethylene, trifluoroethylene, and 1,1-difluoroethylene formed bis(pentafluoroethyl)-mercury (I), bis(1,2,2,2-tetrafluoroethyl)mercury (II), and bis (2,2,2-trifluoroethyl)mercury (III), respectively, under these conditions.

$$HgF_2 + CF_2 = CF_2 \longrightarrow \underset{\text{I}}{Hg(CF_2CF_3)_2}$$

$$HgF_2 + CHF = CF_2 \longrightarrow \underset{\text{II}}{Hg(CHFCF_3)_2}$$

$$HgF_2 + CH_2 = CF_2 \longrightarrow \underset{\text{III}}{Hg(CH_2CF_3)_2}$$

Compounds II and III, prepared for the first time, correspond to the products expected from an ionic addition of mercuric fluoride to double bonds polarized so as to make the difluoromethylene group the more positive end. This result agrees with earlier work on the addition of ionic reagents to fluoroolefins.[4] Bis(1-chloro-1,2,2,2-tetrafluoroethyl)-mercury was prepared by a similar addition of mercuric fluoride to chlorotrifluoroethylene, but sublimation techniques did not effect removal of all the impurities.

Compound I has been prepared previously by reaction of pentafluoroiodoethane with cadmium amalgam.[5] Reduction of I with aqueous sodium stannite to give two equivalents of pentafluoroethane shows that two pentafluoroethyl groups are attached to each mercury atom. The structures of II and III were determined by examination of the nuclear magnetic resonance spectra for H^1 and F^{19}.

The nuclear magnetic resonance spectra of I, II and III exhibit the splittings of F^{19} and H^1 resonances expected for these structures. Fig. 1

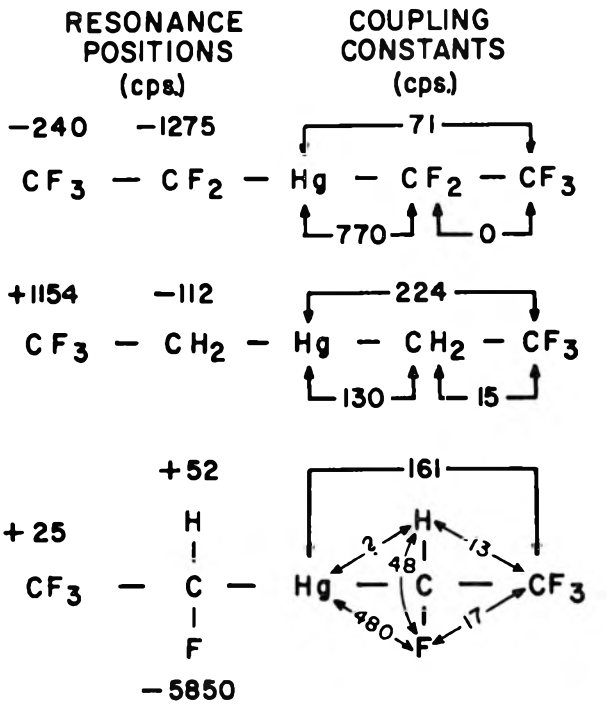

Fig. 1. Summary of coupling constants and centers of group resonances in a 40-megacycle field

Spectra were obtained from a varian high resolution nuclear magnetic resonance spectrometer. Fluorine resonances are relative to trifluoroacetic acid at 0, and proton resonances are relative to water at 0. Resonances at lower magnetic field than the zero points are considered positive

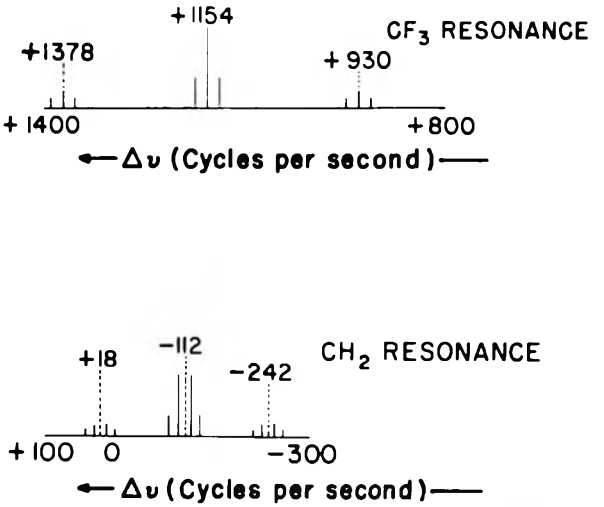

Fig. 2. Graphic representation of F^{19} and H^1 spectra of $Hg(CH_2CF_3)_2$ in carbon tetrachloride at 40 megacycles

Resonances at lower magnetic field than the zero points (CF_3CO_2H for F^{19}, H_2O for H^1) are considered positive

summarizes the centers of group resonances and the coupling constants involved in splitting these resonances. The observation of satellites due to coupling with Hg^{199}, an isotope present in naturally occurring mercury in 17% abundance, is direct evidence for the bonding of the fluoroethyl groups to mercury. To illustrate this coupling with mercury, the spectra for III are presented graphically in Fig. 2.

(2) A. G. Brook and G. F. Wright, *Can. J. Research*, 28B, 623 (1950).

(3) Mercuric chloride does add readily to acetylenic linkages. Such reactions are described by A. N. Nesmeyanov, N. K. Kochetkov, and V. M. Dashunin, *Isvest. Akad. Nauk. S. S. S. R., Otdel Khim. Nauk*, 77 (1950); *Chem. Abstr.*, 44, 7225 (1950).

(4) R. N. Haszeldine and J. E. Osborne, *J. Chem. Soc.*, 61 (1956).

(5) J. Banus, H. J. Emeleus, and R. N. Haszeldine, *J. Chem. Soc.*, 3041 (1950).

Dry mercuric fluoride forms little organomercurial when heated with trifluoroethylene, and can react explosively with tetrafluoroethylene. However, controllable reactions of fluorinated ethylenes occur readily at 100° or lower when an appropriate solvent for the mercuric fluoride is employed. Arsenic trifluoride is a useful reaction medium,[6] and one experiment suggests that in some cases hydrogen fluoride may be satisfactory with either mercuric fluoride or mercuric oxide.

EXPERIMENTAL

Bis(pentafluoroethyl)mercury. A mixture of 95.6 g. (0.40 mol.) of mercuric fluoride and 60 ml. of arsenic trifluoride was heated at 100° for 1 hr. in a 400-ml. shaker tube lined with stainless steel. Ninety grams (0.90 mol.) of tetrafluoroethylene was then injected at 100° in portions over a period of 2 hr., and the reaction mixture was heated at 100° for an additional 12 hr. under autogenous pressure. Evaporation of arsenic trifluoride at 25° (50 mm.) gave a solid residue from which bis(pentafluoroethyl)mercury was sublimed at 90° (1 mm.). Resublimation at 85° (1 atm.) gave 98 g. (56% yield based on mercuric fluoride) of the white crystalline mercurial, m.p. (sealed tube) 105–106° (Ref. 1 reports m.p. 106–107°). The structure of the product was confirmed by determination of the nuclear magnetic resonance spectrum for F^{19} in acetone (Figure 1). A solution of 4.7 g. of sodium hydroxide and 3.8 g. of stannous chloride dihydrate in 20 ml. of water was stirred with 1.0 g. (0.0023 mol.) of bis(pentafluoroethyl)mercury until no more gas evolved.[7] The gas was collected over water and identified by its infrared spectrum as pure pentafluoroethane, obtained in 100% of theory.

An addition to a fluoroethylene of Hg-F in preference to Hg-O is shown by the following reaction in aqueous hydrofluoric acid. Hydrated mercuric fluoride, prepared from 21.7 g. (0.10 mol.) of mercuric oxide and 15 ml. (0.43 mol.) of 50% aqueous hydrofluoric acid, was reacted with 30 g. (0.30 mol.) of tetrafluoroethylene in an 80-ml. shaker tube lined with stainless steel at 100° for 5 hr. The product was heated at 80° (1 mm.), and the volatile material was condensed in a trap at −78°. The contents of the trap were warmed and filtered, and the solid material was pressed dry on filter paper and sublimed at 85° at atmospheric pressure. The sublimate was 2.4 g. (5% yield based on mercuric oxide) of bis(pentafluoroethyl)mercury, identified by comparison of its nuclear magnetic resonance spectrum with that of an authentic sample. The nonvolatile product was extracted with water and then with concentrated nitric acid to remove free mercury and mercury salts. The insoluble residue was 29 g. of polymer.

Bis(1,2,2,2-tetrafluoroethyl)mercury. Except for tetrafluoroethylene, which polymerizes readily under the reaction conditions, good results were obtained by heating the fluoroethylene and mercuric fluoride up to reaction temperature in the presence of the solvent.[8] Thus an 80-ml. shaker tube charged with 23.9 g. (0.10 mol.) of mercuric fluoride, 25 g. (0.30 mol.) of trifluoroethylene, and 15 ml. of arsenic trifluoride was heated at 50° for 4 hr. under the autogenous pressure of the reactants. Arsenic trifluoride was removed from the product by evaporation under reduced pressure, and the residual crystalline solid was heated at 80–90° under atmospheric pressure. The volatile white mercurial, collected on a cold finger, weighed 26.6 g. (66% yield based on mercuric fluoride) and melted at 78–79°.

Anal. Calcd. for $C_4H_2F_8Hg$: C, 11.93; F, 37.75; Hg, 49.82. Found: C, 12.14; F, 36.91; Hg, 49.20.

The structure of the product was established by its nuclear magnetic resonance spectrum in acetone (Figure 1).

Bis(2,2,2-trifluoroethyl)mercury. A mixture of 23.9 g. (0.10 mol.) of mercuric fluoride, 19 g. (0.30 mol.) of vinylidene fluoride, and 15 ml. of arsenic trifluoride was heated at 100° for 7 hr. under autogenous pressure. The product, after removal of arsenic trifluoride under reduced pressure, was heated at 85° at atmospheric pressure to drive the volatile mercurial up to a cold finger. The solidified condensate was 24.2 g. (66% yield based on mercuric fluoride) of bis(2,2,2-trifluoroethyl)mercury, m.p. 40°.

Anal. Calcd. for $C_4H_4F_6Hg$: C, 13.10; F, 31.09; Hg, 54.71. Found: C, 13.04; F, 29.81; Hg, 54.27.

The structure of this product was established by its nuclear magnetic resonance spectra for H^1 and F^{19} in carbon tetrachloride (Fig. 2).

Bis(1-chloro-1,2 2,2-tetrafluoroethyl)mercury. A mixture of 23.9 g. (0.10 mol.) of mercuric fluoride, 35 g. (0.30 mol.) of chlorotrifluoroethylene, and 15 ml. of arsenic trifluoride was heated with agitation at 100° for 7 hr. under autogenous pressure. Arsenic trifluoride was removed from the product by evaporation under reduced pressure, and the solid residue was heated in a sublimation apparatus at 85° under atmospheric pressure. There was obtained in this way 14.6 g. (31% yield based on mercuric fluoride) of crude mercurial, m.p. 93–95°.

Anal. Calcd. for $C_4Cl_2F_8Hg$: C, 10.2; Cl, 15.0; F, 32.2; Hg, 42.6. Found: C, 9.6; Cl, 13.7; F, 33.3; Hg, 41.3.

Although the major component was established as bis(1-chloro-1,2,2,2-tetrafluoroethyl)mercury by the nuclear magnetic resonance spectrum, fluorinated impurities are evidently present.

Acknowledgment. The author is indebted to Dr. H. Foster for the interpretation and calibration of the nuclear magnetic resonance spectra.

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(6) Dr. E. L. Muetterties of these laboratories has shown that a considerable amount of mercuric fluoride can be dissolved in warm arsenic trifluoride.

(7) Method described by H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, 2956 (1949).

(8) C. G. Krespan, U. S. Patent 2,844,614, July 22, 1958.

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, QUARTERMASTER RESEARCH AND ENGINEERING CENTER, U. S. ARMY]

The Reductive Cleavage of Ozonides to Alcohols

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Compounds with ethylenic groups have been ozonized and these ozonized materials, without prior isolation, have been treated with sodium borohydride and lithium aluminum hydride. These reagents reductively cleave the ozonized material to alcoholic products. All previous work on the reduction of ozonides with metal hydrides is also summarized.

In recent years there has been an increased interest in the reductive cleavage of ozonized compounds. Recent reports have shown that lithium aluminum hydride reductively cleaves ozonides to alcohols in good yield.[1-4]

In certain instances the high reactivity of lithium aluminum hydride might be undesirable. In the course of work in this laboratory the applicability of sodium borohydride as a milder reagent for the reductive cleavage of ozonides was investigated in addition to further experiments utilizing lithium aluminum hydride.

The only reported reduction of an ozonide with sodium borohydride is the work of Witkop and Patrick[5] who treated the ozonide of 2-phenylskatole with both lithium aluminum hydride and sodium borohydride and obtained different decomposition products.

value both as a preparative and characterizing reaction and is summarized as follows:

$$R{-}CH{=}CH{-}R' \xrightarrow[2\ \text{metal hydride}]{1\ \text{Ozone}} R{-}CH_2OH + R'CH_2OH$$

Tables I and II summarize the results utilizing sodium borohydride and lithium aluminum hydride, respectively. The tables include all of the reported reductions of ozonides with metal hydrides. The yields of purified products have varied from 46 to 79% in our work, but since most of the experiments were run only once and some on a small scale, it is felt that these yields can be improved. No attempt was made to isolate the smaller cleavage product, methanol, from compounds I, II, III, and VIII, or the expected ethylene glycol from compound VI. The products of the reductive

TABLE I

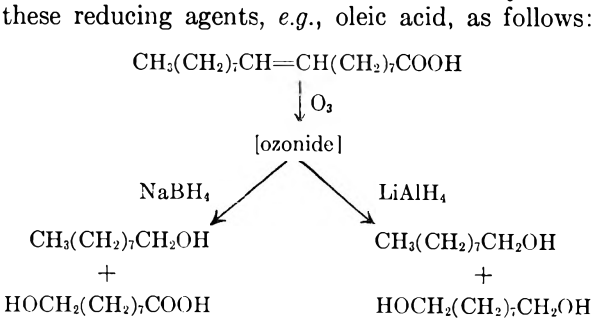
RESULTS OF REACTIONS OF OZONIZED COMPOUNDS WITH SODIUM BOROHYDRIDE

No.	Compound	Product 1	Yield, %	Product 2	Yield, %
I	1-Octene	1-Heptanol	74	[a]	
II	1-Hexadecene	1-Pentadecanol	79	[a]	
III	1,1-Diphenylethylene	Benzohydrol	74	[a]	
IV	Cyclohexene	1,6-Hexanediol	63		
V	Oleic acid	1-Nonanol	63	9-Hydroxynonanoic acid	46
VI	Cinnamyl alcohol	Benzyl alcohol	63	[a]	
VII	2-Phenyl-3-methylindole[b]	1-(2-Benzamidophenyl)-ethanol	93		

[a] No attempt to isolate. [b] Ref. 5.

Ozonolysis products, when reductively decomposed by reagents other than metal hydrides, yield aldehydes or ketones with yields generally ranging from poor to fair.[6] The metal hydrides give good yields of alcohols. The procedure has

decomposition reaction are the same with either sodium borohydride or lithium aluminum hydride, except in those cases where the original compound has substituents which behave differently with these reducing agents, *e.g.*, oleic acid, as follows:



(1) M. Hinder and M. Stoll, *Helv. Chim. Acta*, **33**, 1308 (1950).

(2) W. Voser, D. E. White, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **35**, 830 (1952).

(3) F. L. Greenwood, *J. Org. Chem.*, **20**, 803 (1955).

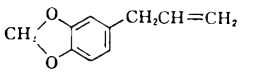
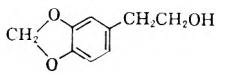
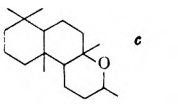
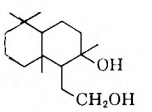
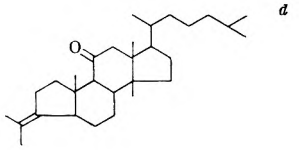
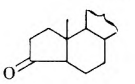
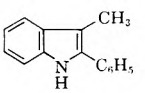
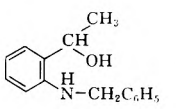
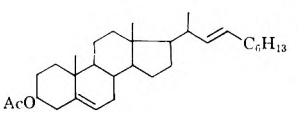
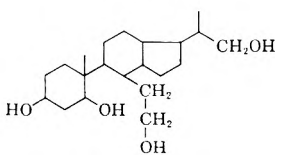
(4) H. Lettré and D. Hotz, *Angew. Chem.*, **69**, 267 (1957).

(5) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855 (1952).

(6) For a comprehensive review of different decomposition methods, see P. S. Bailey, *Chem. Revs.*, **58**, 925 (1958).

TABLE II

RESULTS OF REACTIONS OF OZONIZED COMPOUNDS WITH LITHIUM ALUMINUM HYDRIDE

No.	Compound	Product 1	Yield, %	Product 2	Yield, %
I	$CH_3(CH_2)_6CH{=}CH_2$	$CH_3(CH_2)_6CH_2OH$	70, 93[a]	[b]	
VIII			61	[b]	
V	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$CH_3(CH_2)_7CH_2OH$	79	$HOCH_2(CH_2)_7CH_2OH$	50
IX	$CH_3(CH_2)_3CH{=}CH{-}CH_2CH_3$[a]	$CH_3(CH_2)_3CH_2OH$	87	$CH_3CH_2CH_2OH$	87
X	$CH_3(CH_2)_3CH{=}CH{-}CH_3$[a]	$CH_3(CH_2)_3CH_2OH$	89	CH_3CH_2OH	21
XI	 [c]		17.5		
XII	 [d]				
VII	 [e]		72		
XIII	 [f]		60		

[a] Ref. 3. [b] No attempt to isolate. [c] Ref. 1. [d] Ref. 2, product obtained after reoxidation of the alcoholic intermediate. [e] Ref. 5. [f] Ref. 4.

With sodium borohydride the terminal acid group remains unaffected, but with the more reactive lithium aluminum hydride the acid group is reduced.

Reductive cleavages with sodium borohydride. With the experimental technique employed there is no need to isolate the ozonide itself, since the reductive decomposition is carried out directly with the ozonized solution. This lessens any hazards usually associated with the isolation of pure ozonides. Most of the common solvents which have been utilized for ozonations can be employed. We have used carbon tetrachloride, chloroform, ether and iso-octane. The reductive cleavage takes place in a heterogeneous solvent system, *e.g.*, a carbon tetrachloride solution of the ozonide and an aqueous alcoholic solution of sodium borohydride. Good contact between solutions is maintained by rapid stirring with a Hershberg type stirrer. The initial reaction is carried out at or below room temperature and a heating period after the initial combination of reactants improves the yields of alcoholic products. In the case of octene-1 the alcoholic cleavage product was obtained only after the reaction mixture was warmed to 50°.

In general, ozonides will decompose in aqueous media to yield aldehydes or ketones and carboxylic acids. Although aldehydes are reduced to alcohols with sodium borohydride, carboxylic acids are unaffected by this reagent except in a special catalyst system.[7] The breakdown of the ozonide to yield initially an acid which will then resist reduction results in a lowering of yield of the alcohol. However, initial breakdown to an aldehyde will not, in effect, lower the yield of alcohol. In an alkaline aqueous system decomposition to aldehydes is favored, and when sodium borohydride is dissolved in water some of the slightly alkaline BO_2^- ion is formed. Sodium borohydride does not cleave epoxides,[8] and there is not adequate information on the behavior of peroxides with sodium borohydride. For the present, the course of the borohydride decomposition is ambiguous.

Reductive cleavages with lithium aluminum hydride. To avoid the necessity of isolating the ozonide when lithium aluminum hydride is to be used to effect reductive cleavage, the ozonolysis should be performed in a solvent which is compatible with lithium aluminum hydride. This limits the choice of solvents to ethers and hydrocarbons. Ether has not been recommended as a solvent for ozonolysis as it leads to explosive peroxide formation. However, we used ether without incident. The use of this solvent was not considered objectionable, since the

(7) H. C. Brown and Rao Subba, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

(8) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, N. Y., 1956, p. 673.

peroxides are in solution and are broken down in the reaction with the metal hydrides.

The course of the reaction probably follows the sequence discussed by Gaylord[9] in which the initial reaction involves cleavage of the peroxide linkage, followed by subsequent reduction of the carbonyl intermediates.

EXPERIMENTAL

Materials. The starting materials were commercially obtained, and their purity was checked by either melting point, refractive index, and/or infrared spectrum. The oleic acid was a clear Fisher U.S.P. liquid.

Ozonations. The ozonator was a modified version of the type described by Henne and Perilstein.[10] Most of the compounds were ozonized at a rate of 0.015 mol. ozone/hr. using 8% ozone by volume. The course of many of the ozonations was determined by removing aliquots periodically and recording their infrared spectrum, and noting the disappearance of the C=C stretching frequency at *ca.* 6.2 μ. This technique is useful with compounds which do not react rapidly with ozone, and in which case the end point is difficult to determine by the potassium iodide absorption trap method. This latter technique was used in some experiments.

A typical procedure, utilizing 1-hexadecene and a sodium borohydride reductive cleavage, is described below. The other reactions are summarized.

Sodium borohydride reductive cleavage reactions. 1-Hexadecene (II). 1-Hexadecene (5.0 g., 0.022 mol.) was dissolved in 50 ml. chloroform (reagent grade) and ozonized at −20°. The end point was determined by recording the infrared spectrum at intervals, and following the decrease in intensity of the C=C stretching absorption band at 6.5 μ. At the termination of the ozonation, new bands were present at 9.0–9.48 μ, characteristic of some ozonides.[11,12] The ozonide solution was transferred to a 2-l. 3-necked round-bottom flask equipped with a Hershberg stirrer, a condenser through which a thermometer was suspended into the flask, and an addition funnel. Sodium borohydride (Metal Hydrides Co., 98% purity) (6.69 g., 0.177 mol.) dissolved in 50 ml. cold 50% aqueous ethanol was added slowly to the stirred ozonide mixture. The temperature was maintained at 25° by occasional ice bath cooling. The reaction mixture was then warmed in a water bath for 2.5 hr. with continued stirring. After standing overnight at room temperature, the mixture was acidified with 10% sulfuric acid, the chloroform layer separated, and the aqueous layer further extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and the chloroform removed by warming in a stream of nitrogen. The residue was recrystallized from aqueous ethanol to a constant m.p. of 43.8° sharp, lit.[13] 44°. The infrared spectrum was identical with a reference spectrum of 1-pentadecanol. The yield of purified product was 4.01 g. (79.0%).

1-Octene. This compound (2.5 g., 0.022 mol.) was ozonized in 25 ml. chloroform at −20° and the end point was determined by disappearance of the 6.15 μ band of the infrared spectrum of the reaction mixture. The reductive cleavage was carried out with an 8 to 1 ratio of sodium borohydride to compound at 0°, followed by a 1-hr. heating period at 50°. Heptyl alcohol in 74% yield was obtained by ether extraction, n^{20} = 1.4240, lit.[14] n_D^{20} = 1.4245. The infrared spectrum of the product was identical with that of an authentic specimen.

Cyclohexene (IV). Cyclohexene (1.50 g., 0.018 mol.) in 25 ml. chloroform was ozonized at 0° until the 6.2 μ band in the infrared spectrum of the reaction mixture disappeared. The resinous ozonide was dissolved by addition of absolute ethanol and then decomposed with sodium borohydride as in the previous experiments. The acidified reaction mixture was evaporated almost to dryness in a Rinco rotating evaporator. The residue was taken up in a slight amount of water, made basic with dilute sodium hydroxide, and extracted with chloroform. The residue after evaporation of the chloroform was recrystallized from aqueous ethanol to a constant melting point, 42.0–42.5°, lit.[15] 42°. The yield of 1,6-hexanediol was 63%.

Oleic acid. The ozonation was carried out with oleic acid (5.0 g., 0.018 mol.) in 50 ml. chloroform at 0°. A rapid color change in a potassium iodide trap after the reaction flask indicated the end point. The ozonide was cleaved as in the hexadecene reaction. The acidified reaction mixture was extracted with ether and the ether solution washed with dilute sodium hydroxide. 1-Nonanol was obtained in 62.3% yield from the ethereal portion, with n_D^{20} = 1.4334, lit.[16] n_D^{20} = 1.4338. The infrared spectrum was identical to an authentic spectrum and the *N*-phenylcarbamate derivative melted at 68.5–69.0°, lit.[17] 69°. Ether extraction of the reacidified aqueous basic solution yielded a white solid residue which after recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) afforded material melting at 49.5–51.0°, lit.[18] 51–51.5°. A neutralization equivalent gave a value of 174.2. Calculated for 9-hydroxynonanoic acid ($C_9H_{18}O_3$), neut. equiv. = 176.8.

Cinnamyl alcohol (VI). The ozonation was carried out with cinnamyl alcohol (5.0 g., 0.037 mol.) in 50 ml. ether at 0° to the calculated end point. The reductive decomposition was carried out as in the hexadecene reaction. Ether extraction of the acidified reaction mixture yielded a liquid residue which on distillation afforded a 63.1% yield of benzyl alcohol. The infrared spectrum of the product was identical with that of an authentic specimen, and the product had n_D^{20} = 1.5396, lit.[19] n_D^{20} = 1.53955.

1,1-Diphenylethylene (III). 1,1-Diphenylethylene (2.0 g., 0.011 mol.) was ozonized in 20 ml. iso-octane at 0° with the stoichiometric quantity of ozone as determined by potassium iodide assay. The ozonide, which had precipitated, was redissolved by the addition of *p*-dioxane, and the solution then reductively decomposed as in the hexadecene reaction. The reaction mixture was evaporated in a Rinco rotating evaporator at 50° *in vacuo*. The slushy residue was redissolved in a minimum of water and this solution extracted with ether, from which was obtained a solid residue. Three recrystallizations from ether–petroleum ether (b.p. 30–60°) afforded 1.52 g. (74%) of diphenyl carbinol, m.p. 68.0–68.5°, lit.[20] 68–69°.

Lithium aluminum hydride reductive cleavage reactions. 3,4-Methylenedioxy-1-allylbenzene (VIII). 3,4-Methylenedioxy-1-allylbenzene (3.0 g., 0.018 mol.) was dissolved in 20 ml. dry ether and ozone passed through the solution at 0° for the theoretical time (as determined by potassium iodide assay). The ozonide was decomposed at 0° by slowly adding

(9) Reference 8, p. 686–687.

(10) A. L. Henne and W. L. Perilstein, *J. Am. Chem. Soc.*, **65**, 2183 (1943).

(11) R. Criegee, A. Kerchow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).

(12) P. S. Bailey and S. B. Mainthia, *J. Org. Chem.*, **23**, 1089 (1958).

(13) A. Gascard, *Ann. chim. (Rome)*, **15**, 332 (1921).

(14) M. L. Sherrill, *J. Am. Chem. Soc.*, **52**, 1982 (1930).

(15) R. D. Haworth and W. Perkin, *J. Chem. Soc.*, 598 (1894).

(16) V. J. Harding and C. Weizmann, *J. Chem. Soc.*, 304 (1910).

(17) S. M. McElvain, *The Characterization of Organic Compounds*, revised edition, The Macmillan Co., New York, 1953, p. 202.

(18) P. Chitt and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

(19) J. Meisenheimer, *Ber.*, **41**, 1420 (1908).

(20) F. Y. Wiselogle and H. Sonneborn, *Org. Syntheses*, Coll. Vol. 1, H. Gilman and A. H. Blatt, eds., John Wiley & Sons, New York, 1941, p. 90.

to a 3-fold (stoichiometric)[3] excess of lithium aluminum hydride in ether with stirring in an apparatus adequately protected from atmospheric moisture. The reaction mixture was then further decomposed by addition of 5 ml. water followed by 45 ml. 15% sulfuric acid. The product, 3,4-methylenedioxyphenylethyl alcohol, was obtained in 62% yield by ether extraction, followed by distillation, n_D^{20} = 1.5500, lit.[21] n_D^{20} = 1.5478. The phenylurethan derivative was prepared and melted at 96.6–97.0°, lit.[22] 96.4–97.0°.

Oleic acid. Oleic acid (5.0 g., 0.018 mol.) was ozonized in 40 ml. *n*-heptane solution by a procedure similar to that described in the previous paragraph. The ozonide precipitated and ether was added to obtain a solution which was then reductively decomposed with lithium aluminum hydride. Ether extraction followed by distillation *in vacuo* afforded the two cleavage products. A 79.4% yield of 1-nonanol with n_D^{20} = 1.4334, lit.[16] n_D^{20} = 1.43347 was obtained. The infrared spectrum of the product was identical with that of an authentic specimen. 1,9-Nonanediol obtained in 49.5% yield melted at 44.2°, lit.[23] 45.5°.

1-Octene (I). 1-Octene (2.5 g., 0.022 mol.) was ozonized in 25 ml. carbon tetrachloride at 0°. The solvent was evaporated at room temperature in a current of nitrogen. The residual liquid was dissolved in dry ether and reductively decomposed as in the preceding reaction. Heptanol in 70% yield was obtained by ether extraction, n_D^{20} = 1.4240, lit.[14] n_D^{20} = 1.4245. The infrared spectrum of the product was identical with that of an authentic specimen.

NATICK, MASS.

(21) F. Semmler and K. Bartelt, *Ber.*, **41**, 2752 (1908).

(22) A. L. Bluhm, Ph.D. thesis, Boston University, 1957.

(23) R. Scheuble and E. Loebl, *Monatsh.*, **25**, 1081 (1904).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY SECTION, DIVISION OF CHEMISTRY, NATIONAL BUREAU OF STANDARDS]

Complexes of Diols with Cuprammonium Reagent

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The chelates present in cuprammonium solutions of methyl α-D-galactopyranoside, sucrose, di-D-fructopyranose 1,2′:2,1′-dianhydride, and the *cis*- and *trans*-1,2-cyclohexanediols have been studied by measurements of optical rotation and optical density, and the results evaluated by the method of continuous variation. In each case, a compound having a copper to diol ratio of 2:1 was found. Under the conditions stipulated, there is no evidence of compounds having a copper to diol ratio of 1:1.

The reaction of cuprammonium reagent and the diol groupings of carbohydrates has found extensive practical and theoretical use. Nevertheless, despite the importance of the reaction, the complexes formed have not been isolated and little has been reported on their structures.

The present investigation had its beginning in some measurements of optical rotation conducted by Isbell and Snyder on dextrans in cuprammonium solution.[1] The optical rotation varied widely with the concentrations of both the dextran and the copper reagent. In order to obtain some understanding of this behavior, it seemed desirable to investigate the composition and structure of cuprammonium–diol complexes. Isbell and his associates[2] have shown that in the carbohydrate-borate system, at least three diol-borate complexes exist. For practical and theoretical reasons, copper complexes derived from sucrose, methyl α-D-galactopyranoside, di-D-fructopyranose 1,2′:2,1′-dianhydride, and the *cis*- and *trans*-1,2-cyclohexanediols were selected for the investigation. The cuprammonium compounds from these compounds were studied by measurements of optical rotation (at 436 mμ) and optical density (at 350 mμ).

Measurements conducted with a photoelectric spectropolarimeter revealed a dependence of optical rotation on the proportions of both the diol and the copper reagent in the solution. The results indicated that *two moles of copper reagent react with each molar equivalent of the diol grouping.* This observation was substantiated by examination of optical density employing the method of continuous variation.

Discussion of previous work. Cuprammonium solution presumably contains di-, tri-, tetra-, and penta-ammonia complexes of copper. Bjerrum[3] has determined the stability constants of the four copper–ammonia cations and has shown that, in the presence of excess ammonia (as for the cuprammonium solutions used in the present study), the copper–tetrammonium complex $[Cu(NH_3)_4^{++}]$ greatly predominates.

In 1857, Schweizer[4] published the observation that cellulose disperses in cuprammonium solution. Since then, many practical applications of this reaction have been made.[5] The cuprammonium ion exists only in solutions having a high concentration of ammonia. Therefore, the conditions for forming a complex with a diol are restricted to a limited range of *p*H. Upon acidification, the com-

(1) H. S. Isbell and C. F. Snyder, unpublished work (contained in NBS Report 2400, March 31, 1953).

(2) H. S. Isbell, J. Brewster, N. B. Holt, and H. L. Frush, *J. Research Natl. Bur. Standards*, **40**, 129 (1948).

(3) J. Bjerrum, *Chem. Revs.*, **46**, 381 (1950).

(4) E. Schweizer, *J. prakt. Chem.*, **72**, 109, 344 (1857).

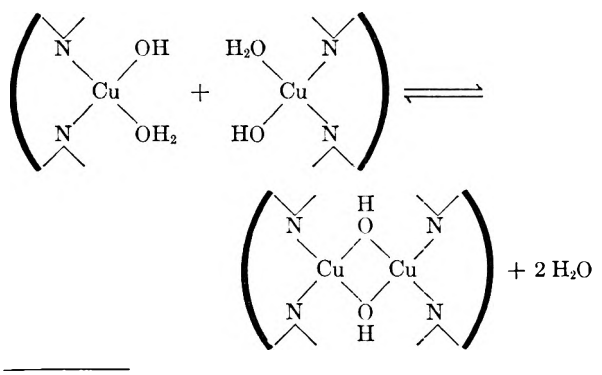
(5) E. Heuser, *The Chemistry of Cellulose*, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 161.

plex of the diol with the copper–ammonia is decomposed, usually with regeneration of the unchanged diol. [However, in some cases, side reactions occur. Thus, when a cellulose–cuprammonium complex is exposed to air and ultraviolet light (especially light in the range of 300 to 400 mμ), the viscosity smoothly decreases, and the solubility of the regenerated "cellulose" is found to have increased. The change seems to be associated with an effect on groups other than "the diol grouping" (the hydroxyl groups on carbon atoms 2 and 3 of the D-glucose residues), since comparable effects are not observed with the complexes of nonreducing monosaccharides.]

Traube and associates[6] determined the amount of copper removed from copper hydroxide solution by the addition of a known weight of cellulose together with a known weight of ethylenediamine. On the basis of their findings, they proposed the formula $[(C_6H_8O_5)_2Cu]$ $[Cu(NH_3)_4]$, having a 1:1 ratio of copper to diol, for the cellulose-cuprammonium compound. Subsequent workers have tacitly assumed a 1:1 copper-diol ratio for all other diols so studied.

Reeves[7] used the reaction of pyranoid sugars (and derivatives) with cuprammonium to study pyranoid conformations. He found that reaction takes place readily when the two oxygen atoms of a diol are separated by 2.51 Å, but that no reaction occurs when they are more than 3.45 Å apart. He found[14] that equilibrium constants for the reaction of 0.01*M* cuprammonium reagent with 1,6-anhydro-β-D-mannopyranose ("D-mannosan") support "a simple bimolecular association of the form mannosan + cupra ⇌ [mannosan-cupra]."

In recent studies[8,9] on the hydrolytic tendencies of metal chelate compounds, it is suggested that Cu(II) chelates of a series of diamines form monohydroxo complexes that are in equilibrium with binuclear compounds.



Similar compounds have not been reported for carbohydrate complexes, but their formation might be anticipated. Copper–diol complexes of this type (each diamine of the above equation being replaced by a diol), as well as those represented by Reeves' equation, require a 1:1 copper-diol proportion.

Discussion. Sucrose, methyl α-D-galactopyranoside, and di-D-fructopyranose 1,2′:2,1′-dianhydride were selected as representative carbohydrates containing at least one active diol grouping per molecule and various numbers of extra hydroxyl groups. In order to be sure that the results did not reflect the reactions of the single hydroxyl groups, *cis*- and *trans*-1,2-cyclohexanediol were included in the study. Kwart and Gatos[10] have shown by conductivity measurements that the latter two compounds react with the cuprammonium reagent.

The hydroxyl groups of sucrose are so arranged that the cuprammonium reagent can react with either the 3,4-diol or the 4,5-diol of the D-glucose residue; the D-fructofuranose residue contains no reactive diol grouping. Methyl α-D-galactopyranoside is similar to the D-glucose residue of sucrose in that the hydroxyl groups of both C3-C4 and C4-C5 could be involved in the reaction. Since one hydroxyl group (at C4) is common to both these diol groupings, both compounds contain only one active diol grouping per molecule. Di-D-fructopyranose 1,2′:2,1′-dianhydride, however, contains two active diol groupings per molecule. Hydroxyl groups at C4 and C5 of each D-fructopyranose residue form an active diol grouping, but the hydroxyl group at C3 would not be expected to enter into the reaction.

It is well known that the interaction of many carbohydrates with cuprammonium produces a large shift in their specific rotation at 436 mμ. Measurement of the optical rotation of the blue solutions with visual polarimeters is unsatisfactory, but accurate values were obtained with a photoelectric spectropolarimeter. Cuprammonium solutions of the selected carbohydrates were prepared in which the copper-diol ratio was varied. In each case, the specific rotation (calculated on the basis of carbohydrate content) changed rapidly, until a copper-diol ratio of 2:1 was reached; it then became relatively stable. These results indicated that *two* copper atoms are required for the complexing of one diol group.

The optical rotation of varying concentrations of di-D-fructopyranose 1,2′:2,1′-dianhydride is typical of these reaction changes (see Table 1). Observations made after the solutions had been stored for twenty-four hours are included with those made at the time of preparation. The small difference in specific rotation for the two series of observations indicates that the complexing reaction takes place with great rapidity.

(6) W. Traube, G. Glaubitt, and V. Schenck, *Ber.*, **63**, 2083 (1930); W. Traube and A. Funk, *Ber.*, **69**, 1476 (1936).

(7) R. E. Reeves, *Advances in Carbohydrate Chem.*, **6**, 107 (1951).

(8) R. Gustafson and A. Martell, *J. Am. Chem. Soc.*, **81**, 525 (1959).

(9) R. Courtney, R. Gustafson, S. Chaberek, and A. Martell, *J. Am. Chem. Soc.*, **81**, 519 (1959).

(10) H. Kwart and G. Gatos, *J. Am. Chem. Soc.*, 80, 881 (1958).

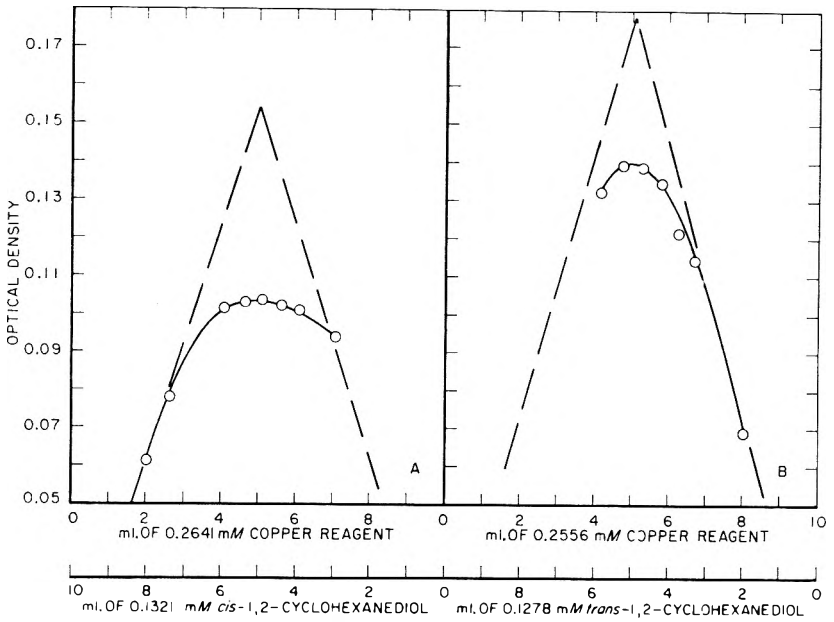


Fig. 1. Experimental observations on the reaction of *cis*-and *trans*-1,2-cyclohexanediols and cuprammonium reagent. (In curve A, the maximum at 5 ml. of 0.2641 m*M* copper and of 0.1321 m*M* *cis*-1,2-cyclohexanediol indicates a 2:1 ratio of copper to diol in the reaction product. In curve B, the maximum at 5 ml. of 0.2556 m*M* copper and of 0.1278 m*M* *trans*-1,2-cyclohexanediol indicates a 2:1 ratio of copper to diol in the reaction product.)

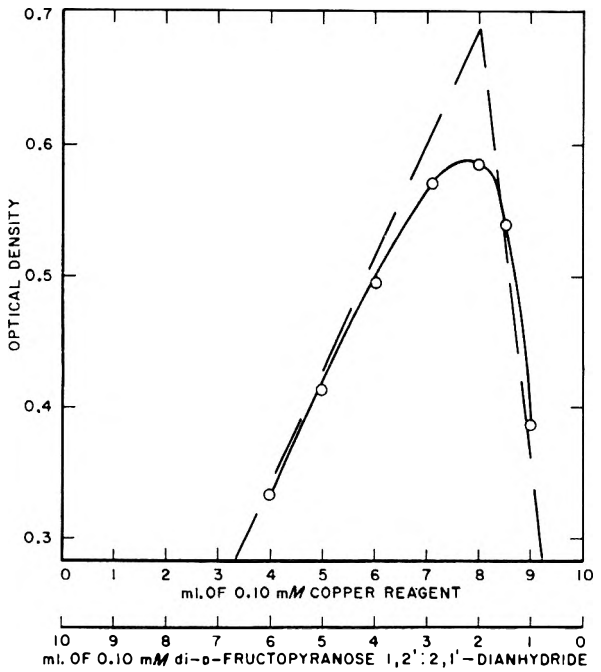


Fig. 2. Experimental observations on the reaction between di-D-fructopyranose 1,2′:2,1′-dianhydride and cuprammonium reagent. (The maximum absorption observed when 8 ml. of 0.1 m*M* copper reagent and 2 ml. of 0.1 m*M* di-D-fructopyranose 1,2′:2,1′-dianhydride react indicates combination of eight molecules of copper per two molecules of the disaccharide for the reaction product. This is equivalent to two molecules of copper per molar equivalent of diol grouping.)

The composition of the complex was further studied by the method of continuous variation.[11–13]

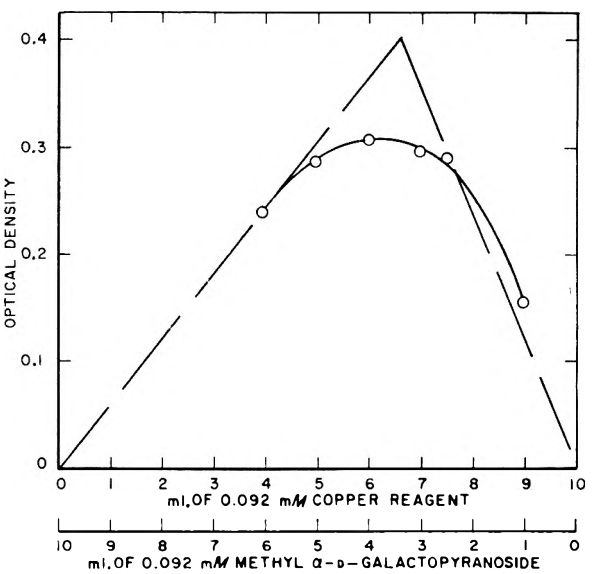


Fig. 3. Experimental observations for the reaction of methyl α-D-galactopyranoside and cuprammonium reagent. (The maximum absorption observed in the region of 6.7 ml. of 0.092 m*M* copper reagent and 3.3 ml. of 0.092 m*M* methyl α-D-galactopyranoside indicates two molecules of copper per molecule of glycoside in the reaction product.)

By this method, measurements of some physical property of the reaction product are made on a

(11) P. Job, *Ann. chim.*, [10] 9, 113 (1928).

(12) W. C. Vosburgh and G. R. Cooper, *J. Am. Chem. Soc.*, **63**, 437 (1941).

(13) A. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Academic Press Inc., New York, N. Y., 1952, p. 29.

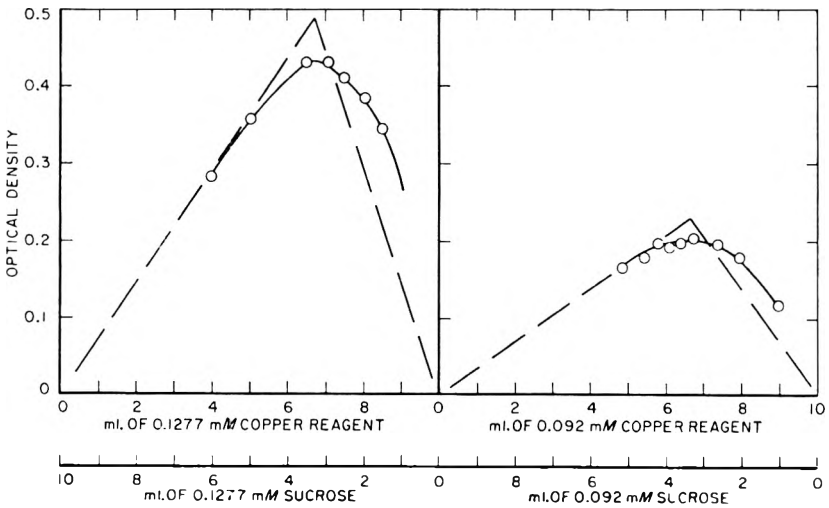


Fig. 4. Experimental observations on the reaction between sucrose and cuprammonium reagent. (The maximum absorption observed in the region of 6.7 ml. of cuprammonium reagent and 3.3 ml. of sucrose solution of equal molality indicates two molecules of copper per sucrose molecule in the reaction product)

TABLE I

Optical Rotation of Di-D-Fructopyranose 1,2′:2,1′-Dianhydride in Cuprammonium Reagent

Di-D-fructopyranose 1,2′:2,1′-dianhydride (g./100 ml. of sol.)	Molar Ratio Cu[a]/disaccharide	Molar Ratio Cu/diol	α_{436}[b,c]	$[\alpha]_{436}$[c]	$[\alpha]_{436}$[d]
8.062	1.02	0.51	1.638	81.3	81.1
6.542	1.26	0.63	1.983	121.2	120.2
4.236	1.95	0.97	2.436	230.0	227.0
2.030	4.07	2.00	2.015	397.1	394.1
1.274	6.48	3.20	1.387	403.8	443.3
0.784	10.50	5.20	0 801	408.6	429.5
0.257	32.10	16.00	0 268	417.1	442.0

[a] The reagent contained 1.6181 g. of copper per 100 ml. [b] The solutions were contained in a 0.25-dm. polarimeter tube. The zero point was observed on the cuprammonium reagent. All rotations were measured by use of a photoelectric spectropolarimeter (manufactured by O. C. Rudolph and Sons), in a room maintained at 20°. [c] After 24 hours. [d] Initial.

series of reaction mixtures in which the sum of the molar proportions of the reactants is kept constant. Measurements of optical density were made on (a) the cuprammonium reagent and (b) reaction mixtures containing the cyclohexanediols at wave lengths from 320 to 400 mμ. It was found that increased optical density accompanies the copper–diol complexing. This observation is in agreement with Reeves' results on D-mannosan–cupra solution.[14] The wave length 350 mμ was selected as suitable for making observations during the present study.

At each concentration, the optical density of the cuprammonium reagent-blank was subtracted from that of the reaction mixture. The values resulting represent the increase in optical density produced by the copper-diol complex. They are, therefore, proportional to the concentration of copper-diol complex. Graphs obtained by plotting the optical densities observed at each concentration against the concentration of copper are shown in Figs. 1–4. In these applications of the method of continuous variation, the maximum absorption occurs when the amounts of diol and copper used are in the same ratio as that in which they occur in the reaction product.

Absorption data observed when 0.1321 m*M* *cis*-1,2-cyclohexanediol reacted with 0.2641 m*M* cuprammonium reagent, and when 0.1278 m*M* *trans*-1,2-cyclohexanediol reacted with 0.2556 m*M* copper reagent are shown in Fig. 1. Ammonia concentration remained constant throughout each series. In both cases, the optical density reaches a maximum when the concentration of diol used is one half that of the copper, thus giving a 2.1 ratio of copper to diol.

Experimental data presented in Fig. 2 indicate maximum concentration of the complex when an 8:2 ratio of copper to di-D-fructopyranose 1,2′:2,1′-dianhydride exists. Again, the copper-diol ratio is 2:1 because each molecule of anhydride contains two diol groupings.

Sucrose and methyl α-D-galactoside contain one active diol grouping per molecule. Figs. 3 and 4 show that the maximum optical density occurs when the molar ratio of copper to carbohydrate is 2, *i.e.*, copper to diol is 2:1.

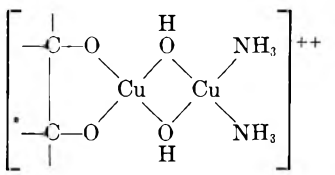
When a large excess of copper is present, some reaction appears to take place with hydroxyls not included in the active diols. This is indicated by the dissymmetry of the absorption curves in Fig. 4, based on the reaction of sucrose with its six additional hydroxyl groups. In contrast, the experimental curves of Fig. 1, representing the reaction of

(14) R. E. Reeves, *J. Am. Chem. Soc.*, **73**, 957 (1951).

cyclohexanediols with cuprammonium reagent, more nearly approach the theoretical curves.

A remote possibility is that another (soluble) copper-containing compound (not involving a diol) is formed simultaneously with the copper-diol complex. Should this occur, the copper–diol ratio in the complex could be 1:1.

The structure of a probable cuprammonium–diol complex having a copper–diol ratio of 2:1 is as follows. Coordination compounds of copper are planar; thus, the ammonia groups must be located at the four corners of a square, with the copper atom in the middle. A possible interpretation is that a binuclear complex of the form



exists in the strongly ammoniacal solution. Occurrence of such a reaction would account for (a) the decrease in conductivity that accompanies formation of the copper–diol complex and (b) the 2:1 copper–diol ratio.

EXPERIMENTAL

The cuprammonium reagent was prepared, and analyzed for copper and ammonia, according to the procedure described by TAPPI.[15] Each diol was dissolved in concentrated ammonia water in which the ammonia concentration was the same as that in the cuprammonium reagent. An appropriate amount of the cuprammonium reagent and of the respective diol solution were placed in a 10-ml. flask, and the solution was made up to 10 ml. with concentrated ammonia water. All solutions were kept in an ice bath until each reaction mixture had been brought to final volume. Each was then transferred to a capped vial and allowed to warm up to room temperature. Ammonia analyses on a series of sucrose–cuprammonium reaction mixtures showed that a uniform ammonia concentration was still present after 24 hr. Absorption observations were made with a Beckman spectrophotometer at room temperature; cell depths of 0.4 cm. were used. In all experiments, the absorption values of the blanks, which contained the cuprammonium reagent plus ammonium hydroxide, were found to follow Beer's law. The experimental points shown in Figs. 1–4 were obtained by subtracting the absorption of the blank cuprammonium solution from that of the reaction mixture at each concentration.

cis-1,2-Cyclohexanediol was prepared by oxidation of cyclohexene with permanganate, according to the procedure of Clarke and Owen,[16] m.p. 98°. *trans*-1,2-Cyclohexanediol was prepared by oxidation of cyclohexene with performic acid, as described by Roebuck and Adkins,[17] m.p. 104–105°.

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(15) Recommended Practices of the Technical Association of the Pulp and Paper Industry, T 206 m-55.

(16) M. Clarke and L. Owen, *J. Chem. Soc.*, 318 (1949).

(17) A. Roebuck and H. Adkins, *Org. Syntheses*, **28**, 35 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LITHIUM CORP. OF AMERICA]

Analysis and Stability of *n*-Butyllithium Solutions in *n*-Heptane

CONRAD W. KAMIENSKI AND DONALD L. ESMAY

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The purity of the ether has been shown to have a marked effect when the "double titration" procedure is used in analyzing solutions for *n*-butyllithium content. Results of these studies show that a reasonably accurate determination of the *n*-butyllithium content in *n*-heptane solutions is obtained by a single, direct acid titration of a hydrolyzed sample of the solution. Determination of the *n*-butyl chloride content by use of the disodium biphenyl reagent has been shown to be suitable for direct analysis of *n*-butyllithium solutions in *n*-heptane. Essentially no change in *n*-butyllithium content occurred on storing *n*-heptane solutions at room temperature for over three months. The density at 26° of a 2.59 molar solution of *n*-butyllithium in *n*-heptane was found to be 0.697 ± 0.001.

The analysis and stability of organolithium solutions have been of continuing interest for many years. Stability studies have been complicated by the necessity of determining the amount of an organolithium compound present in the presence of compounds formed during its deterioration. Any one of several methods can be used for such an analysis with varying degrees of accuracy and convenience. The "double titration" or "indirect titration" procedure developed by Gilman and Haubein[1] probably has been used the most widely. This procedure involves hydrolyzing directly one sample of the organolithium solution followed by acid titration to determine the total base present. A second sample is treated with benzyl chloride then hydrolyzed and titrated with acid. As most organolithium, particularly, alkyllithium, compounds react rapidly with benzyl chloride to form non-alkaline products, this titration determines the residual alkalinity due to materials originally present which did not contain carbon-lithium bonds. The difference between the total alkalinity and the residual alkalinity should provide an accurate measure of the amount of organolithium compound present. Certain difficulties encountered in obtain-

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

TABLE I

VARIATION OF RESIDUAL ALKALINITY WITH VARYING REACTION CONDITIONS

Run No.	Solvent for *n*-Butyllithium	Normality of *n*-Butyllithium Solution	Vol. of Aliquot, Ml.	Solvent[a] for Reaction with Benzyl Chloride, Ml.	Benzyl Chloride, Ml.	Alk. Titer of[b] Benzyl Chloride Reaction Mixture, Meq./Ml.	Description of Reaction Mixture
1	*n*-Heptane	1.96	1	*n*-Heptane, 10	1	1.42	No ppt.[c]
2	*n*-Heptane	1.96	1	Ether, 30	1	0.764	Ppt.[c,d]
3	*n*-Heptane	1.96	1	Ether, 50	2 (R.A.)[e]	1.85	Slight ppt.[f,g]
4	*n*-Heptane	1.96	1	*n*-Heptane, 10	2 (R.A.)	1.38	No ppt.[c]
5	Anhyd. Et_2O	0.50	5	Ether, 10	1	0.31	Ppt.[c,d]
6	Anhyd. Et_2O	1.29	5	Ether, 10	2	0.20	Ppt.[c,d]
7	Anhyd. Et_2O	1.29	5	Ether, 10	2 ϕ-CH_2Br	0.19	No ppt.[c,d]
8	Anhyd. Et_2O	1.00	5	Ether, 10	1	0.23	Ppt.[c,d]
9	Anhyd. Et_2O	1.00	5	Ether, 10	2	0.22	Ppt.[c,d]
10	Anhyd. Et_2O	1.00	10	Ether, 10	3	0.16	Ppt.[c,d]

[a] The *n*-heptane was Phillips Pure Grade (99 mol.%) which had been dried over sodium ribbon. The ether was Mallinckrodt Anhydrous Grade which had been shaken with lithium hydride and stored several months over the same reagent. [b] Color test I negative before hydrolysis. [c] Heat evolved. [d] Yellow color. [e] (R.A.) = reverse addition. [f] No heat evolved. [g] No color formed.

ing consistent results by the "double titration" method were recently reported[2] which parallel in some respects observations in our laboratories. This prompts us to report the results of certain analytical and associated experiments carried out during a thorough study of the preparation of *n*-butyllithium.

The data given in Table I are an indication of some of the inconsistent results which we obtained with the "double titration" procedure during our early studies. For example, the first four runs listed show that rather minor changes in the analytical procedure had gross effects on the answers obtained. The results of Runs 6 and 7 confirmed an early conclusion that the difficulties encountered were not necessarily associated with the benzyl chloride being used since essentially identical results were obtained using benzyl bromide in place of the benzyl chloride.

Review of a large number of data, such as given in Table I, indicated that the use of impure ether could be the cause of the erratic results. The results given in Table II provided confirming evidence of this concept in that increasing the amount of ether used in the "double titration" apparently increased the amount of non-butyllithium alkaline material in the sample. This could be explained by assuming that the ether contained a limited amount of impurity, for example, water, which reacted with the *n*-butyllithium. Extrapolation of the results given in Table II indicated that sufficient impurity should be present in 100 ml. of the ether to destroy all of the *n*-butyllithium in a 1-ml. aliquot. This proved to be essentially correct.

(2) A. F. Clifford and R. R. Olsen, Papers presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April 5–10, 1959.

TABLE II

VARIATION OF RESIDUAL ALKALINITY WITH VARYING AMOUNTS OF SLIGHTLY IMPURE ETHER[a]

Ether,[b] Ml.	Acid Used in Titration, Ml.	Base in Sample, Meq.
5	0.65[c]	0.33
7.5	0.72	0.36
10	1.08[c]	0.54
15	1.21[c]	0.61
20	1.47[c]	0.74
25	1.87[c]	0.94
30	2.34	1.18

[a] Constants: Normality of *n*-heptane solution of *n*-butyllithium = 1.97. Volume of aliquot used = 1.0 ml. Volume of benzyl chloride used = 1.0 ml. [b] The ether was Mallinckrodt Anhydrous Grade which had been shaken with lithium hydride and then stored over it for several months. [c] Average of two values.

TABLE III

VARIATION OF RESIDUAL ALKALINITY WITH THE SIZE OF THE ALIQUOT USING SLIGHTLY IMPURE ETHER

Aliquot,[a] Ml.	Total Base in Aliquot, Meq.	Benzyl Chloride, Ml.	Ether,[b] Ml.	Acid Used in Titration, Ml.	Base in Blank, Meq.	% Total Base in Blank
1	2	0.5	20	1.88	0.94	47
2	4	1.0	20	2.04[c]	1.02	26
3	6	2.0	20	2.09	1.05	18
5	10	2.5	20	2.49	1.25	13
10	20	5.0	20	3.15	1.58	8

[a] Aliquots were taken from the same *n*-butyllithium solution described in Table II. [b] The ether was Mallinckrodt Anhydrous Grade which had been shaken with lithium hydride and stored over it for several months. [c] Average of two values.

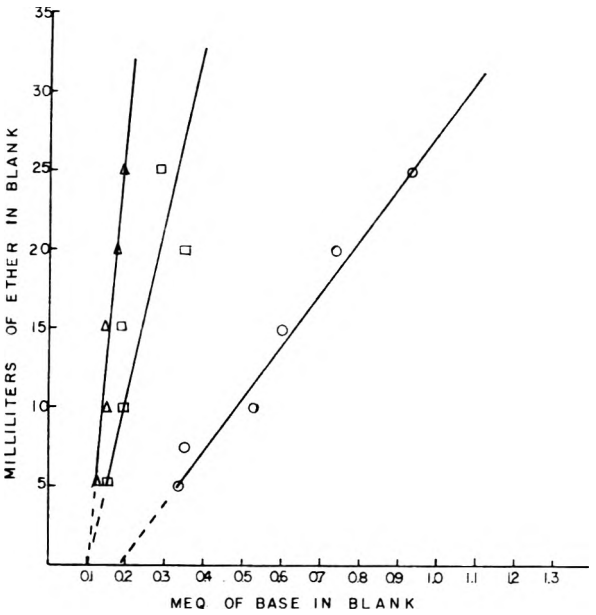

Fig. 1. Variation of residual alkalinity with varying methods of purifying the ether solvent. See Tables II and IV

△ Ether dried by lithium aluminum hydride
□ Sodium-dried ether
○ Ether dried by lithium hydride

The results shown in Table III provided further evidence that slightly impure ether was the cause of our trouble. As the size of the *n*-butyllithium aliquot was increased, there was a regular decrease in the per cent of the total base found in the benzyl chloride "blank."

The data given in Tables IV and V show that use of rigorously purified ether essentially eliminated the variations reported in Tables II and III. The ether was purified by refluxing over and then distilling from lithium aluminum hydride into carefully dried storage containers. In order to emphasize the above results, selected data from Tables II and IV and from Tables III and V are shown graphically in Figs. 1 and 2, respectively. Included are some results from similar tests using ether freshly purified over sodium wire. Although the sodium-dried ether gave results that were

TABLE IV

VARIATION OF RESIDUAL ALKALINITY WITH VARYING AMOUNTS OF PURIFIED ETHER[a]

Ether,[b] Ml.	Acid Used in Titration, Ml.	Base in Blank, Meq.
5	0.23	0.115
10	0.30	0.150
15	0.30	0.150
20	0.34	0.170
25	0.38	0.190

[a] Same constants used as in Table II. [b] The ether was Mallinckrodt Anhydrous Grade which had been refluxed over $LiAlH_4$ for 3 hr. and distilled from this reagent into thoroughly dried glass-stoppered bottles.

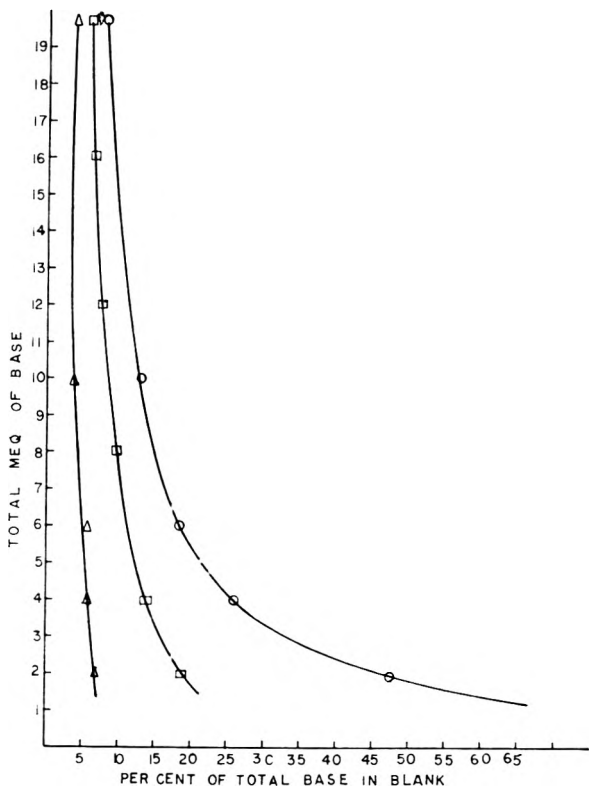

Fig. 2. Variation of residual alkalinity with variation in the size of the *n*-butyllithium aliquot using ether purified in various ways. See Tables III and V

△ Ether dried by lithium aluminum hydride
□ Sodium-dried ether
○ Ether dried by lithium hydride

better than those obtained with the ether which had been stored several months over lithium hydride, the best results were obtained with the ether rigorously purified with lithium aluminum hydride. It is quite possible, of course, that distillation from sodium or lithium hydride, or that use of some other purifying method will give an ether solvent of equivalent purity.

The data given in Tables VI and VII, and graphically presented in Fig. 3, show that consistent

TABLE V

VARIATION OF RESIDUAL ALKALINITY WITH THE SIZE OF THE ALIQUOT USING PURIFIED ETHER

Aliquot,[a] Ml.	Total Base in Aliquot, Meq.	Benzyl Chloride, Ml.	Ether,[b] Ml.	Acid Used in Titration, Ml.	Base in Blank, Meq.	% Total Base in Blank
1	2	0.5	20	0.28	0.14	7.0
2	4	1.0	20	0.45	0.225	5.6
3	6	2.0	20	0.69	0.345	5.7
5	10	2.5	20	0.83	0.415	4.1
10	20	5.0	20	1.60	0.80	4.0

[a] Aliquots were taken from the same *n*-butyllithium solution described in Table II. [b] The ether was Mallinckrodt Anhydrous Grade which had been refluxed over $LiAlH_4$ for 3 hr. and distilled from this reagent into thoroughly dried glass-stoppered bottles.

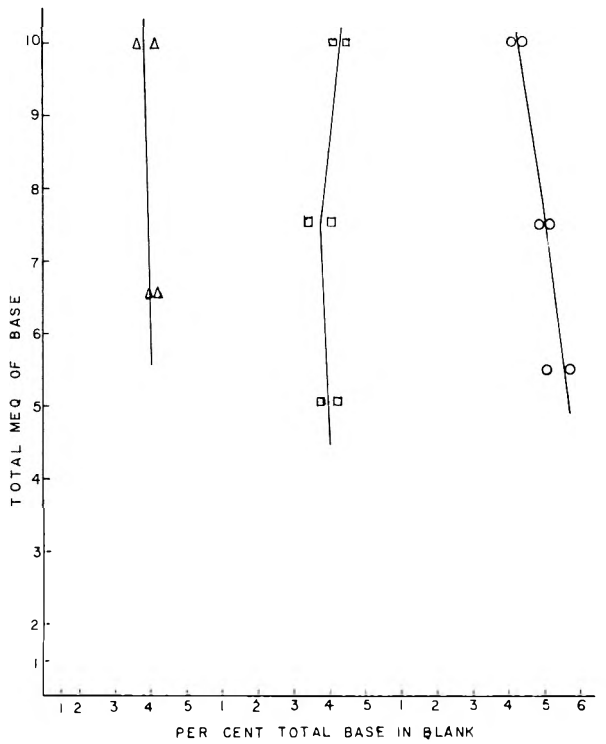

Fig. 3. Variation of residual alkalinity with various concentrations of *n*-butyllithium in *n*-heptane using ether dried by lithium aluminum hydride. See Table VI

△ 3.31 molar *n*-butyllithium soln.
□ 2.51 molar *n*-butyllithium soln.
○ 1.96 molar *n*-butyllithium soln.

results were obtained using the "double titration" analytical procedure for analyzing solutions of *n*-butyllithium in *n*-heptane of various concentrations when rigorously purified ether was used. Further, and of considerable importance, these results show that a direct acid titration of a hydrolyzed sample of *n*-butyllithium in *n*-heptane determines the amount of *n*-butyllithium present with less than 5% error. Conceivably the accuracy of a direct titration may be even better than this as the essentially constant blank of 4 to 5% may be inherent to the "double titration" procedure under the conditions used. These results confirmed our early assumption that essentially no basic lithium-containing materials other than *n*-butyllithium should be present in the *n*-heptane solutions because of the insolubility of such substances in *n*-heptane. Additional confirming evidence was obtained by the preparation of the derivative triphenyl-*n*-butylsilane in essentially quantitative yield.

Having shown that the *n*-heptane solutions contained essentially no basic materials other than *n*-butyllithium, it next became of interest to determine whether any inert materials were present for example, unreacted *n*-butyl chloride or olefins formed by thermal decomposition. Direct analysis of the *n*-heptane solution of *n*-butyllithium by use

TABLE VI

VARIATION OF RESIDUAL ALKALINITY WITH VARYING CONCENTRATIONS OF *n*-BUTYLLITHIUM IN *n*-HEPTANE USING PURIFIED ETHER

Normality of *n*-BuLi Soln. (in *n*-Heptane)	Aliquot,[a] Ml.	Benzyl Chloride, Ml.	Ether,[b] Ml.	Base Titrated, Meq.	% Total Base in Blank
3.31	2	2.2	10	0.255	3.8
	2	2.2	10	0.273	4.1
	3	3.3	10	0.368	3.7
	3	3.3	10	0.390	3.9
1.96	3	2.0	10	0.310	5.3
	3	2.0	10	0.333	5.7
	4	2.3	10	0.400	5.1
	4	2.3	10	0.380	4.8
	5	2.5	10	0.425	4.3
	5	2.5	10	0.423	4.3
2.51	2	1.7	10	0.208	4.1
	2	1.7	10	0.198	3.9
	3	2.5	10	0.265	3.5
	3	2.5	10	0.298	4.0
	4	3.3	10	0.423	4.2
	4	3.3	10	0.420	4.2

[a] The range of the final concentration of *n*-butyllithium in ether was adjusted, by varying the size of the aliquots, in such a manner as to give a range of from 5 meq./10 ml. of ether to 10 meq./10 ml. of ether. [b] The ether was Mallinckrodt Anhydrous Grade which had been refluxed over $LiAlH_4$ for 3 hr. and distilled from this reagent into thoroughly dried glass-stoppered bottles.

TABLE VII

SUMMARY OF RESULTS OF TABLE VI

Normality of *n*-BuLi	Average % of Total Base in Blank	Average Deviation from Average	% Average Deviation from Average
3.31	3.9	0.13	3.2
1.96	4.9	0.45	9
2.51	4.0	0.2	5

of the disodium biphenyl reagent[3] was found to be a dependable method for determining *n*-butyl chloride content. It was interesting to note that less than 2% of the starting *n*-butyl chloride remained in those solutions of *n*-butyllithium in *n*-heptane obtained in runs where the yields of *n*-butyllithium based on *n*-butyl chloride ranged above 70%. Since these yields of *n*-butyllithium were less than theoretical, loss of *n*-butyl chloride to some side reaction(s) was indicated. Incomplete studies now in progress using gas chromatography indicate that the amount of *n*-octane in the *n*-heptane solvent increases by an amount approximately equal to the amount of *n*-butyl chloride lost. Thus, it appears that some portion of the *n*-butyl chloride couples with the *n*-butyllithium as it is being formed.

The analyses for unsaturated materials showed that essentially no olefins were formed during the *n*-butyllithium preparations. These results provided

(3) L. M. Liggett, *Anal. Chem.*, 26, 748 (1948).

evidence that *n*-butyllithium was quite stable at or slightly above room temperature. Additional evidence for this stability was obtained from the shelf-life tests. The results showed that the *n*-butyllithium concentration in *n*-heptane solution remained essentially unchanged for at least 3 months when stored at room temperature in properly sealed containers. The latter is necessary because of the rapid reaction of the *n*-butyllithium solutions with air and water. It was interesting to find from the pyrophoricity studies, however, that these reactions of themselves did not cause ignition of the solution.

EXPERIMENTAL[4]

n-Butyllithium concentration in n-heptane by indirect (double) titration. The procedures followed in these analyses were essentially those given by Gilman and Haubein.[1] Variations and results are given in Tables I through VII. Selected data from the various Tables are shown graphically in Figs. 1 through 3.

n-Butyl chloride concentration in n-heptane solutions of n-butyllithium. (A) *Direct analysis with the disodium biphenyl reagent.* The procedure followed was essentially that of Liggett[3] with certain modifications. A 15-ml. aliquot of an approximately 2.5 molar solution of *n*-butyllithium in *n*-heptane was pipetted into a 250-ml. separatory funnel (previously flushed with argon) containing 50 ml. of dry *n*-heptane (Phillips Pure) and the solution shaken to insure thorough mixing. Twenty ml. of the disodium biphenyl reagent[3] was then pipetted into the separatory funnel and the mixture shaken for 1 to 2 min. with the funnel being inverted and carefully vented at frequent intervals. Persistence of a dark green color indicated the presence of excess disodium biphenyl reagent. The mixture was then extracted with 25 ml. of distilled water, being sure to agitate cautiously until the excess reagent was destroyed (disappearance of color). The lower aqueous layer was drawn off and the upper layer extracted twice with 3*N* nitric acid. The main aqueous layer and extracts were then diluted to 100 ml. in a volumetric flask and titrated with standard silver nitrate solution by the Mohr method.

Weighed amounts of *n*-butyl chloride have been added to control samples of *n*-butyllithium and chloride values with 1–2% accuracy obtained by this method.

(B) *Direct analysis by gas chromatography.* It is entirely possible that *n*-butyl chloride could be determined quantitatively by gas chromatography in the presence of solvents other than *n*-heptane. This solvent, however, appears to mask the presence of *n*-butyl chloride due to the closeness of the relative positions of their peaks. Further work on this method of analysis remains to be done.

(C) *Indirect analysis by determination of by-product lithium chloride.* An estimate of the amount of *n*-butyl chloride remaining in a solution of *n*-butyllithium has been indirectly determined by analysis of the solid, reaction residue isolated after removal of the product solution by filtration. This residue was decomposed by slowly adding it, as a slurry in *n*-heptane, to a large excess of methanol (chloride-free). The resulting mixture was diluted with distilled water, and the aqueous layer separated and acidified carefully with reagent grade dilute nitric acid. The solution was filtered to remove suspended material and the methanol and *n*-heptane azeotroped out. The remaining aqueous solution was diluted to the mark in a volumetric flask and analyzed for chloride ion by the Mohr titration procedure.

Use of methods (A) and (C) has shown that in those *n*-butyllithium preparations performed in this laboratory where the yields ranged above 70%, the amount of unreacted *n*-butyl chloride in 2.0 to 2.5 molar solutions was always less than 1% of the solution.

Olefin concentration in n-heptane solutions of n-butyllithium. (A) *Olefin formed during reaction.* A run of *n*-butyllithium in *n*-heptane (2.5 molar) was made at 35° yielding 1395 g. of solution. During this run the gases were led off through a length of glass tubing running from the reaction flask into a 250-ml., 3 necked flask containing 50 ml. of chloroform and immersed in a Dry Ice–acetone bath. After the run was over, the chloroform solution was titrated with a solution of 4 g. of bromine in 99 g. of glacial acetic acid immediately after removing from the cooling bath. The sample took 16.5 ml. of the bromine solution to produce a permanent yellow color in the solution.

Calculations: 1 ml. of bromine solution was equivalent to 0.25 millimole of monoolefin.

$$16.5 \text{ ml.} \times 0.25 \text{ mmole} = 4.1 \text{ mmole of monoolefin}$$

This amount of monoolefin was formed from 6.25 mol. of *n*-butyl chloride and is equivalent to a 0.06% yield based on *n*-butyl chloride. Based on the 1395 g. of solution and expressed as butene-1, the percentage of unsaturates was less than 0.1%.

(B) *Olefins present in the final product solution.* A 25-ml. sample of a 3.5 molar *n*-butyllithium solution was added dropwise to 100 ml. of distilled water with stirring. The evolved gases were passed into 50 ml. of chloroform contained in a receiver cooled to −78° by a Dry Ice–acetone bath. After the addition was completed, the water-heptane mixture was heated to 55–60° to insure removal of all evolved gases from the reaction vessel. The chloroform solution was then titrated with a bromine solution (see A). The sample took 1 ml. of the bromine solution to produce a permanent yellow color in the solution.

Calculations: 1 ml. of the bromine solution was equivalent to 0.25 millimole of monoolefin. Based on the sample weight of 17.75 g. and expressed as butene-1, the percentage of unsaturates was 0.08%. (The *n*-heptane initially contained 0.04–0.1% unsaturates.)

Triphenyl-n-butylsilane. The procedure followed in this preparation was essentially that given by Gilman, Benkeser, and Dunn.[5] The triphenylchlorosilane (Dow Corning purified grade, m.p. 90–95°) was further purified by distillation at reduced pressure and recrystallization from an anhydrous ethyl ether–petroleum ether (b.p. 60–71°) mixture (1:10). The melting point of this material was 97–99°.

A 25-ml. aliquot of a 2.38 molar *n*-butyllithium solution in *n*-heptane (0.06 mol.) was added dropwise during 15 min. to a stirred solution of 17.8 g. (0.06 mol.) of purified triphenylchlorosilane in 85 ml. of purified diethyl ether (Mallinckrodt anhydrous grade distilled from lithium aluminum hydride). After stirring for 30 min., the mixture was hydrolyzed with 50 ml. of water, the layers were separated, and the ether-heptane layer was dried over anhydrous calcium chloride. On evaporation to dryness, 19.00 g. (quantitative yield) of crude *n*-butyl-triphenylsilane, m.p. 82–88°, was obtained. This was recrystallized from 300 ml. of absolute methyl alcohol to yield 15.75 g. of pure triphenyl-*n*-butylsilane, m.p. 87.5–89° (lit.[6] m.p., 87.5–88.5°). A second crop of 1.21 g. of product was recovered, m.p. 86–87.5°. The combined yield of product to this point was 16.96 g. (89.5%). A third impure crop weighing 0.66 g. was also obtained, m.p. 80–86°.

Density of an n-butyllithium solution in n-heptane. A 10 ± 0.02-ml. aliquot of a solution of *n*-butyllithium in *n*-heptane, 2.59 molar in *n*-butyllithium (as determined by direct titration), was transferred to a tared weighing bottle (previously flushed with argon). The sample weighed 6.956

(4) All *n*-butyllithium solutions used in these studies had been filtered through a Pall Corporation stainless steel filter. All melting points are uncorrected.

(5) H. Gilman, R. A. Benkeser, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 1690 (1950).

g. The ambient temperature was 26°. The *n*-butyllithium solution contained, in addition to *n*-butyllithium, 2.8% heavy mineral oil and less than 9% *n*-octane. Thus, the density of this solution at 26° was 0.697 = 0.001.

Shelf-life of n-butyllithium solutions in n-heptane. Two solutions of *n*-butyllithium in *n*-heptane were prepared and placed in screw-topped cans (sealed with electrical tape) for shelf-life tests. Can No. 1 (1 quart capacity) contained 340 ml. of 0.639 molar *n*-butyllithium solution, while can No. 2 (1 gallon capacity) contained 1750 ml. of 2.05 molar *n*-butyllithium solution. The data given in Table VIII indicate stability as determined by periodic removal of aliquots from each of the cans (under argon) and analysis of these by hydrolysis and titration with standard acid.

TABLE VIII

RESULTS OF STABILITY TESTS

Can No.	Date of Analysis	Size of Aliquot Taken, Ml.	Concentration of Solution, Molarity	% Change in Molarity from Date of Preparation
1	2/26/58[a]	5	0.639	0
	3/19/58[b]	5	0.620	−3.1
	4/10/58	2	0.615	−3.8
2	3/13/58[a]	2	2.050	0
	4/3/58	2	2.075	+1.2
	6/9/58	2	2.069	+0.9

[a] Date of preparation of these solutions. [b] Screw cap tightened as much as possible and resealed with fresh electrical tape after this aliquot was taken. The old electrical tape had been extensively attacked by the solvent.

Pyrophoricity of n-butyllithium solutions in n-heptane. (A) *Small scale.* A small amount (approx. 1 ml.) of 2 molar *n*-butyllithium in *n*-heptane was placed on a 2-inch-diameter watch glass and allowed to evaporate to dryness. The dry sample did not ignite spontaneously, but formed a white crust. This crust did not react vigorously with water. Another 1-ml. portion of the *n*-heptane solution was placed on a watch glass and a few drops of water added to it. Heat was evolved with some fuming and loss of solvent, but no ignition of the material occurred.

(B) *Large scale.* Two 25-ml. portions of the 2-molar *n*-butyllithium solution were placed in 600-ml. beakers. After standing for 10 minutes, 10 drops of water was added to one of the beakers and 25 ml. of water to the other. A hard white crust formed in both cases with accompanying vigorous frothing in the latter case. In neither case was there spontaneous ignition.

MINNEAPOLIS, MINN.

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

The Effect of Triethylamine on the Decomposition of Amylsodium[1]

AVERY A. MORTON AND FRANK K. WARD

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The decomposition of amylsodium appears to be more a cascade of metalations, eliminations of sodium hydride and polymerization than a splitting into simple fragments. Triethylamine hastens these changes but is not itself metalated or cleaved.

Previous work[2] showed that certain halide salts and alkoxides accelerated the decomposition of amylsodium. Presumably these salts were associated or coordinated with the organosodium salt. The present paper reports that triethylamine, a strong coordinating agent, accelerates the decomposition of amylsodium without being metalated or cleaved itself. To a large extent, however, this decomposition (and probably the previous ones[2] also) was largely a metalation of pentene and other unsaturated hydrocarbon units, accompanied by elimination of sodium hydride and polymerization. So much do these secondary processes prevail that any study of the primary dissociation of the organosodium salt into simple fragments is difficult.

The decomposition of amylsodium, prepared by equation 1, was observed at room temperature during 2 years and at 0°, 50° and 80° for shorter times, mostly 3 hr. and not exceeding 10 hr. For

$$C_5H_{11}Cl + 2Na \longrightarrow C_5H_{11}Na + NaCl \qquad (1)$$

analysis, a preparation or an aliquot thereof was carbonated. Thereby sodium hydride became sodium formate. This action was quantitative when very small quantities were used, but this fact was not known until later stages of the work. Consequently the data for formic acid and sodium hydroxide in the tables are not complete. Amylsodium was also converted to sodium caproate and sodium butylmalonate, the latter by a secondary reaction[3,4] which was difficult to suppress, even at −72°, because the thickness of the reaction mixture prevented good contact with carbon dioxide. Pentenylsodium became a mixture of sodium hexenoates. In addition, there was formed the sodium salt of a tarry carboxylic acid, the ultimate analysis of which approached one carboxyl group for each five carbon atoms and approximately five hydrogen atoms. Metallic sodium did not react

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) A. A. Morton and E. F. Cluff, *J. Am. Chem. Soc.*, 75, 134 (1953).

(3) A. A. Morton, J. B. Davidson, and H. A. Newey, *J. Am. Chem. Soc.*, 64, 2240 (1942).

(4) H. Gilman and H. A. Pacewitz, *J. Am. Chem. Soc.*, 62, 1301 (1940).

with carbon dioxide but subsequently became sodium hydroxide by hydrolysis. The total carboxylates and hydroxide were determined by conductometric titration. Extraction of the aqueous layer with pentane removed caproic and hexenoic acids. Ether withdrew butylmalonic acid. The highly soluble formic acid was identified by Duclaux values. The tarry carboxylic acid precipitated with the initial addition of acid, but then redissolved and was finally recovered after the ether extraction by salting and extracting with special organic solvents such as *t*-butyl alcohol. No attention was given this material until the later stages of the work.

Equation 2 represents the initial formation of pentene followed by

$$C_5H_{11}Na \longrightarrow NaH + C_5H_{10} \longrightarrow C_5H_{11}Na + C_5H_{12} \quad (2)$$

metalation to give pentenylsodium. The conversion to tar is shown overall by equation 3.

$$4C_5H_{11}Na \longrightarrow [C_5H_5Na] + 3C_5H_{12} + 3NaH \quad (3)$$
$$\downarrow CO_2$$
$$\longrightarrow \text{polymer carboxylate}$$

Table I gives the results for the two-year experiment, in which the changes were slow enough to be followed easily. The most noteworthy features were (a) the nearly constant values maintained for the total carboxylates (column 3) and (b) the absence of appreciable hexenoic acid during the first six months as shown by the near sameness of the refractive index in column 6 during that period. Table II shows the effect of three equivalents of triethylamine. Within 3 hr. the amine had caused 18% more decomposition at 0° and 54% more at 50°. At 80° the decomposition in the presence of the amine was 90% complete in ten minutes as compared with 60% in 3 hr. in its absence.

TABLE I

DECOMPOSITION OF AMYLSODIUM AT ROOM TEMPERATURE

Time, Months,	Na Metal, %	Yield of Sodium Carboxylates: Titr.,[a] %	Extracted: Total,[b] %	Extracted: Pentane,[c] %	n_D^{25}	Extracted: Ether,[d] %
0	5	95	92	89	1.4150	3
1			75	64	1.4151	11
2	5	95	51	40	1.4149	11
3	5	95	45	26	1.4150	19
4	5	95	32	11	1.4151	21
5			26	6	1.4153	20
6	5	95	26	6	1.4155	21
7	5	95	27	6	1.4270	21
9			26	8	1.4369	18
24			26	6	1.4372	20

[a] This column records the total carboxyl groups as determined by conductometric titration. [b] This column shows the sum of caproic, butylmalonic and hexenoic acids. All acids except formic and tarry acids were extracted readily. [c] This column represents caproic and hexenoic acids. [d] Butylmalonic acid is removed by ether.

TABLE II

EFFECT OF THREE EQUIVALENTS[a] OF TRIETHYLAMINE ON THE DECOMPOSITION OF AMYLSODIUM

Temp.	Time, Hrs.	Total Carb.[b] with Amine, %	Extractable Carboxylates[c]: No Amine, %	Extractable Carboxylates[c]: With Amine, %
0	0		85–92	
0	2	95–96	88	71–77
0	4		88	65–67
0	6			60–65
0	8			54
0	10			55
50	3	95–96	83–86	20–41
80	1/6	90–96		9–11
80	3	94	35–38	3–8

[a] Equivalents of triethylamine per organosodium reagent. [b] This column represents the sum of all carboxylic acids as determined by conductometric titration. [c] These columns represent the sum of the caproic, butylmalonic, and hexenoic acids which have been extracted by pentane and ether.

The tarry acid formed according to Equation 3 probably accounts for a large share of the reaction, although the actual amount isolated was low. It was not measured until the end of the work when the search for nitrogen-containing organic material led to combustion analyses. Then its importance was realized. The estimated final weight was about 5% of the amyl chloride used, and the composition approximated a singly carboxylated amyl fragment which had lost over half of its hydrogen atoms. Theoretically this tar accounted for about 40% of the amyl chloride. The second largest organic reaction product was the 26% (see Table I) of hexenoic acid and a malonic acid. About 5% of the amyl chloride must have been consumed in a Wurtz preparation of decane with some formation of pentane and pentene.[5] The remaining 21% might have been primary decomposition to sodium hydride and pentene.

This material balance is only approximate, but shows that metalation was the predominant reaction, amounting to more than 66%. The excess of pentane over pentene in the initial stages of pyrolysis[6] is accordingly understandable, because this decomposition is more metalation than a dissociation to simple fragments. Other sodium salts have behaved similarly. For instance, ethane was obtained before ethylene in the pyrolysis of ethylsodium,[7] cyclopropane was obtained without appreciable, if any, cyclopropene from the decom-

(5) A. A. Morton and G. M. Richardson, *J. Am. Chem. Soc.*, **62**, 123 (1940)

(6) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **20**, 839 (1955); **21**, 93 (1956).

(7) W. H. Carothers and D. D. Coffman, *J. Am. Chem. Soc.*, **51**, 588 (1929).

position of cyclopropylsodium,[8] and benzene, unaccompanied by biphenyl or other volatile products, was collected from the pyrolysis of phenylpotassium.[9]

The change of amylsodium to tar took place apparently with great ease, probably because each succeeding step was metallated more easily than the previous one. This rapid cascade of reactions, so typical of many processes[10] with organoalkali metal reagents, accounts nicely for the fact that an early step in the process, pentenylsodium, was not demonstrated to be present in the decompositions at room temperature until after 7 months (see Table I, column 6) when most of the amylsodium had been consumed and the drive toward the final product of decomposition had largely ceased. This absence of appreciable quantity of intermediate product is in general accord with an earlier study[11], where small amounts only of impure dicarboxylic were obtained from a decomposition which was not allowed to reach the tarry condition.

Three equivalents of triethylamine accelerated the decomposition, but more caused no further increase. (See Table III.) Therefore its effect is not reasonably attributed to increased solubility of the reagent (actually no appreciable solution of reagent was observed visually), or else the amount would have increased continually. The amine was not metallated or cleaved because no acid or tar which contained nitrogen, and no diethyl amine, were found. The prime role of the amine seems to have been coordination. In an earlier paper[6] coordination of reactants about the cation was described as one of the factors which caused bond stretching in an early phase of chemical reaction and for several years such coordination has been assumed[12] to be important in the reactions of these reagents.

Special attention is called to the fact, mentioned also in earlier work,[2] that during the decomposition at 80° the metallic sodium agglomerated into large balls which occluded amylsodium and the products of decomposition. When the balls were cut open and carbonated and those products were added to the others, the total amount of sodium metal (see Table II) was the same as in the other experiments. Hence no appreciable amount of sodium metal formed during decomposition, contrary to an earlier supposition.[2] The analytical methods used in this work, however, do not exclude the possibility that

TABLE III

EFFECT OF THE AMOUNT OF TRIETHYLAMINE ON THE DECOMPOSITION OF AMYLSODIUM AT 0° DURING 2 HR.

Et_3N Mole Equiv.	No. of Tests	Yield of Carboxylic Acids		
		Total Extr., %	Pent. Sol., %	Ether Sol., %
0	1	88	85	3
1	1	77	44	33
3	4	71–77	45–30	26–47
4	3	69–77	49–51	20–26
5	2	72	50–47	22,25
6	1	69	42	27
7	1	70	44	26
9	1	70	49	21
10	1	69	49	20

a tiny amount of atomic sodium (formed as a consequence of dissociation to amyl and atomic sodium[2,6] as in equation 4 and of failure of the sodium radical to disproportionate with the amyl radical to give pentene and sodium hydride) could have deposited upon the particles of metallic sodium left over because of the failure of the preparation by Equation 1 to be quantitative. Only a tiny

$$C_5H_{11}Na \longrightarrow [C_5H_{11}\cdot + \cdot Na] \longrightarrow C_5H_{10} + NaH \quad (4)$$

amount of the atomic sodium is needed to coat the tiny sodium particles. In this connection it is possibly significant that this agglomeration has not occurred in ordinary metalations at 80°, although approximately the same amount of metallic sodium, left over from the preparation of amylsodium, was present in such cases. In metalations, however, there is present a large quantity of hydrocarbon to which the atomic sodium is shifted rather rapidly and the new salt thus formed is thermally relatively stable.

EXPERIMENTAL

Decomposition of amylsodium during two years. Amylsodium was prepared from 0.5 mol. of amyl chloride and 1 g. atom of sodium in heptane in the manner regularly employed in this laboratory.[13,14] After the preparation was completed, the reaction mixture was transferred to a nitrogen-filled bottle and stoppered with a cork covered with a glyptal cement. Three such preparations were made and stored in three separate bottles. From one bottle aliquots were removed for 7 consecutive months for analysis. Each time the bottle was well shaken by hand and a sample was removed by forcing the liquid upward into a pipette by nitrogen pressure. The other two preparations were carbonated entirely after 9 and 24 months, respectively.

Each aliquot was carbonated by forcing the mixture onto solid carbon dioxide. For this operation to be quantitative with respect to sodium hydride, no more than 60 meq. of that salt should be present. Roughly that amount was present in one-eighth of the ordinary preparation of amyl-

(8) E. J. Lanpher, L. M. Redman, and A. A. Morton, *J. Org. Chem.*, **23**, 1370 (1958).

(9) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1639 (1958).

(10) A. A. Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950).

(11) A. A. Morton and H. A. Newey, *J. Am. Chem. Soc.*, **64**, 2247 (1942).

(12) A. A. Morton, *Chem. Revs.*, **35**, 1 (1944); *J. Am. Chem. Soc.*, **69**, 969 (1947); *Ind. Eng. Chem.*, **42**, 1488 (1950); A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955).

(13) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, Jr., and R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 3785 (1950).

(14) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2973 (1954).

sodium. Approximately 24 hr. later, 300 ml. of distilled water was added to the carbonated product. After the heptane and aqueous layers were clear, the hydrocarbon layer was extracted twice with 50 ml. of water and the aqueous portion was extracted twice with 200 ml. of ethyl ether. Then the combined aqueous portions were made up to 500 ml. A 2-ml. aliquot was titrated conductometrically against 0.1*N* hydrochloric acid with a Serfass direct reading MHO-OHM model conductance bridge[15] and a dip conductance cell having a constant of 0.98. An input current of 1000 cycles per sec. was used. The solvent was a mixture of 200 ml. of denatured alcohol and 150 ml. of distilled water. A control test of a mixture of 1.77 meq. of caproic acid and 1.83 meq. of sodium hydroxide gave 1.78 meq. of sodium caproate.

The remainder of the aqueous solution was acidified with sulfuric acid and extracted first with three 150-ml. portions of pentane and next with three 150-ml. portions of ether. The extracts were dried with anhydrous calcium sulfate, filtered and diluted to 500 ml. A 5-ml. aliquot was removed and titrated to a phenolphthalein endpoint in order to determine the carboxylic acid in the respective combined extracts.

The pentane extract was evaporated and the caproic or hexenoic acid was removed by distillation through a 35-mm. column of the Podbielniak type. They did not need careful fractionation. Only caproic acid appeared during the first 6 months (see Table I); hexenoic acid was almost the sole product from the later stages of the decomposition. Caproic acid was identified by its boiling point, 50°/1 mm. to 80°/4 mm., neutralization equivalent equal to 116 (calculated 116), refractive index of n_D^{25} 1.4151 (recorded[16] 1.4149), its amide derivative which melted at 99–100° (recorded[17] 101°), and its failure to decolorize bromine. The hexenoic acids (mostly 3-hexenoic) decolorized bromine in carbon tetrachloride and showed strong infrared absorption at 1640 and 965 cm.$^{-1}$, moderate at 990 cm.$^{-1}$, in accord with data published by Bellamy.[18] The boiling point was 80°/4 mm. and the neutralization equivalent was 112.5 (calculated 114). The refractive index was n_D^{25} 1.4369, which agreed with a value, 1.4375, found previously[13] in this laboratory.

The ether extract, after evaporation, yielded butylmalonic acid, which melted at 100–101° (recorded[19] 101.5°) and showed no depression when mixed with an authentic sample. It was further identified by the neutralization equivalent of 80 (calculated 80) and the melting point of its amide derivative 197–199° (recorded[20] 200°). After 9 months (see Table I) this extract contained not only butylmalonic acid but also some unsaturated (to bromine) product as might be expected. Infrared absorption showed strong absorption bands at 1640 and 965 cm.$^{-1}$, typical[18] for unsaturated acids. After numerous precipitations tiny amounts of acids which melted at 144°, 152°, and 183° were recovered, each well above the value for butylmalonic acid. No attempt was made to characterize them.

The tarry acid was soluble in common organic solvents. Neither the acid nor its methyl ester (made from methanol with acid catalyst) distilled when heated to 250°/1 mm. The neutralization equivalent was 155° ± 10 depending on the sample and its solubility during titration. A carbon-hydrogen analysis showed an oxygen percentage by difference of 35.12, equivalent to more than one carboxyl per five carbon atoms. The percentages of carbon and hydrogen were 59.3 and 5.6 respectively, equivalent after deduction for carboxyl to an atom ratio of hydrogen to carbon of 1.17. At that ratio the tar could be derived from an acetylene system. Davis[21] has found some evidence for acetylene type compounds from the decomposition of amylsodium.

The aqueous layer remaining after extraction with ether was steam distilled until about 50% of the original volume was collected. Two drops of this distillate was analyzed by the chromotropic acid color test described by Feigl.[22] The test varied from weak to strong depending upon the amount of formic acid which was present. The remainder of the distillate was fractionally distilled and 150 ml. of the fraction boiling at 100° was analyzed for formic acid by Duclaux numbers[17] (found: 3.90, 4.36, 4.51; recorded[17] 3.95, 4.40, 4.55). The remaining portion of the 150-ml. fraction was made alkaline and evaporated to a small volume. It was then reduced with magnesium powder and acid. The resulting formaldehyde yielded a dimethone derivative which melted at 187–189° in accord with Horning's[23] result (191°).

The residue from the original distillation of the aqueous portion was tested for oxalic acid by the method described by Feigl.[22] No aniline blue color was obtained.

Effect of time and temperature on the decomposition of amylsodium. The amylsodium was prepared as described in the previous section, but the stirring at 10,000 rpm. was continued for the times and temperatures specified in Table II. The separations and identifications of the products were essentially the same as already described.

Decomposition in the presence of triethylamine. The triethylamine obtained from Eastman Kodak Company was distilled and the fraction collected from 88.5° to 89.5° (recorded[24] 89.4°) was dried for several months over potassium hydroxide. The refractive index was n_D^{25} 1.3989 (recorded[25] n_D^{20} 1.4003). Later this material was shown by polymerization tests[21] to contain a trace of water, possibly 0.05%, but this small amount would not reduce the quantity of sodium reagent appreciably. The tests for the usual products of decomposition were as described in a previous section. In addition, tests were carried out for compounds which might contain nitrogen, such as diethylamine from cleavage, amino carboxylic acids from metalation, and nitrogen-containing tar.

The hydrocarbon layers obtained after carbonation and hydrolysis were fractionated through a four-foot, one-inch diameter column packed with 3/32-inch single-turned helices. The fraction boiling from 40° to 70°, which should have contained any diethylamine, was treated with hydrochloric acid gas but no diethylamine hydrochloride was obtained. The aqueous layer, after extraction of the carboxylic acids with pentane and ether, was made alkaline and extracted with three 150-ml. portions of ether. The ether extract was dried over anhydrous calcium sulfate and treated with hydrochloric acid gas. No diethylamine hydrochloride separated. In control tests a mixture of diethylaminesodium and amylsodium was carbonated. Subsequent distillation of the

(15) H. H. Willard, L. L. Merrill, and J. A. Dean, *Instrumental Methods of Analysis*, D. van Nostrand Co. Inc., New York, N. Y., 2nd Ed., 1953, p. 225.

(16) I. Simon, *Bull. Soc. chim. Belg.*, **38**, 59 (1929).

(17) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 231.

(18) L. J. Bellamy, *The Infrared Spectra of Complex Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1954.

(19) C. Hell and G. Lumpp, *Ber.*, **17**, 2219 (1884).

(20) A. W. Dox and L. Yoder, *J. Am. Chem. Soc.*, **44**, 1578 (1922).

(21) P. Davis Burke Research Laboratory, Detroit, Mich. Private communication.

(22) F. Feigl, *Qualitative Analysis by Spot Tests*, 3rd Ed., Elsevier Pub. Co. Inc., New York, N. Y., 1946, p. 377, 402.

(23) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

(24) J. Timmermans, *Physico-Chemical Constants of Pure Organic Compounds*, Elsevier Pub. Co. Inc., New York, N. Y., 1950.

(25) J. W. Brühl, *Ann.*, **200**, 182 (1879).

(26) A. A. Morton and F. K. Ward, *J. Org. Chem.*, **24**, 929 (1959).

TABLE IV

EFFECT OF TRIETHYLAMINE UPON THE FORMATION OF TAR

	Without Amine		With Amine
Preparation			
Temp.	Room	80	80
Time, hr.	[3.5][a]	3	3
Analyses			
C, %	59.32	52.70	63.46[b]
H, %	5.56	6.13	5.65
O,[c] %	35.12	31.17	30.89
Atoms or groups			
C	3.48	3.43	4.48
H	4.06	5.18	4.85
CO_2H	1	1	1
H[d]/C	1.17	1.51	1.08
$CO_2H/5C$[d]	1.44	1.45	1.12

[a] Time in months. This tar was dissolved in methyl ethyl ketone, treated with decolorizing carbon, precipitated, redissolved and reprecipitated in an attempt to separate a pure compound. [b] A combustion analysis for nitrogen showed none present. [c] Oxygen by difference. [d] For these ratios the hydrogen and carbon attached to the carboxyl group are deducted from the total atoms of hydrogen or carbon, respectively.

hydrocarbon fraction and of the aqueous portion by the above described methods yielded diethyl amine hydrochloride in both fractions.

After the butylmalonic acid was extracted with ether, the acidic aqueous layer was salted and extracted successively with *t*-butyl alcohol, methyl ethyl ketone, and ethyl acetate, which should remove some or all of any aminocarboxylic acid, had any such material formed by one of a variety of methods which might be assumed to have occurred. The tarry residues, obtained by evaporation of the solvent, in each case showed no nitrogen when tested by a sodium fusion–Prussian blue test. In another case the tarry residues were burned in the customary ultimate analysis for nitrogen, but no such gas was collected.

Table IV shows a comparison of the tarry carboxylic acids prepared with and without the amine. The products are essentially the same except for the fact that the action seemed to have been carried further by the amine.

Attempts were also made to repeat the observation recorded in an earlier paper[27] that some nitrogen-containing carboxylic acid was obtained. The conclusion was that traces of triethylamine were difficult to remove and had been codistilled with the acid.

Acknowledgments. The authors are indebted to Dr. Nagy for the combustion analyses and to Professor Nelson for the infrared measurements.

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(27) A. A. Morton, M. L. Brown, and E. Magat, *J. Am. Chem. Soc.*, 69, 161 (1947).

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, DUQUESNE UNIVERSITY]

The Rhodium-Catalyzed Hydrogenation of Ethyl-5,6-benzocoumarin-3-carboxylate[1]

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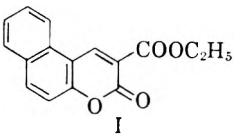
Room temperature, low pressure hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate (I) employing rhodium (5%) on alumina as the catalyst afforded a decalin derivative, ethyl β-(α-decalyl)isobutyrate (II). The structure of (II) was elucidated by the preparation of the amide and acid derivatives and by an unambiguous synthesis starting with malonic ester.

Since rhodium (5%) on alumina was shown to be effective in the hydrogenation of such aromatic systems as pyridine[2] and arylphosphonic acids,[3] it was thought feasible to use this catalyst in the hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate (I), in connection with the synthesis of potential oxytocics. It has been shown[4] that the W-1 Raney nickel catalyzed hydrogenation of I yielded a decalin derivative, but only at 2900 pounds per square inch and at 140°; at this temperature, extensive hydrogenolysis of the lactone and ester occurred.



I

When a mixture consisting of a one to one- and-one-half ratio of I to rhodium (5%) on alumina was hydrogenated for thirty-nine hours at room temperature and at a hydrogen pressure of 55 pounds per square inch, an oil was obtained. The ultraviolet spectrum of the oily product showed no absorption indicating that aromaticity had been destroyed. An infrared spectrum of the compound revealed a strong band at 1735 cm.$^{-1}$, suggestive

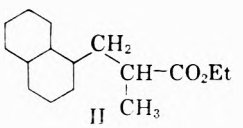
(1) Abstracted from a thesis submitted by O. LeRoy Salerni to the faculty of Duquesne University in partial fulfillment of the requirements for the degree of Master of Science, August 1959.

(2) C. D. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.*, 77, 4100 (1955).

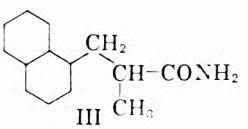
(3) L. D. Freedman, G. O. Doak, and E. L. Petit, *J. Am. Chem. Soc.*, 77, 4262 (1955).

(4) J. E. Gearien and K. J. Liska, *J. Org. Chem.*, 23, 45 (1958).

of an ester and/or lactone grouping. Furthermore, there was no absorption in the alcoholic hydroxyl region, indicating that if hydrogenolysis had occurred, there was subsequent removal of the resulting hydroxyl groups. The compound did not react with acetyl chloride and gave a positive hydroxamic acid test, in support of the findings of the infrared. No decolorization of dilute potassium permanganate solution was observed, indicating that hydrogenation had not stopped at the octalin. On the basis of these findings and elemental analyses, it was possible to propose ethyl β-(α-decalyl)-



II



III

isobutyrate (II) as the hydrogenated product of ethyl 5,6-benzocoumarin-3-carboxylate (I)

Ammonolysis of II, catalyzed by methoxide ion according to the method of Russell,[5] gave a crystalline amide. The nitrogen analysis agreed with that of the expected product, and the compound was identified as β-(α-decalyl)isobutyramide (III).

Alkaline hydrolysis of II and subsequent acidification gave a product which dissolved in 5% sodium bicarbonate solution. The infrared spectrum of the hydrolysis product showed a sharp band at 1707 cm.$^{-1}$ and a weak band centered around 2840 cm.$^{-1}$, characteristic of a carboxyl group, but no absorption attributable to an alcoholic hydroxyl group. The isolation of this hydrolysis product eliminated the possibility of survival of the lactone group during the hydrogenation, for hydrolysis of a lactone would have resulted in recovery of the starting material, or a hydroxy acid which would have given absorption in the alcoholic hydroxyl region of the infrared

To give unequivocal proof of the structure of II, β-(α-decalyl)isobutyramide (III) was synthesized by an unambiguous route. β-(α-Naphthyl)-isobutyric acid, prepared by the scheme of Blicke and Maxwell,[6] was hydrogenated over rhodium (5%) on alumina using a one to one-and-one-half ratio of unsaturated compound to catalyst. The presumed product, β-(α-decalyl)isobutyric acid, obtained as an oil which could not be crystallized, was converted to the amide by treating successively with thionyl chloride and ammonia. The nitrogen analysis supported the desired structure, β-(α-decalyl)isobutyramide (III). The melting point of the compound compared very favorably with the melting point of β-(α-decalyl)isobutyramide obtained from (II) by ammonolysis catalyzed by methoxide ion. There was no depression in mixed melting point.

When a one-to-one weight ratio of catalyst to coumarin ester was employed in low pressure hydrogenations, reduction to the decalin was incomplete as shown by the isolation of the previously reported ethyl 2,3,7,8,9,10-hexahydro-3-keto-1H-naphtho[2,1-b]pyran-2-carboxylate.[4]

It is therefore apparent that the room temperature, low pressure hydrogenation of the coumarin ester (I) to a decalin derivative is possible employing rhodium (5%) on alumina as the catalyst, but that even under these mild conditions hydrogenolysis of the lactone (but not of the ester) is unavoidable.

EXPERIMENTAL[7]

Ethyl 5,6-benzocoumarin-3-carboxylate was prepared from 2-hydroxy-1-naphthaldehyde by the method of Smith and Horner.[8] The 2-hydroxy-1-naphthaldehyde was prepared from 2-naphthol by the method of Russell and Lockhart.[9]

Ethyl β-(α-decalyl)isobutyrate (II). A solution of ethyl 5,6-benzocoumarin-3-carboxylate (4.0 g., 0.015 mol.) in 175 ml. of absolute ethanol was hydrogenated at a pressure of 55 p.s.i. and at room temperature, using 6 g. of rhodium (5%) on alumina as the catalyst. After 39 hr., absorption of hydrogen ceased and the catalyst and solvent were removed. The crude yield was 3.30 g. (89%). Fractional distillation in a Todd Fractionating Apparatus yielded 1.55 g. (42%) of colorless mobile oil. b.p. 134–136° at 2 mm., n_D^{25} 1.4803. There was no absorption in the ultraviolet.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 75.90; H, 10.82. Found: C, 75.95; H, 10.81.

β-(α-decalyl)isobutyramide (III). A. Ethyl β-(α-decalyl)-isobutyrate (1.0 g., 0.004 mol.) was added to 3 ml. of a 6% ammonia in methanol solution plus 6 ml. of sodium methoxide solution (0.1 g. sodium in 100 ml. of absolute ethanol). The mixture was allowed to stand in a stoppered flask at room temperature for 48 hr. Reducing the volume of the solution to 2 ml. and chilling deposited 0.75 g. of white crystals, m.p. 110–115°. After three recrystallizations from dilute ethanol, 0.25 g. (30%) of product, m.p. 129–131°, was obtained.

Anal. Calcd. for $C_{14}H_{25}ON$: N, 6.27. Found: N, 6.35.

β-(α-decalyl)isobutyric acid. A solution of β-(α-naphthyl)-isobutyric acid (3.0 g., 0.013 mol.) in 150 ml. of absolute ethanol was hydrogenated at room temperature using 4.5 g. of rhodium (5%) on alumina catalyst at a hydrogen pressure of 55 p.s.i. Hydrogenation was allowed to proceed until the theoretical amount of hydrogen was absorbed (15 hr.). Distillation of the product at reduced pressure gave 2.05 g. (67%) of colorless thick oil, b.p. 172–176° at 1.0–1.2 mm. There was no absorption in the ultraviolet.

β-(α-decalyl)isobutyramide (III). B. For proof of structure, III was also synthesized by the following route: A mixture of 1.0 g. (0.004 mol.) of β-(α-decalyl)isobutyric acid and 0.8 g. of thionyl chloride was heated in an all-glass apparatus equipped with drying tube on the steam

(5) P. R. Russell, *J. Am. Chem. Soc.*, 72, 1853 (1950).

(6) F. F. Blicke and C. E. Maxwell, *J. Am. Chem. Soc.*, 61, 1780 (1939).

(7) Melting and boiling points are uncorrected. Analyses by Galbraith Labs, Knoxville, Tenn.

(8) L. I. Smith and J. W. Horner, *J. Am. Chem. Soc.*, 60, 678 (1938).

(9) A. Russell and L. Lockhart, *Org. Syntheses*, 22, 63 (1942).

bath for 3 hr. The solution was then chilled and poured into 4 ml. of cold 28% ammonia water and stirred. The precipitated amide was purified by three recrystallizations from dilute ethanol and amounted to 0.75 g. (84%) of white crystals, m.p. 129.5–132°, mixture m.p. with amide derived from the benzocoumarin (II).

Anal. Calcd. for $C_{14}H_{25}ON$: N, 6.27. Found: N, 6.15.

Acknowledgment. One of the authors is indebted to the American Foundation for Pharmaceutical Education for financial assistance during the period of this work.

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[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Aryl and Alkylchlorodialkoxysilanes[1]

L. W. BREED AND WILLIAM J. HAGGERTY, JR.

Received July 23, 1959

Good yields of chlorodiethoxymethylsilane, suitable for use in alkylation and arylation reactions, are obtained by the ethanolysis of methyltrichlorosilane. The synthesis of chlorodiethoxyphenylsilane, chloro-*p*-chlorophenyldiethoxysilane, and *p*-anisylchlorodiethoxysilane in high yields, and the preparation of their intermediates is described.

In the synthesis of silane monomers for use in high temperature resin systems, it was necessary to prepare certain methyl- and arylalkoxychlorosilanes as intermediates. The alkylation and arylation of these compounds with various organometallic reagents will be described in a subsequent publication.

Although the alcoholysis of silicon tetrachloride has been discussed by numerous investigators, and the stability of the various chlorosilicates against redistribution has been studied, considerably less information is available in the literature regarding the methyl- and arylalkoxychlorosilanes. The reported experimental details are seldom complete, but it appears that, as in the case of the alcoholysis of silicon tetrachloride, mixtures of all possible alkoxychlorosilanes are obtained regardless of the stoichiometry of the reactants, and that yields of individual alkoxychlorosilanes are not high. Treating 6.0 mol. of methyltrichlorosilane with 7.2 mol. of ethanol, Andrianov[2] obtained only 35.9 per cent chlorodiethoxymethylsilane and 21.3 per cent dichloroethoxymethylsilane. Servais[3] reports chlorodiethoxymethylsilane and chlorodiethoxyphenylsilane, but omits properties and yields. Rosnati prepared chlorodimethoxyphenylsilane.[4] Redistribution reactions have been studied both with regard to the preparation and stability of alkoxyalkylchlorosilanes.[2,5,6] It appears that alkoxychloromethylsilanes are more stable than the chlorosilicates against redistribution, and may be distilled at atmospheric pressure without significant changes in their composition.

In our laboratory, the ethanolysis of methyltrichlorosilane resulted in a complex mixture which contained all possible products. However, with a suitable proportion of reactants, chlorodiethoxymethylsilane was obtained in about a 72% conversion. Although the components of the crude alcoholysis mixture were difficult to separate by distillation, the use of an efficient fractionating column gave a 63% yield in fractions suitable for use in alkylation and arylation reactions.

Ethanolysis of aryltrichlorosilanes, however, gave the arylchlorodialkoxysilanes in yields between 88 and 95% even when simpler distillation procedures were used.

The alkoxychlorosilanes were prepared by the action of anhydrous ethanol on the chlorosilane in the absence of any solvent, and the products were collected by fractional distillation. Approximations of the purity of the distillation fractions were carried out by vapor phase chromatography. A sample from each distillation fraction was chromatographed and the identity of each peak was assigned on the basis of the stoichiometry of the starting materials, the known tendency of these systems to form all possible alkoxychlorosilanes, and a comparison of the elution times for the various peaks on the different chromatograms.

With the assumption that peak area is proportional to weight per cent of the component in each fraction on the chromatogram, the weight per cent of each alkoxychlorosilane in all the distillation fractions was calculated. The data are shown in Table I.

In distilling a typical reaction product with a 30-plate Oldershaw column no sharp breaks in the

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(1) This research was supported in whole or in part by the United States Air Force under Contract AF 33(616)-3675, monitored by the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

(2) K. A. Andrianov, S. A. Golubtsov, and N. P. Lobusevich, *J. Gen. Chem. U.S.S.R.*, 26, 207 (1956).

(3) R. C. Servais (to Dow Chemical Co.), U. S. Patent 2,485,928, Oct. 25, 1949.

(4) L. Rosnati, *Gazz. chim. ital.*, 78, 516 (1948); *Chem. Abstr.*, 43, 1006 (1949).

(5) Dow Corning Corp., Brit. Patent 653,238, May 9, 1951; *Chem. Abstr.*, 46, 1025 (1952).

(6) M. Kumada, *J. Inst. Polytech. Osaka City Univ.*, Ser. C., 2, 139 (1952).

TABLE I

COMPOSITION (WT. %) OF CHLORODIETHOXYMETHYLSILANE DISTILLATION FRACTIONS

Compound Assignment	Fraction No. 1	2	3	4
—	5.28	—	—	—
Methyltrichlorosilane	14.74	0.48	—	—
Dichloroethoxymethylsilane	25.39	2.40	0.12	0.19
Chlorodiethoxymethylsilane	52.41	94.55	97.75	81.80
Methyltriethoxysilane	2.18	2.52	2.15	17.99

head temperature of the distillation column were observed; during the collection of fractions 1 and 4, only a gradual rise in the temperature occurred, suggesting some redistribution during the distillation.

Distillate was collected between 77° and 141°. The normal boiling points recorded in the literature for the possible alkoxychlorosilanes are: Methyltrichlorosilane 65.7[7]; dichloroethoxymethylsilane, 101.2,[6] 99–9.5[2]; chlorodiethoxymethylsilane, 129[6]; 126.5–7.5[2]; and methyltriethoxysilane, 143[7].

It is evident from Fig. 1 that significant quantities of lower boiling materials are found only in fraction 1. The materials in fractions 2, 3, and 4 are all suitable for use in alkylation and arylation reactions. The presence of methyltriethoxysilane may be considered as an inert diluent in these reactions because of the preferential reactivity of organometallic reagents toward silicon-attached chlorine.

Measurement of the areas in Fig. 1, taking into account that the total product accounted for 97.0 weight per cent of the theoretical chlorodiethoxymethylsilane, indicated the approximate yields of the various products. The following per cent conversions were obtained: Methyltriethoxysilane, 6.2; chlorodiethoxymethylsilane, 72; dichloroethoxymethylsilane, 5.1; and methyltrichlorosilane, 2.7. These figures do not include the material which was contained in the distillation residue, mainly additional methyltriethoxysilane and possibly some siloxanes, or certain very low boiling fractions. Taken as chlorodiethoxymethylsilane, the fractions boiling lower than chlorodiethoxymethylsilane represented an 8.6% conversion and those boiling higher, a 16.3% conversion.

Arylchlorodialkoxysilanes, prepared by a similar procedure, include those listed in Table II. Yields of the compounds indicate that the ethanolysis of arylsilanes does not produce as complex a reaction product.

An attempt was made to prepare chloro-*p*-*N*,*N*-dimethylaminophenyldiethoxysilane by the ethanolysis of a solution *p*-dimethylaminophenyltrichlorosilane in toluene and triethylamine. The attempt was unsuccessful, presumably because of the insolubility of the complex formed between *p*-dimethylaminophenyltrichlorosilane and triethylamine, and a conversion of 45% of the starting material to *p* - dimethylaminophenyltriethoxysilane contaminated with a little of the desired product was obtained.

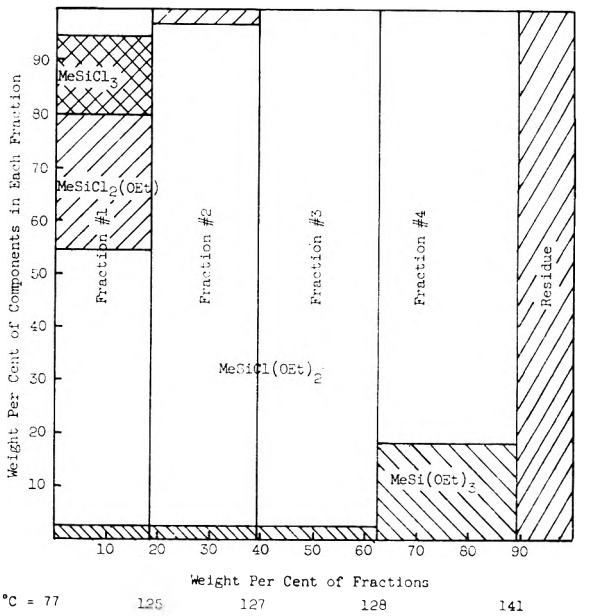

Fig. 1. Composition of distillate from the alcoholysis of methyltrichlorosilane

The aryltrichlorosilanes required for the ethanolysis reactions were prepared by treating silicon tetrachloride with a suitable Grignard reagent. One compound, *p*-*N*,*N*-dimethylaminophenyltrichlorosilane, has not been previously reported.

EXPERIMENTAL

Chlorodiethoxymethylsilane. In a 3 l. flask equipped with an addition funnel, stirrer, thermometer and Dry Ice cold finger condenser was placed 1500 g. (10 mol.) redistilled commercial methyltrichlorosilane. The contents were cooled to 0° with a Dry Ice bath, then stirred rapidly while 920 g. (20 mol.) of anhydrous ethanol was added dropwise over 3.5 hr. After the addition was complete, nitrogen was bubbled through the mixture, and the temperature was gradually raised to 60° over a 3 hr. period. Purging and heating at 60° were continued for an additional hour. The product was distilled through an Oldershaw column having 30 plates and collected from a distillation head set for 30% take-off. The following fractions were collected: fraction 1, 292 g., b.p. 77–125°; fraction 2, 347 g., b.p. 125–127°; fraction 3, 384 g., b.p. 127–128°; fraction 4, 441 g., b.p. 128–141°; residue, 173 g.

Analysis of the fractions was carried out with a Perkin-Elmer model 154B Vapor Fractiometer using column "C" at 125° with 20 p.s.i. helium.

Arylchlorodiethoxysilanes. Compounds shown in Table II were similarly prepared from the appropriate aryltrichlorosilane except that they were purified by distillation through a 15-in. column packed with berl saddles.

Phenyltrichlorosilane used in the preparation of chlorodiethoxyphenylsilane was redistilled commercial grade.

(7) E. G. Rochow, *Chemistry of the Silicones*, 2nd Edition, John Wiley and Sons, Inc., New York (1951).

TABLE II

ARYLCHLORODIETHOXYSILANES PREPARED AND THEIR PROPERTIES

Compound	Yield	B.P., °C./mm.	Analysis					
			Calcd. (%)			Found		
			C	H	Si	C	H	Si
Chlorodiethoxyphenylsilane	95.2	124–126/20	52.06	6.55	12.17	52.68	6.27	12.32 12.27
Chlorodiethoxy-*p*-chlorophenylsilane	88.2	139–142/16	45.28	5.32	10.59	45.41	5.20	10.61 10.82
Chlorodiethoxy-*p*-methoxyphenylsilane	92.4	155–162/14–16	50.64	6.57	10.77	51.10	6.78	10.96 10.58

Other aryltrichlorosilanes were prepared as described below.

p-N,N-dimethylaminophenyltrichlorosilane. A Grignard reagent prepared by the method of Rosenberg[8] from 200 g. (1.0 mol.) *p*-bromo-*N,N*-dimethylaniline in 245 ml. tetrahydrofuran and 27 g. (1.1 g. atoms) magnesium turnings was added dropwise to a stirred solution of 340 g. (2.0 mol.) of redistilled silicon tetrachloride in 1000 ml. heptane which was maintained at 30–40° with an ice bath during the addition. After the product was filtered and concentrated by downward distillation at atmospheric pressure, 104 g. (40.4%) *p-N,N*-dimethylaminophenyltrichlorosilane b.p. 168–171°$_{16\ mm.}$ was obtained as a solid by distillation through a 15-in. Vigreux column.

Anal. Calcd. for $C_8H_{10}Cl_3NSi$: C, 37.73; H, 3.96; Si, 11.02. Found: C, 37.34; H, 4.01; Si, 10.82, 11.00.

Other aryltrichlorosilanes. p-Anisyltrichlorosilane was similarly prepared in a 32.4% yield by adding a Grignard reagent obtained from 200 g. (1.4 mol.) *p*-chloroanisole and 37.5 g. (1.5 g. atoms) magnesium in 383 ml. tetrahydrofuran to 476 g. (2.8 mol.) to silicon tetrachloride in 1500 ml. heptane. The product was obtained by fractional distillation and boiled 117–119°/5.5 mm. Literature, 94–97°/1 mm.[8] and 128–130°/15 mm.[9] *p*-Chlorophenyltrichlorosilane was obtained in a 39.4% yield by treating 680 g. (4 mol.) silicon tetrachloride with a Grignard reagent prepared by the method of Burkhard[10] from 383 g. (2.0 mol.) *p*-bromochlorobenzene and 650 ml. anhydrous ether. Fractional distillation gave the product boiling 115–117°/20 mm. Literature, 99–100°/11.[11]

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(8) S. D. Rosenberg, J. J. Walburn, and H. E. Ramsden, *J. Org. Chem.*, **22**, 1606 (1957).

(9) C. D. Hurd and W. A. Yarnell, *J. Am. Chem. Soc.*, **62**, 1180 (1940).

(10) C. A. Burkhard, *J. Am. Chem. Soc.*, **68**, 2103 (1946).

(11) A. D. Petrov, V. A. Ponomarenko, B. A. Sokolov, and V. U. Roshal, *Zhur. Obshcheĭ Khim.*, **26**, 1229–33 (1956); *Chem. Abstr.*, **50**, 14604 (1956).

Notes

A department for short papers of immediate interest.

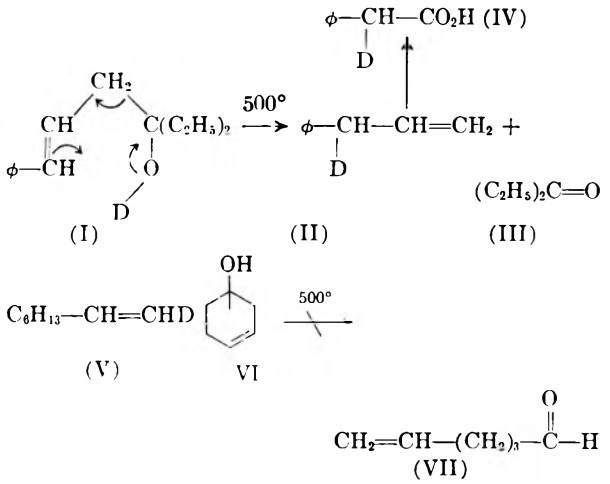
The Mechanism of Pyrolysis of β-Hydroxyolefins

R. T. Arnold and G. Smolinsky

Received August 20, 1959

In a previous publication[1] it was demonstrated that the pyrolytic degradation of β-hydroxyolefins at 500° to form new olefinic substances and aldehydes (or ketones) is a general reaction, and that the well known decomposition of ricinoleic acid into heptaldehyde and undecylenic acid is merely a specific example of this transformation.

Two pieces of evidence have now been found to support the proposal[1] that this thermal degradation occurs *via* a six-membered cyclic transition state. The first of these follows from results of a study of the pyrolysis of 1-phenyl-4-ethylhexen-1-ol-4-*d* (I) to give 3-phenylpropen-1-3-*d* (II) and pentanone-3 (III).



No evidence for the presence of excess deuterium in III was found by careful examination of its infrared spectrum.[2] The —C—D stretching frequency at 4.7μ as well as other differences characteristic of the presence of deuterium[3,4] were, however, found in II and IV. That the deuterium atom in II was located at C_3 and not at C_1 was clearly indicated by the fact that the intensity of the $=CH_2$ deformation bands at 10.04μ and 10.91μ in II and in an authentic sample of allylbenzene were indistinguishable. The presence of any appreciable amount of =CHD should markedly reduce the absorption intensities in the 10–11μ region.[5] Further experimental evidence in support of this view was found by an examination of the infrared spectrum of octene-1-1-*d* (V) which showed the normal —C—D stretching frequency (4.5μ), but the intensity of the deformation bands at 10.1μ and 10.9μ were approximately one half of those observed in an undeuterated sample of octene-1 when measured under identical conditions.

The second piece of evidence in favor of a cyclic mechanism follows from geometric considerations. This mechanism requires the β-hydroxyolefin to have at least one readily attainable conformation in which the hydrogen atom of the hydroxyl group can come into close proximity with the π-electrons of the carbon-carbon double bond. An examination of molecular models indicated that such a conformation is not favorable in cyclohexen-3-ol-1 (VI), and it was predicted that VI upon pyrolysis would not be transformed into its "normal" product VII. This, in fact, proved to be the case. When VI was subjected to the usual conditions for the pyrolytic decomposition of β-hydroxyolefins (*i.e.* 500°), there was obtained a condensate whose infrared spectrum showed the absence of carbonyl compounds. Fractionation of this crude product led to a recovery of starting material (73%) plus a low-boiling component (9%) which we regard as a mixture of cyclohexadienes formed by thermal dehydration. Dehydration has been observed invariably as a side reaction during the pyrolytic decomposition of β-hydroxyolefins.

EXPERIMENTAL

Pyrolysis of 1-phenyl-4-ethylhexen-1-ol-4-d (I). The undeuterated alcohol[1] (17 g.) was dissolved in dry ether (25 ml.) and shaken successively with four portions (1 g. each) of essentially pure deuterium oxide. The etheral solution was dried (sodium sulfate) and distilled to give a quantitative yield of product, b.p. 115–117°/1 mm. This material showed extremely weak absorption in the hydroxyl region, but strong absorption in the 3.7–3.9μ region expected for the —O—D stretching vibration.[6] From the ratio of intensities of the absorption bands, it was estimated that the exchange reaction had occurred to the extent of 90–95%. This material was pyrolyzed (500°), as described earlier, for the undeuterated alcohol[1] to give allylbenzene (b.p. 156°) and pentanone-3 (b.p. 101–102°) in 72% yield. The infrared spectrum of the pentanone-3 was identical with that of

(1) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, *in press*.

(2) All infrared spectra reported in this paper were measured on CCl_4 solutions.

(3) A. Streitwieser and J. R. Wolfe, *J. Am. Chem. Soc.*, **79**, 904 (1957).

(4) R. D. Shutz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959).

(5) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3722 (1958).

(6) A. Weissberger, *Technique of Organic Chemistry*, Interscience Publishers, Inc., New York, Vol. IX, p. 333.

an authentic sample, and no bands attributable to deuterium could be detected. The allylbenzene fraction, however, showed —C—D stretching bands at 4.7μ as well as differences in the 7–13μ region[3,4] when compared with an authentic undeuterated sample of allylbenzene. The strong absorption bands at 10.04μ and 10.91μ[7] were identical in the deuterated and undeuterated samples of allylbenzene indicating the absence of any appreciable =CHD in the former compound. Oxidative degradation of the deuterated allylbenzene (630 mg.) with ozone in ethyl acetate afforded phenylacetic acid (m.p. 74–76°) whose infrared spectrum—compared with authentic undeuterated phenylacetic acid—exhibited differences in the 7–12μ region characteristic of deuterium containing analogs.

Octene-1-1-d (V). Lithium metal (1.38 g.) and 1-bromooctene[8] (20 g.) were allowed to react in ether solution as previously described.[1] The resulting lithium octenyl solution was decomposed with deuterium oxide (4 ml.). The ether solution was dried (sodium sulfate) and fractionated to give octen-1-1-*d*. Yield 7 g. (60%); b.p. 121°; n_D^{25} 1.4078. Reported[9] for 1-octene, b.p. 121–122°; n_D^{19} 1.4085. The intensity of the out-of-plane bending vibrations at 10.1μ and 10.9μ for octen-1-1-*d* were approximately one half of those found in 1-octene. Our sample of octen-1-1-*d* showed the expected —C—D stretching band at 4.5μ.[3]

Pyrolysis of cyclohexen-3-ol-1 (VI). The procedure of Owen and Robins[10] was used in the preparation of this unsaturated alcohol. Cyclohexen-3-ol-1 (7.5 g.) was added dropwise to the pyrolysis tube at 500° in an atmosphere of nitrogen using the procedure normally employed.[1] The infrared spectrum of the condensate showed no carbonyl bands. Fractionation of this material gave a small forerun (0.6 g., 9%)—presumably a mixture of cyclohexadienes and starting material (5.45 g., 73%, b.p. 160–163°, n_D^{25} 1.4840). The nonvolatile residue weighed 0.45 g.

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(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 39.

(8) G. B. Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933).

(9) M. A. Kirrmann, *Bull. soc. chim. France*, [4] **39**, 990 (1926).

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

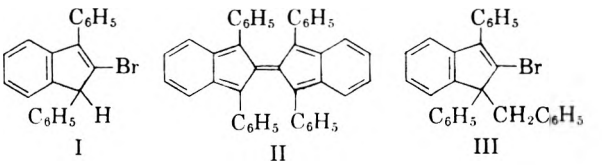
An Attempt to Synthesize 3,5-Diphenylbenzocyclopentatriene, a Cyclic Allene

C. F. KOELSCH

Received August 6, 1959

1,2-Cycloheptadiene has been prepared, but attempts to obtain 1,2-cyclohexadiene have led only to polymers.[1]

Considerable distortion, both bending and twisting, would be involved if the allenic system were present in the still smaller five-membered ring. In spite of this, it was considered of interest to discover what would happen if the sodio derivative of 2-bromo-1,3-diphenylindene (I) were prepared, for the heavy substitution might inhibit polymerization of the expected cyclic allene. If the allene



I II III

could not be isolated, it was considered possible that a dimer (II) might be isolated, and this would be of interest since such a dimer has the structure originally proposed for rubrene,[2] and unsuccessful attempts to synthesize a compound having this structure have been reported.[3]

Surprisingly, it has now been found that the anion of 2-bromo-1,3-diphenylindene shows no tendency to eliminate a bromide anion. When the indene was added to sodium *iso*-propoxide in *iso*-propyl alcohol, a bright yellow solution resulted, and no sodium bromide was formed when this solution was boiled for thirty minutes. That the anion was present was shown by addition of benzyl chloride. This caused immediate disappearance of the yellow color and formation of 1-benzyl-2-bromo-1,3-diphenylindene (III) in nearly quantitative yield. The benzyl derivative was identical with the product of bromination of 1-benzyl-1,3-diphenylindene.

The author thanks the Graduate School of the University of Minnesota for a grant supporting this research, and Mrs. O. Hamerston for the analytical work.

EXPERIMENTAL

2-Bromo-1,3-diphenylindene (I). Bromination of 1,3-diphenylindene has been investigated previously[4] but the 2-bromo derivative has not been reported. It was obtained easily in nearly quantitative yield by adding 3.2 g. of bromine in 5 ml. of carbon tetrachloride to a cooled solution of 5.3 g. of 1,3-diphenylindene in 20 ml. of carbon tetrachloride. The solvent was then removed by distillation and the residue was heated at 100° under reduced pressure for a few minutes. Solution in hexane and chromatography over alumina gave 6.55 g. of colorless oil which solidified completely when it was rubbed with ether-hexane at −70°. Recrystallization from hexane furnished prisms, m.p. 66–68°.

Anal. Calcd. for $C_{21}H_{15}Br$: C, 72.6; H, 4.3. Found: C, 72.5; H, 4.5.

Oxidation of the bromo compound with chromic acid in acetic acid gave *o*-dibenzoylbenzene identified by mixed melting point and infrared spectrum.

(1) A. Favorsky and N. A. Domnin, *Bull. Soc. Chim.*, (4) **3**, 1727 (1936); N. A. Domnin, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 461 (1945); *Chem. Abstr.*, **40**, 4682 (1946); *Vestnik Leningrad Univ.*, I, No. 3, 103 (1946); *Chem. Abstr.*, **42**, 3337 (1948).

(2) C. Moureu, C. Dufraisse, and A. Willemart, *Compt. rend.*, **187**, 266 (1928); Dufraisse and Loury, *Compt. rend.*, **194**, 1832 (1932).

(3) J. C. Eck and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 1898 (1935); C. F. Koelsch and H. J. Richter, *J. Am. Chem. Soc.*, **57**, 2010 (1935).

(4) R. Weiss and S. Luft, *Monatsh.* **48**, 337 (1927); C. Dufraisse and L. Enderlin, *Bull. Soc. Chim.* (5) **1**, 267 (1934).

1-Benzyl-2-bromo-1,3-diphenylindene (III). (a) A solution of sodium *iso*-propoxide from 0.2 g. of sodium in 5 ml. of *iso*-propyl alcohol was treated with 0.7 g. of I and then with 1 g. of benzyl chloride. Volatile materials were removed with steam, and the colorless residue (0.85 g.) was crystallized from ligroin, giving 0.8 g. of prisms, m.p. 117–118°.

(b) A solution of 0.5 g. of 1-benzyl-1,3-diphenylindene[5] in 5 ml. of carbon tetrachloride was treated with 0.2 g. of bromine. The solvent and hydrogen bromide were then removed by short warming at 100° under reduced pressure. Crystallization from ligroin gave 0.5 g. of prisms, m.p. 117–118° alone or mixed with (a); the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{26}H_{21}Br$: C, 76.9; H, 4.8. Found: C, 76.8; H, 5.1.

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(5) C. F. Koelsch, *J. Am. Chem. Soc.*, **56**, 1605 (1934).

Seven-Membered Ring Compounds. X. Hydroxy- and Methoxybenzosuberones

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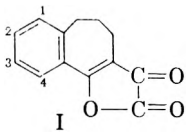
In previous investigations[1] the condensation of benzosuberones with oxalate esters was found to yield cyclic enol esters (I) of the expected glyoxylates, provided that the 4-position of the benzosuberone contained no substituent. In a search for precursors which would be convertible to 4-substituted benzosuberones, we have prepared a number of hydroxybenzosuberones.



I

The condensations of the benzyl ethers of hydroxyaldehydes with diethyl ethylidenemalonate[2] (Table I) proceeded in better yields than the hydroxyaldehydes themselves. Reduction of the cinnamylidenemalonic acids by means of Raney alloy and alkali[3] gave γ-phenylpropylmalonic acids with hydrogenolysis of the benzyl group. The crude malonic acids were heated without purification to obtain the phenylvaleric acids (Table I). As a second usable method, catalytic hydrogenation of several benzyloxycinnamylidenemalonic acids followed by decarboxylation gave benzyl ethers which were hydrolyzed to hydroxyphenyl valeric acids.

The cyclization of hydroxyphenylvaleric acids in polyphosphoric acid (PPA) proceeded in low yield. A cyclization of δ-4-acetoxy-3-methoxyphenylvaleric acid gave material which resisted purification and the attempted cyclization of 4-benzyloxy-3-methoxyphenylvaleric acid gave polymeric material. The cyclization of the benzoates of 2- and 4-hydroxy-3-methoxyphenylvaleric acids by means of PPA gave yields of 51% and 42% respectively.

The assistance of a grant from the National Science Foundation is gratefully acknowledged.

EXPERIMENTAL[5]

4-Benzyloxy-3-methoxycinnamylidenemalonic acid. The following illustrates a convenient modification of the reported method[2] for the condensation of aromatic aldehydes with ethylidenemalonic ester. The cinnamylidenemalonic acids in Table I were obtained by this procedure.

Benzyltrimethylammonium chloride was prepared by the addition of 190 g. of benzyl chloride over a 10 min. period to 350 g. of 25% aqueous trimethylamine at a temperature below 40° maintained by stirring and cooling in an ice bath. After stirring for 3 hr. and standing overnight, the solution was distilled on the water bath at aspirator pressure. The residual solid, after drying for 1 week in a vacuum dessicator, weighed 193 g. (70%).

A solution containing 17 g. of sodium hydroxide in 164 ml. of methanol was added to a flask containing 77.6 g. of benzyltrimethylammonium chloride. After the solution of the salt and standing overnight, the material was filtered by suction and the sodium chloride pressed and washed with a small portion of methanol. To the base was added 23.6 g. (0.0975 mol) of benzylvanillin[6] and 36.6 ml. of ethylidenemalonic ester.[7] The flask was swirled without cooling and stored for 48 hrs. It was diluted with 500 ml. of water, refluxed for 1 hr., cooled, and acidified with 1:1 hydrochloric acid. After standing at 5° for 24 hr. the crystals were filtered, washed with cold water and dried on the steam bath. The orange-yellow solid weighed 26.1 g. (75%) (see Table I).

4-Benzyloxy-3-methoxycinnamylideneacetic acid. A solution of 3.20 g. of the above cinnamylidenemalonic acid in 6.3 ml. of acetic anhydride and 2.7 ml. of pyridine was warmed on the water bath and allowed to stand at room temperature overnight.[8] After dilution with water and decomposition of the acetic anhydride, the solution was extracted with benzene yielding 2.21 g. (79%) of orange-brown crystals m.p. 184–192°. Further purification from ethyl acetate–petroleum ether (b.p. 60–71°) gave fine pale yellow crystals m.p. 203.0–204.0°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.36; H, 5.93.

Phenylvaleric acids. The acids in Table I were obtained by reduction with Raney alloy as described[2,3] with subsequent decarboxylation of the crude malonic acids at 180°. *γ-4-Hydroxy-3-methoxyphenylpropylmalonic acid* was iso-

(1) W. J. Horton, C. E. Hummel, and H. W. Johnson, *J. Am. Chem. Soc.*, **75**, 944 (1953); C. L. Anderson, W. J. Horton, F. E. Walker, and M. R. Weiler, *J. Am. Chem. Soc.*, **77**, 598 (1955).

(2) P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves, *J. Am. Chem. Soc.*, **74**, 5527 (1952).

(3) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 586 (1942).

(4) W. J. Horton and B. W. Rossiter, *J. Org. Chem.*, **23**, 488 (1958).

(5) Melting points of analytically pure materials are corrected.

(6) R. M. Anker, A. H. Cook, and I. M. Heilbron, *J. Chem. Soc.*, 920 (1945).

(7) W. S. Fones, *Org. Syntheses*, **32**, 54 (1952).

(8) F. W. Hinrichsen and W. Triepel, *Ann.*, **336**, 198 (1904).

TABLE I

CINNAMYLIDENEMALONIC ACIDS

	Yield, %	M.P.[a]	M.P. (Cor.)[a] for Anal.	Compound	Calcd. C	Calcd. H	Found C	Found H
3-CH_3O	100	189–196	201.6–202.0[b]	$C_{13}H_{12}O_5$	62.91	4.88	62.88	4.72
3-$C_6H_5CH_2O$	89	162–176	192.0[c]	$C_{19}H_{16}O_5$	70.36	4.97	70.71	5.01
2-$C_6H_5CH_2O$-3-CH_3O	95	130–139	162.3–163.9[d]	$C_{20}H_{18}O_6$	67.79	5.12	68.05	5.15
4-$C_6H_5CH_2O$-3-CH_3O	75	140–154	195.0–195.5[e]	$C_{20}H_{18}O_6$	67.79	5.12	68.10	5.03
PHENYLVALERIC ACIDS								
3-HO	81.5	89–112	115.2–117.0[f]	$C_{11}H_{14}O_3$	68.02	7.27	68.21	7.27
3-CH_2O	79	B.p. 200–220 (1 mm.-bath)	B.p. 142–143 (0.17 mm.)	$C_{12}H_{16}O_3$	69.20	7.75	70.22	7.79
2-HO-3-CH_3O	42	81–88	86.2–88.2[g]	$C_{12}H_{16}O_4$	64.27	7.19	64.61	7.24
4-HO-3-CH_3O	74	86–89	90.5–92.5[h]	$C_{12}H_{16}O_4$	64.27	7.19	63.66	7.31
4-$C_6H_5CH_2O$-3-CH_3O	81[i]	93.5–100	100.5–102[j]	$C_{19}H_{22}O_4$	72.59	7.06	72.62	7.17
BENZOSUBERONES								
2-HO	18[k]	156.5–163.5	164.4–166.1[l]	$C_{11}H_{12}O_2$	74.97	6.87	75.06	6.95
2-CH_3O	94	54–58	58.9–60.3[m]	$C_{12}H_{14}O_2$	75.76	7.42	75.81	7.42
1-$C_6H_5CO_2$-2-CH_3O	51	124–139	138.0–141.4	$C_{19}H_{18}O_4$	73.53	5.85	73.39	5.89
1-HO-2-CH_3O	(82)[n]	88–95	98.4–100.6	$C_{12}H_{14}O_3$	69.88	6.84	69.83	6.84
3-$C_6H_5CO_2$-2-CH_3O	42[o]	119–124	126–127.4[p]	$C_{19}H_{18}O_4$	73.53	5.85	73.65	5.68
3-HO-2-CH_3O	30	106–109	112.0–113.2[q]	$C_{12}H_{14}O_3$	69.88	6.84	70.24	7.04

[a] All cinnamylidenemalonic acids melted with gas evolution. [b] From benzene–ethyl acetate, canary yellow. [c] Instantaneous; from benzene–ethyl acetate, canary yellow. [d] From benzene–ethyl acetate, canary yellow. [e] Golden yellow clumps of spears from methanol. [f] From benzene. [g] From cyclohexane–acetone or aqueous methanol; dark green ferric chloride test. The *benzoate* melted at 98–99.6° (cor.). Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.39; H, 6.10. [h] From cyclohexane; green ferric chloride test. The *acetate*, from benzene–petroleum ether (b.p. 65–110°) melted at 76.5–78.1° (cor.). Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.27; H, 6.85. [i] From the catalytic reduction of the cinnamylidenemalonic acid followed by heating at 180° and extraction with hot cyclohexane. [j] From cyclohexane. [k] Cyclization time 30 min. (95°). [l] From benzene-cyclohexane; identical to the compound obtained (by Mr. Irwin Schmeltz) from 2-methoxybenzosuberone by cleavage with aluminum chloride. The *benzoate* from methanol melted at 60.2–61.2° (cor.). Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.24; H, 5.65. [m] From cyclohexane and sublimed at 0.16 mm. (90° bath). The *oxime*, from cyclohexane and sublimed at 0.12 mm. (140° bath) melted at 127.0–128.8° (cor.). Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.35; H, 7.55. [n] By saponification of the benzoate; deep green ferric chloride test. [o] Cyclization time 25 mins. (90°). [p] From benzene-petroleum ether (b.p. 60–71°). Saponification of the benzoate gave 3-hydroxy-2-methoxybenzosuberone which was methylated to 2,3-dimethoxybenzosuberone, identical to known material.[4] [q] From benzene-petroleum ether (b.p. 60–71°); green ferric chloride test. The *acetate* from petroleum ether (b.p. 90–110°) melted at 104.8–106.4° (cor.). Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.96; H, 6.57.

lated prior to decarboxylation in virtually quantitative yield m.p. 112–119° (gas evol.). From benzene–petroleum ether (b.p. 65–110°) and ethyl acetate–petroleum ether, material melting at 122.8–124.0° (gas evol.) was obtained.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.15; H, 6.01.

The catalytic reduction of 4-benzyloxy-3-methoxycinnamylidenemalonic acid in alcohol over platinum gave a malonic acid with retention of the benzyl group. Decarboxylation gave the benzyl ether of the valeric acid (Table I). Debenzylation[9] gave δ-4-hydroxy-3-methoxyphenylvaleric acid (93.2%) identical to the material produced *via* Raney alloy–sodium hydroxide.

δ-4-Benzoyloxy-3-methoxyphenylvaleric acid. The dried mixture of the benzoate and benzoic acid, m.p. 89–102°, obtained by treatment with benzoyl chloride in aqueous sodium hydroxide was either (a) sublimed 24 hr. at 70° (0.3 mm.) to yield material (76%) m.p. 118–123° which depressed the melting point of benzoic acid or (b) digested three times with water at 90°, filtering after each digestion, to yield product (77%) m.p. 121–124°, similarly depressing the melting point of benzoic acid. By repeated crystallization from benzene–petroleum ether (b.p. 90–110°) 1:10, colorless material m.p. 126.0–127.8° was obtained.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.51; H, 6.13.

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(9) F. E. King, T. J. King, and K. Sellars, *J. Chem. Soc.*, 95 (1952).

2,4′-Diphenylbiphenyl

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Of the nine possible $C_{24}H_{18}$ hydrocarbons consisting of four linked benzene rings, eight are recorded.[1–8] We now report the synthesis of the re-

(1) J. Schmidlin, *Ber.*, **45**, 3179 (1912).

(2) G. F. Woods and I. W. Tucker, *J. Am. Chem. Soc.*, **70**, 3340 (1948).

(3) G. F. Woods, A. L. Van Artsdale, and F. T. Reed, *J. Am. Chem. Soc.*, **72**, 3221 (1950).

(4) W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, **49**, 2089 (1927).

(5) S. T. Bowden, *J. Chem. Soc.*, 1111 (1931).

(6) E. Knoevenagel, *Ann.*, **281**, 72 (1894).

maining compound, 2,4′-diphenylbiphenyl (IV). 2,4′-Dinitrobiphenyl (I)[9] was reduced to 2,4′-diaminobiphenyl (II)[10] and tetrazotized. The tetrazonium hydroxide was decomposed in the presence of benzene[11] to give 2,4′-diphenylbiphenyl (IV), m.p. 209–210° in less than 1% yield. In an alternative synthesis 2,4′-diacetamidobiphenyl (III) was nitrosated and the *N*-nitroso compound was decomposed in benzene solution[12] to give a 3% yield of 2,4′-diphenylbiphenyl.

The availability of 2,4′-diphenylbiphenyl makes possible some further correlations of the ultraviolet absorption characteristics of the quaterphenyls. Ultraviolet absorption data for quaterphenyls and related compounds are recorded in Table I.

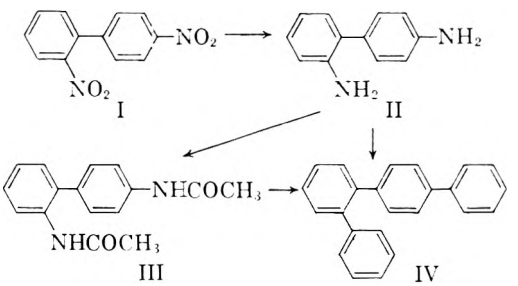
TABLE I
ULTRAVIOLET ABSORPTION DATA FOR QUATERPHENYLS AND RELATED COMPOUNDS

Compound	λ_{max}, mμ	Log ε	Solvent[a]	Ref.
Biphenyl	248	4.3	C	13
p-Terphenyl	276	4.54	H	14
p-Quaterphenyl	292	4.75	H	14
3,4′-Diphenylbiphenyl	~267	4.54	C	3
3,3′-Diphenylbiphenyl	250	4.74	C	3
2,4′-Diphenylbiphenyl	257	4.55	M	
	274	4.55	M	
2,3′-Diphenylbiphenyl	235	4.65	C	3
	255sh.	—	C	3
2,2′-Diphenylbiphenyl	<230	>4.5	E	15
1,3,5-Triphenylbenzene	251	4.76	H	16

[a] The letters stand for the following solvents: C, cyclohexane; H, hexane; M, methanol; E, ethanol.

Two generalizations have been drawn[14] from the spectra of the polyphenyls: For all *p*-polyphenyls, both λ_{max} and ε increase with the number of nuclei present; and for all *m*-polyphenyls, the λ_{max} remains constant (approx. 250 mμ), while ε increases with the number of nuclei present. It has also been observed[3] that an *o*-configuration in a polyphenyl interferes with through-conjugation. The data given in Table I confirm these postulates for the quaterphenyl series. In *p*-quaterphenyl the maximum is at the longest wave length for the series and presumably the chromophore covers the entire molecule. Where *m*- or *o*- configurations are present, the chromophore is broken at that point. Thus, 3,4′-diphenylbiphenyl, in which a *p*-terphenyl structure is found, shows absorption similar to that of *p*-terphenyl, and 3,3′-diphenyl shows absorption at the same wave length as biphenyl, but with almost three times the intensity. 2,4′-Diphenylbiphenyl shows absorption corresponding to both biphenyl and *p*-terphenyl chromophores. 2,3′-Diphenylbiphenyl shows mainly absorption corresponding to single benzene nuclei with a shoulder in the region corresponding to the biphenyl chromophore, and 2,2′-diphenylbiphenyl shows only end absorption in the 230–300 mμ region. 1,3,5′-Triphenylbenzene shows absorption at the same wave length as biphenyl with almost three times the intensity. Presumably each pair of linked rings contributes to the absorption in this case. The spectra of the other two triphenylbenzenes are not recorded.

2,4′-Diphenylbiphenyl shows possibilities as a scintillation solute. It shows a pulse height relative to terphenyl of 1.06 at 3 g./l in toluene[17] and a solubility of 3% in toluene at 27°.



EXPERIMENTAL

2,4′-Diaminobiphenyl. 2,4′-Dinitrobiphenyl, obtained as a by-product from the nitration of biphenyl,[9] was reduced with tin and hydrochloric acid[10] to give the diamine in 65% yield.

2,4′-Diacetamidobiphenyl. Fifteen g. of 2,4′-diaminobiphenyl was heated on the steam bath for 2 hr. with 25 g. of acetic anhydride. The solution was poured into 400 ml. of ice water. The resulting suspension was warmed on a steam bath for 30 min., cooled, and filtered. The crude product was recrystallized from aqueous ethyl alcohol to give 10 g. (61%, from dinitrobiphenyl) of 2,4′-diacetamidobiphenyl, m.p. 198–200°. Reported[10] m.p. 202°.

2,4′-Diphenylbiphenyl. 1. *From 2,4′-diaminobiphenyl.* Six g. of 2,4′-diaminobiphenyl was tetrazotized at 0° in hydrochloric acid. The solution was allowed to warm to 5–6° as 100 ml. of benzene was added. The solution was kept at 5–6° as excess 5*N* sodium hydroxide was added over 1 hr., with rapid stirring. The stirring was continued at 5–6° for 1 hr. and then at room temperature for 20 hr. The benzene layer was separated and dried, and the benzene was removed by distillation to leave 5 g. of a black tar. Sublimation gave 15 mg. of a white solid, m.p. 190–192°. On recrystallization from benzene the m.p. was raised to 208–210°.

(7) J. D. Rose and F. S. Statham, *J. Chem. Soc.*, 69 (1950).
(8) A. F. Odell and C. W. Hines, *J. Am. Chem. Soc.*, **35**, 82 (1913).
(9) H. C. Gull and E. E. Turner, *J. Chem. Soc.*, 494 (1929).
(10) G. Schultz, H. Schmidt, and H. Strasser, *Ann.*, **207**, 354 (1881).
(11) J. Harley-Mason and F. G. Mann, *J. Chem. Soc.*, 1383 (1940).
(12) H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1364 (1938).
(13) R. A. Friedel, M. Orchin, and L. Reggel, *J. Am. Chem. Soc.*, **70**, 199 (1948).
(14) A. E. Gillam and D. H. Hey, *J. Chem. Soc.*, 1173 (1939).
(15) W. S. Rapson, H. M. Schwartz, and E. T. Stewart, *J. Chem. Soc.*, 73 (1944).
(16) W. H. Rodebush and I. Feldman, *J. Am. Chem. Soc.*, **68**, 896 (1946).
(17) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

2. *From 2,4′-diacetamidobiphenyl.* Ten g. of 2,4′-diacetamidobiphenyl was dissolved in 150 ml. of glacial acetic acid and 75 ml. of acetic anhydride. Ten g. of anhydrous potassium acetate and 1 g. of phosphorus pentoxide were added, and the solution was cooled to −5°. The solution was stirred and a solution of 5.5 g. of redistilled nitrosyl chloride in 10 ml. of acetic anhydride was added at −20°. Stirring was continued for 15 min., the mixture was poured onto 500 g. of ice and water and the solution was extracted twice with 200 ml. of benzene. The benzene extract was washed twice with 50 ml. of ice water and dried over anhydrous sodium sulfate. The solution was warmed to 35–40° until no more nitrogen was evolved (1 hr.), filtered, and the benzene removed by distillation to leave 10 g. of a black tar. The black tar was chromatographed on acid alumina (Woelm, Grade I), using benzene as eluant. The eluate coming through the column before the colored material was evaporated to dryness to give 0.3 g. (3%) of 2,4′-diphenylbiphenyl, m.p. 209–210° from benzene or toluene. Ultraviolet absorption: λ_{max} 257 mμ (log ε, 4.55); 274 mμ (log ε, 4.55) in methanol (Beckman DK-2 spectrophotometer). Infrared absorption: 1605(w), 1529(w), 1484(m), 1456(w), 1403(w), 1350(w), 1170(w), 1076(w), 1005(m), 908(w), 839(s), 748(v.s.), 686(s) cm.$^{-1}$ All bands attributable to *o*-, *p*- or monosubstituted benzenes. (KBr pellet; Baird recording double-beam spectrometer).

Anal.[18] Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 93.90; H, 6.20.

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(18) Analysis by Micro Tech Laboratories, Skokie, Ill.

Application of the Equilibrium Theory of Solvent Isotope Effects to Deoxymercuration

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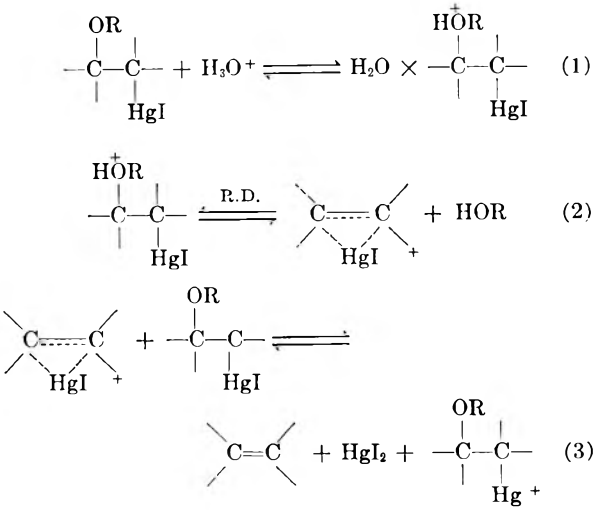
In previous papers[1,2] the mechanism of deoxymercuration induced by nonhalogen acids has been discussed, and evidence favoring a prototropic equilibrium followed by a rate-determining reaction of the protonated substrate was presented. The suggested mechanism is shown in Equations 1–3.



For such a mechanism it would be expected that the equilibrium theory of solvent isotope effects[3] would successfully predict the dependence of rate on solvent deuterium content in partially deuterated water when R is an alkyl group. Although the precision was inadequate for a definite conclusion, the work on 2-methoxy-1-iodomercuripropane (I) suggested that there were systematic differences between observed and predicted rates.[1]

The reason for the lack of precision in the earlier work was that I is deoxymercurated at an inconveniently high rate. The dependence of rate on solvent deuterium content has now been examined for 2-methoxy-1-iodomercuriethane (II). Deoxymercuration of II is slower than deoxymercuration of I by a factor of about 10, so that considerably better precision could be obtained. The present results are in accord with the predictions of the equilibrium theory of solvent isotope effects.[3]

Rates were obtained spectrophotometrically at 25° by following the build-up of the mercuric iodide absorption at 2800 Å. The initial substrate concentration was 3×10^{-5} and the acid was always in large excess. Reactions were followed to 50–80% of completion. With a large excess of acid the mechanism shown in Equations 1–3 leads to the rate law shown in Equation 4,

$$k_1 = \frac{2.303}{2(t - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - D_t)} \qquad (4)$$

where k_1 is the pseudo first-order rate constant and D_t is the optical density at time t.[1] The quantity $\log [(D_\infty - D_0)/(D_\infty - D_t)]$ was evaluated from semilogarithmic plots of $(D_\infty - D_t)$ *vs.* t. A typical example of such a plot is shown in Fig. 1. None of the present plots showed the negative curvature mentioned previously,[1] but such curvature was not specifically sought.

(1) M. M. Kreevoy, *J. Am. Chem. Soc.*, **81**, 1099 (1959).
(2) M. M. Kreevoy and Frances R. Kowitt, *J. Am. Chem. Soc.*, in press.
(3) E. L. Purlee, *J. Am. Chem. Soc.*, **81**, 263 (1959); this paper gives earlier references.

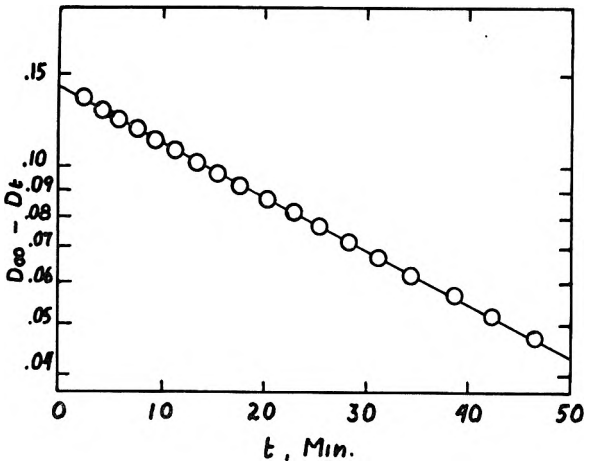


Fig. 1. Typical semilogarithmic plot of $(D_\infty - D_t)$ *vs.* t. The circles are not error circles; they merely identify the points

In undeuterated water, 9 values of k_1 were obtained at acid concentrations ranging from 1.21×10^{-1} to 8.47×10^{-3}. The mean value of $k_2^{H_2O}$ ($k_2 = k_1/(H^+)$) was 3.31×10^{-2}, the average deviation from the mean was 0.07×10^{-2} and the probable error of the mean was 0.02×10^{-2}.[4] No systematic variations in k_2 with acid concentration could be observed. Fourteen determinations of k_2 were made in partially deuterated solutions, the deuterium content ranging up to 98.0 atom %.

Purlee[3] has recently reworked the equilibrium theory of solvent isotope effects, introducing modern values for the various parameters. From his work the rate constant, k_2^n, in a solvent containing 100 n atom % deuterium, is given by Equation 5.

$$\frac{k_2^n}{k_2^{H_2O}} = \frac{1}{Q'(n)}\left[1 - n\left(\frac{k_2^{D_2O}}{3.32k_2^{H_2O}} - 1\right)\right] \qquad (5)$$

In Equation 5, $Q'(n)$ is an empirically determined function of n, tabulated by Purlee,[3] and $k_2^{D_2O}$ is the rate constant in pure D_2O. It has been customary[3] to plot calculated and observed values of $k_2^n/k_2^{H_2O}$ against n. This procedure has two disadvantages: (1) $k_2^{D_2O}$ is not usually available from direct measurements and must be obtained by a short extrapolation; (2) the resulting plots are nonlinear. In the present work it seems desirable to rearrange Equation 5 to get Equation 6, which gives the quantity $Q'(n)k^n$ as a linear function

$$Q'(n)k_2^n = k_2^{H_2O} + n\left(\frac{3.32k_2^{H_2O} - k_2^{D_2O}}{3.32}\right) \qquad (6)$$

of n with intercept k^{H_2O} and slope $(3.32\ k_2^{H_2O} - k_2^{D_2O})/3.32$.[5] Fig. 2 shows the plot of $Q'(n)k_2^n$ *vs.* n obtained from the present data.

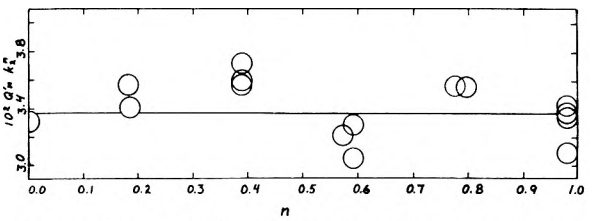


Fig. 2. A plot of $Q'(n)k_2$ *vs.* n. The circles show the error that would be introduced into $Q'(n)k_2^n$ by an uncertainty of ~2% in k_2^n. The latter is the average deviation from the mean for rate constants in H_2O. The point for $n = 0$ is the mean of nine determinations. The line is the least-squares slope

The best straight line, obtained by the method of least squares from all 23 pieces of data, has a slope of 0.000 (apparently accidental) and an intercept, $k_2^{H_2O}$, of 3.37×10^{-2} 1. mole^{-1} sec.$^{-1}$ From the zero slope and the least-squares value of $k_2^{H_2O}$, $k_2^{D_2O}$ has a value of 11.2×10^{-2} 1. mole^{-1} sec.$^{-1}$, and $k_2^{D_2O}/k_2^{H_2O}$ is 3.32. This value is similar to and more accurate than solvent isotope effects previously reported for closely related reactions.[1,2]

The average deviation of the points from the line corresponds to a 5% uncertainty in the quantity $Q'(n)k_2^n$. This is somewhat larger than the average deviation from the mean value of the rate constants in H_2O, but the deviations are not systematic and the fraction D is involved here as an additional variable, because $Q'(n)$ is a function of n. This result is in accord with the expectations following from the suggested mechanism and gives further support to that mechanism.

EXPERIMENTAL

2-Methoxy-1-iodomercuriethane was prepared by the method of Schroeller, Schrauth, and Essers,[6,7] and had a m.p. of 42.5° (uncorr.). Its m.p. has previously been reported to be 42°.[7] Its infrared spectrum was about what one would expect of an aliphatic ether.

Deuterium oxide was obtained from Stuart Oxygen Co. and was certified to be >99.5% D. Three determinations of its deuterium content were made during the course of the kinetic measurements, by determining its density.[8] The results indicated 98.3, 97.5, and 99.7 atom % D, and the D_2O used was all assumed to be 98.5 atom % D, the average of the three.

Methods of making up standard acids and solvents, and the technique of measuring rates have been described previously.[1] The substrate, II, was handled as a stock solution in methanol, with the result that all solutions in which rates were measured contained 2% of methanol by volume. It has been shown, however, that small quantities of methanol have little or no effect on the rate of reactions of this type.[1]

(4) R. Livingston, *Physico Chemical Experiments*, The Macmillan Co., New York, 1957, Chap. I.

(5) Equation 6 is similar to equations used by N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **78**, 582 (1956) to analyze solvent isotope data.

(6) W. Schroeller, W. Schrauth, and W. Essers, *Ber.*, **46**, 2867 (1913).

(7) F. A. Cotton and J. R. Leto, *J. Am. Chem. Soc.*, **80**, 4823 (1958).

(8) I. Kirshenbaum, *Physical Properties and Analysis of Heavy Water*, McGraw-Hill Book Co., Inc., New York, 1951, p. 16

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The Kolbe Electrolysis in Dimethylformamide

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Previous reports[1] from this laboratory have indicated the efficacy of *N,N*-dialkylamides in encouraging the dimerization of cathodically generated organic free radicals. This note describes an extension of the principle to anodic syntheses and presents the results of attempts to improve the yield of dimer in the Kolbe electrolysis[2] of two organic acids.

The most commonly used solvents for the Kolbe electrosynthesis are methanol and water. To a varying degree the Kolbe dimer is accompanied by ethers, alcohols, esters, and monomeric paraffins and olefins.[3] The failure to isolate higher yields of dimer in many of the reactions can be ascribed in part to diversion of the intermediate by reaction with the solvent. To obviate this difficulty a nonreacting, highly polar solvent, dimethylformamide, was used as the electrolysis medium.

The electrolysis of diphenylacetic acid in methanol has been studied previously by Riccobini[4] and by v. d. Hoek and Nauta.[5] In methanol-pyridine mixtures, these workers obtained 6% and 8.9% respectively of tetraphenylethane. Among other products, the latter workers obtained 42.6% of methyl benzhydryl ether. In our hands the electrolysis of diphenylacetic acid in methanol with triethylamine added as the base afforded an 80% yield of methyl benzhydryl ether identified by infrared comparison with authentic material. No tetraphenylethane could be isolated. Likewise, Linstead, Shephard, and Weedon[6] obtained a 73% yield of benzhydrol on saponification of the acetate formed from the electrolysis of diphenylacetic acid in acetic acid.

When the electrolysis medium was changed to dimethylformamide, a 24% yield of tetraphenylethane was obtained. This experiment was conducted for the isolation of only the Kolbe dimer and no attempt was made to find other products.

No description of the Kolbe electrolysis of hydratropic acid could be found in the literature and it was studied in somewhat more detail. Triethylamine again served as the base and the electrolysis was performed in methanol and in dimethylformamide.

In methanol the products obtained in minor amounts included styrene, α-phenethyl alcohol and acetophenone. The major products were 21% of 2,3-diphenylbutane (*meso* and *dl*) and 20% of methyl α-phenethyl ether. The products were analyzed and identified through infrared spectroscopy, vapor phase chromatography and formation of derivatives.

All of the products can be readily explained by the intermediate formation of an α-methylbenzyl radical which can dimerize, react with the solvent or with radicals generated from the solvent, be oxidized, or lose a hydrogen atom.

In dimethylformamide as the solvent the amount of dimer was doubled. 2,3-Diphenylbutane (*meso* and *dl*) was isolated in 41% yield and α-phenethyl alcohol was obtained in 8.2% yield. The latter product could arise from the reaction of the intermediary radical with water present in the dimethylformamide.

It thus appears that dimethylformamide is a good solvent in which to perform the Kolbe electrosynthesis to the relative exclusion of the common side products.

EXPERIMENTAL

All melting points and boiling points are uncorrected. A Perkin-Elmer *154B* vapor fractometer with a "K" column and helium as the carrier gas was used for analysis.

Electrolysis procedure. The electrolysis cell consisted of a 150 ml. tall-form beaker containing the appropriate solution. The cell was cooled with an ice water bath and the cell contents were mixed with a magnetic stirrer. The electrodes were pieces of smooth platinum, 2 cm. × 3 cm., 1 cm. apart and totally immersed in the solution. Current was supplied by a voltage regulated D.C. power supply. An ammeter was connected in series. The initial and final applied voltages for each experiment are indicated. The current was 0.4 amp. and did not vary more than 10% during any of the electrolyses. In each case a solution of 0.1 mol. of the acid, 3 ml. of triethylamine, and 100 ml. of the solvent was used.

Electrolyses. Diphenylacetic acid in methanol. The solution was electrolyzed for 20 hr. and the voltage was increased from 95 volts to 135 volts during the electrolysis. The methanol was partially evaporated at room temperature and the dark residue was poured into a liter of salt water and extracted four times with chloroform. The extract was washed twice with saturated sodium bicarbonate solution and several times with water. It was dried over magnesium sulfate and the chloroform was distilled, leaving a dark tar which would not crystallize. Distillation at 3 mm. gave 16 g. (80%) of methyl benzhydryl ether. Redistillation afforded 15 g., b.p. 86–90° at 0.3 mm., n_D^{28} 1.5623 (reported[7]

(1) M. Finkelstein, R. C. Petersen, and S. D. Ross, *J. Am. Chem. Soc.*, 81, 2361 (1959); S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, in press.

(2) B. C. L. Weedon, *Quart. Revs. (London)*, 6, 380 (1952).

(3) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 580.

(4) L. Riccobini, *Gazz. chim. ital.*, 70, 747 (1940).

(5) A. J. v. d. Hoek and W. T. Nauta, *Rec. trav. chim.*, 61, 845 (1942).

(6) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 3624 (1952).

(7) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, 76, 1207 (1954).

n_D^{29} 1.5685). The infrared spectrum of an authentic sample was identical with that of the electrolysis product.

Diphenylacetic acid in dimethylformamide. The solution was electrolyzed for 17.8 hr. and the voltage was increased from 130 volts to 220 volts during the electrolysis. The reaction mixture was poured into water and extracted three times with ether. Some organic material remained suspended in the ether layer and it was filtered, air dried, and crystallized from chloroform. The ether extract was washed with water, sodium bicarbonate solution, and again with water. The ether was distilled *in vacuo* and the residue was crystallized from chloroform. A further crop of crystals was obtained on concentration of the combined chloroform mother liquors.

A total of 4 g. (24%) of crude product was obtained and was recrystallized from chloroform, m.p. 207–208°. A mixed m.p. with authentic tetraphenylethane[8] was undepressed at 206–207°.

Hydratropic acid[9] *in methanol.* The solution was electrolyzed for 10.7 hr. and the voltage was increased from 80 volts to 120 volts during the electrolysis. The reaction mixture was poured into a liter of salt water and was extracted three times with ether. The ether was washed successively with water, saturated sodium bicarbonate solution, water, 1:1 hydrochloric acid, water, sodium bicarbonate solution, and again with water. After drying over magnesium sulfate the ether was distilled through a Vigreux column and the yellowish residue was distilled at 19 mm. A clear liquid, 3.1 g., b.p. 56–60°, n_D^{28} 1.4950 (reported[10] for methyl α-phenethyl ether n_D^{25} 1.4911) was obtained as the first fraction. Analysis by vapor phase chromatography showed it to consist of 87% of α-phenethyl methyl ether, 3% of styrene (dibromide, m.p. 70–71°, reported[11] m.p. 73°) and a third unidentified component.

The residue was a tan oil, 5.9 g., which solidified on cooling. Crystallization from methanol afforded 721 mg. (6.9%) of solid, m.p. 122–123°, mixed m.p. with authentic *meso*-2,3-diphenylbutane, 122–123°.

The methanol mother liquor was distilled at 0.08 mm. through a short path still. Two fractions were collected: (1) 2.262 g., n_D^{28} 1.5408 and (2) 1.042 g., n_D^{28} 1.5523. Analysis by vapor phase chromatography indicated the following total yield: *meso* and DL-2,3-diphenylbutane, 2.2 g. (21%); α-phenethyl methyl ether, 2.7 g. (19.9%); α-phenethyl alcohol, 0.18 g. (1.5%); and acetophenone, traces.

The infrared spectra of fractions (1) and (2) confirm the presence of the identified substances. A pair of bands at 5.88μ and 7.96μ seem to indicate that the unisolated and unidentified substance retained by the column is an ester.

Hydratropic acid in dimethylformamide. The solution was electrolyzed for 10.3 hr. and the voltage was increased from 130 volts to 260 volts during the electrolysis. The reaction mixture was poured into a liter of salt water and extracted four times with 150-ml. portions of ether. The ether extract was washed successively with water, 1:1 hydrochloric acid, water, saturated sodium bicarbonate solution, again with water, and dried over magnesium sulfate. The ether was distilled through a Vigreux column and the residue was taken up in methanol. Cooling afforded 1.32 g. of *meso*-2,3-diphenylbutane, m.p. 116–120°. The methanol mother liquor was distilled *in vacuo* and three fractions were obtained: (1) 0.7 g., b.p. 96–112° at 15 mm., n_D^{25} 1.5170; (2) 0.4 g., b.p. 112–145° at 15 mm., n_D^{25} 1.5238; (3) 2.8 g., b.p. 115–145° at 0.8 mm., n_D^{25} 1.5455; a further 0.1 g. of *meso*-2,3-diphenylbutane was obtained as a solid in the distillation apparatus. Fractions (1), (2), and (3) were analyzed by vapor phase chromatography.

The total yield of *meso* and *dl*-2,3-diphenylbutane was 4.3 g. (41%) and of α-phenethyl alcohol, 1 g. (8.2%).

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SPRAGUE ELECTRIC COMPANY
NORTH ADAMS, MASS.

(8) F. J. Norris, R. Thomas, and B. M. Brown, *Ber.*, **43**, 2959 (1910).

(9) E. L. Eliel and J. P. Freeman, *J. Am. Chem. Soc.*, **74**, 923 (1952).

(10) S. I. Miller, *J. Org. Chem.*, **21**, 247 (1956).

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 315.

Palladium Catalysts. IX.[1] Kinetic Studies

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Previous papers report that the qualitative character of palladium-on-carbon catalysts may be influenced by such factors as the presence of other metals,[4] the ratio of metal to carrier,[5] and by the nature of the anion present when the metal is deposited on the carrier.[1,6] There is also evidence that a product formed during the hydrogenation reaction may inhibit the catalytic reaction.[7] Results of further studies along these lines are now presented.

In order to control external variables during the hydrogenation reaction the apparatus shown schematically in Fig. 1 was designed. With it one may maintain a constant pressure of hydrogen within the vicinity of one atmosphere throughout the entire course of the reaction; the rate of agitation is constant; the temperature may be controlled to within 0.2°. Results obtained with this apparatus permit the observation of the kinetic order of the reaction and allow for more valid comparison of one reaction with another and, it is hoped, contribute to a better understanding of the catalytic mechanisms.

In Fig. 2 are shown graphically the effects of temperature variation on the reduction of nitrobenzene. In all instances the rate of hydrogen absorption with respect to substrate is zero order as was previously observed by Rampino and Nord.[8]

The phenylcarbonyl compounds with one molecule of hydrogen form the corresponding carbinols, and with two molecules of hydrogen undergo

(1) For number VIII see W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.*, **21**, 999 (1956).

(2) Sharp and Dohme Fellow 1952–1955. Present address: Polychemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Del.

(3) Experimental work performed at the University of North Carolina.

(4) W. H. Hartung and Y.-T. Chang, *J. Am. Chem. Soc.*, **74**, 5927 (1952).

(5) J. G. Young and W. H. Hartung, *J. Org. Chem.*, **18**, 1659 (1953).

(6) E. W. Reeve and W. H. Hartung, unpublished. See note in ref. (4).

(7) K. L. Waters and W. H. Hartung, *J. Org. Chem.*, **10**, 524 (1945).

(8) L. D. Rampino and F. F. Nord, *J. Am. Chem. Soc.*, **65**, 429 (1943).

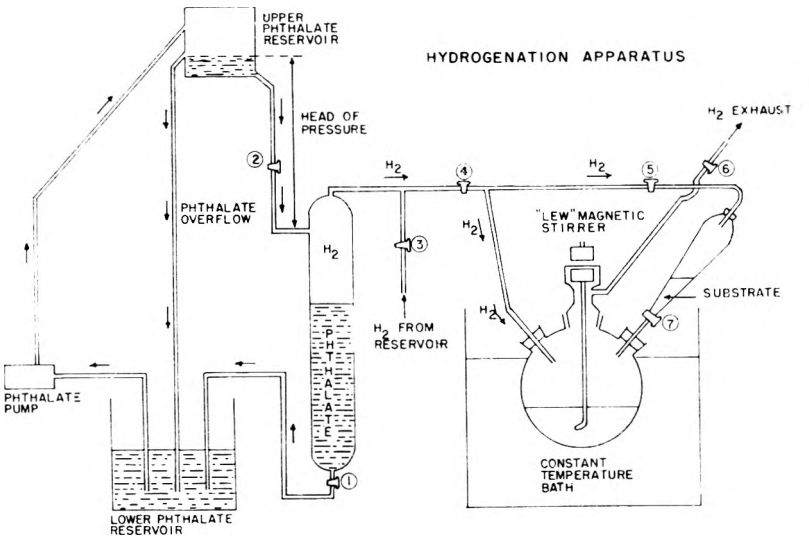

Fig. 1. Scheme of hydrogenation apparatus. The upper phthalate reservoir may be adjusted up or down, depending on the barometric reading and the vapor pressure of the solvent at the temperature of the reaction. Di-*n*-butyl phthalate, because of its negligible vapor pressure, is used to displace the hydrogen in the gas buret. The air in the apparatus may be swept out and displaced by hydrogen through stopcock 3 and out at stopcock 6. The pressure is measured by attaching a manometer at stopcock 3. Constant rate of stirring is maintained by a constant voltage regulator and the speed is measured with a hand tachometer

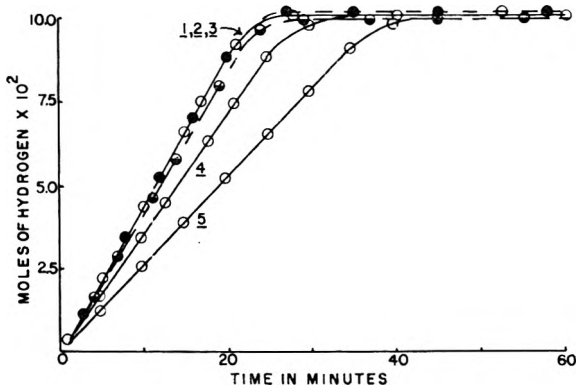

Fig. 2. Reduction of nitrobenzene. Solvent: ethanol. Total volume: 100 ml. 0.033 mol. nitrobenzene. 2 g. of catalyst, 20 mg. $PdCl_2$ per gram. Curves 1, 2, and 3 at 35°; curve 4 at 30°; curve 5 at 25°

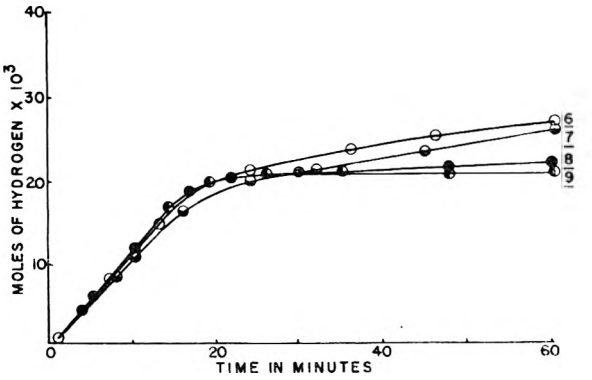

Fig. 3. Reduction of propiophenone. Solvent: ethanol. Total volume: 100 ml. 0.02 mol. propiophenone. 2.0 g. of catalyst, 50 mg. $PdCl_2$ per gram. Curve 6: no propylbenzene; curve 7: 0.040 mol. propylbenzene; curve 8: 0.060 mol. propylbenzene; curve 9: 0.10 mol. propylbenzene

hydrogenolysis to form the hydrocarbon. Hartung and Crossley,[9] reported that propiophenone was reduced to propylbenzene without evidence of forming the intermediate carbinol; presumably during a single contact of the substrate with the catalyst two molecules of hydrogen were transferred.[10] The palladium then employed regrettably is no longer available.[11] Subsequent studies have been carried out with catalysts prepared from pure palladium.[12] The results now point to a reduction in two steps, first to the carbinol and then hydrogenolysis to the hydrocarbon. Typical results are shown graphically for propiophenone in Fig. 3. The first half of the reaction is zero order; the second half is indeterminate, the hydrogenolysis of the carbinol being progressively inhibited by the hydrocarbon as it forms in increasing amounts. Thus curve 6 of Fig. 3, for example, had the reaction been continued (as observed in other experiments) would have approached with decreasing slope the value of hydrogen uptake calculated for complete conversion to propylbenzene. Curve 7, showing the reduction of 20 millimoles of propiophenone in the presence of 40 millimoles of propylbenzene, slopes off much earlier; and curves 8 and 9, with 60 and 100 millimoles, respectively, of propylbenzene, become substantially parallel with the time axis when the ketone is reduced to carbinol.

(9) W. H. Hartung and F. S. Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).

(10) E. W. Reeve (unpublished) later repeated these experiments and was able to detect, by interrupting the reaction, traces of carbinol in the mixture comprised principally of unreduced propiophenone and propylbenzene. This is felt to establish only that with the catalyst then available only a small amount of product was desorbed after the transfer of one molecule of hydrogen into the ketone.

(11) W. H. Hartung and Y.-T. Chang, *J. Am. Chem. Soc.*, **74**, 5927 (1952).

(12) *Cf.* footnote 8 in ref. (11).

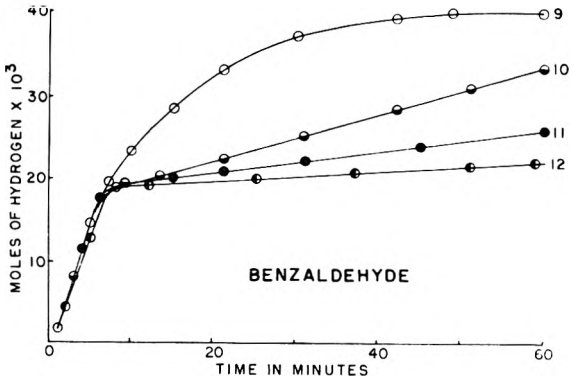

Fig. 4. Reduction of benzaldehyde. Solvent: ethanol. Total volume: 100 ml. 0.020 mol. benzaldehyde. 2 g. of A-50 catalyst.[1] Curve 9: no toluene; curve 10: 0.05 mol. toluene; curve 11: 0.1 mol. toluene; curve 12: 0.30 mol. toluene

[1] For explanation see ref. (1)

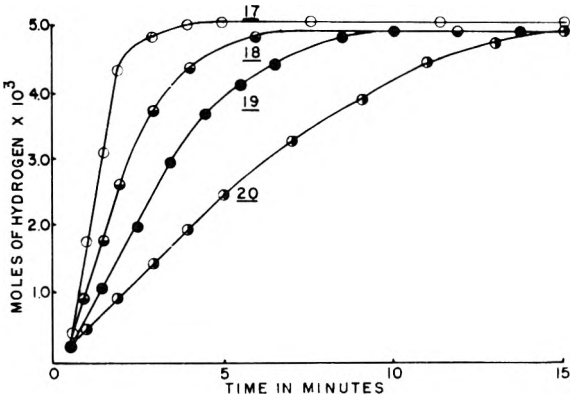

Fig. 6. Reduction of benzyl acetate. Solvent: ethanol. Total volume: 100 ml. 0.005 mol. benzyl acetate. Curve 17: 2 g. of A-100 catalyst; curve 18: 1 g. of A-100 catalyst; curve 19: 0.5 g. of A-100 catalyst; curve 20: 0.25 g. of A-100 catalyst

A similar phenomenon is seen with benzaldehyde, Fig. 4. The reduction to benzyl alcohol proceeds at zero order, and even large amounts of toluene in the solvent have no significant effect on this rate. However, the presence of increasing amounts of toluene have increasing inhibitory effect on the hydrogenolysis of benzyl alcohol.

Other phenylcarbonyl compounds show similar behavior. Desoxybenzoin is rapidly reduced to the carbinol, and the hydrogenolysis of the carbinol then proceeds at a progressively decreasing rate; if diphenylethane is added at the start of the reaction, it has no observable effect on the rate at which the ketone reduces, but has a marked retarding effect on the hydrogenolysis of the carbinol. Acetophenone behaves in an analogous manner.

The hydrogenolysis of benzyl acetate yields interesting results, Figs. 5 and 6. In ethyl acetate solvent the inhibitory effect of the toluene formed during the reaction is sufficiently pronounced to modify the initial zero order to a progressively slowing and indeterminate rate. The addition of toluene at the beginning of the reaction causes earlier deviation. In ethanol solvent the inhibitory effect of the toluene is less pronounced and is absent if adequate catalyst is employed; as the amount of catalyst is decreased, the inhibitory effect becomes correspondingly more pronounced.

A mechanism for the inhibitory effect of propylbenzene in the reduction of the corresponding carbinol is proposed in Fig. 7.

It is not suggested, however, that all deviations from zero order reaction rates are to be attributed to inhibition such as here observed. Another factor that is expected to show similar kinetic results is the erosion or inactivation of the catalyst. A discussion of such phenomena will be delayed until more data become available.

The two-stage hydrogenation as observed with the conversion of phenylcarbonyl compounds to the corresponding hydrocarbon poses an interesting question as to the character of the active sites in the palladium-on-carbon catalysts, especially in view of the observation by Beamer and co-workers[13] that these catalysts have centers which appear to be substrate-specific. It will be observed from Fig. 3 that propylbenzene does not compete with propiophenone for the active sites but does compete with the carbinol; and toluene does not compete with benzaldehyde but does inhibit benzyl alcohol. Does this signify that in the catalyst there are different sites for the carbonyl compound than for the carbinol? This question is all the more interesting since once there was available a catalyst[9] with quite different properties. Further studies are projected.

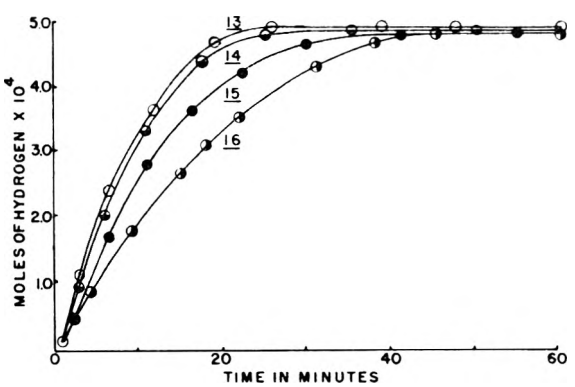

Fig. 5. Reduction of benzyl acetate. Solvent: ethyl acetate. Total volume: 100 ml. 0.005 mol. benzyl acetate. 2 g. of A-100 catalyst.[1] Curve 13: no toluene; curve 14: 0.01 mol. toluene; curve 15: 0.02 mol. toluene; curve 16: 0.04 mol. toluene

[1] For explanation see ref. (1).

EXPERIMENTAL

All reagents were carefully purified, and all substrates were "detoxified" by standing in contact for 24 hr. or more with unused Pd-C catalyst.

(13) R. L. Beamer, J. D. Smith, J. Andrako, and W. H. Hartung, *in press.*

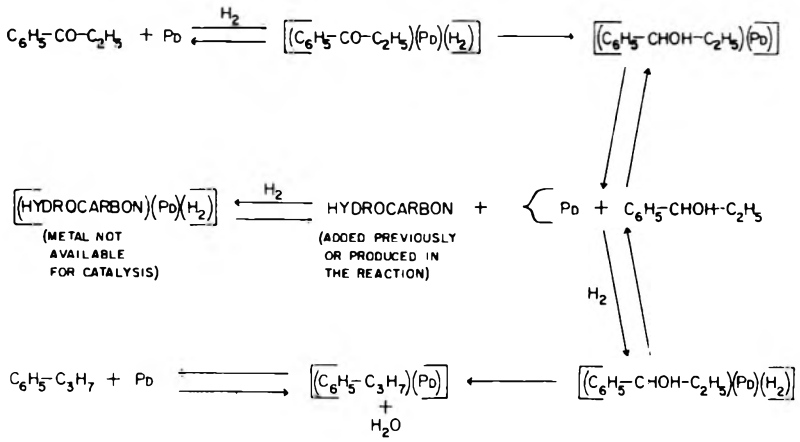

Fig. 7. Mechanism of inhibition

The catalysts were prepared as described in earlier papers of this series.

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o-Hydroxyphenylphosphonic Acid

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Although a number of hydroxy-substituted arylphosphonic acids are known,[1] the preparation of *o*-hydroxyphenylphosphonic acid, the phosphorus analog of salicylic acid, has not previously been accomplished. Kennedy, Lane, and Willans[2] have investigated two possible methods for the synthesis of this phosphonic acid. They found that attempts to demethylate *o*-methoxyphenylphosphonic acid caused cleavage of the carbon-phosphorus bond; and they reported that the diazo reaction could not be used to convert *o*-benzyloxyaniline to *o*-benzyloxyphenylphosphonic acid (which they planned to debenzylate by hydrogenation). The present study was undertaken in the hope of developing a satisfactory method for the preparation of *o*-hydroxyphenylphosphonic acid and related compounds.

As noted by Kennedy, Lane, and Willans,[2] the demethylation of *o*-methoxyphenylphosphonic acid is not a promising route to the synthesis of the corresponding hydroxy compound. In this laboratory we found that after the *o*-methoxy compound was refluxed with 42% hydrobromic acid for 24 hr., over 90% of the phosphorus had been converted to inorganic phosphate. Attempts to replace the bromine in *o*-bromophenylphosphonic acid with the hydroxyl group were also unsuccessful. Thus, heating the *o*-bromo compound with 4*N* sodium hydroxide in an autoclave at 120° resulted in splitting little or no bromine from the ring. In the presence of cuprous oxide the bromine could be replaced by the hydroxyl group. In the process, however, a certain amount of phosphorus was also cleaved from the ring, and we were never able to isolate any *o*-hydroxyphenylphosphonic acid from the reaction mixture. In brief, the results we obtained in trying to convert *o*-methoxy- or *o*-bromophenylphosphonic acid into the hydroxy compound were similar to those reported[3] for the corresponding *para*-substituted acids.

We were successful, however, in obtaining *o*-hydroxyphenylphosphonic acid by the catalytic hydrogenolysis of *o*-benzyloxyphenylphosphonic acid. Several methods for preparing the latter compound were examined. We first investigated the preparation of the acid from the corresponding diazonium fluoborate. Although the diazonium compound could not be prepared by diazotizing *o*-benzyloxyaniline in fluoboric acid, the amine was readily diazotized in hydrochloric acid and the diazonium fluoborate precipitated by the addition of sodium fluoborate. The diazonium salt was then suspended in ethyl acetate and treated with phosphorus trichloride and cuprous bromide under the usual conditions.[4] Steam distillation of the reaction mixture in the customary manner, however, resulted in cleavage of the ether linkage. Accordingly, the conditions were modified to avoid debenzylation; details of the procedure used for iso-

(1) (a) G. B. Arnold and C. S. Hamilton, *J. Am. Chem. Soc.*, **63**, 2637 (1941); (b) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 753 (1952). (c) R. W. Bost and L. D. Quin, *J. Org. Chem.*, **18**, 358 (1953); (d) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 6307 (1953).

(2) J. Kennedy, E. S. Lane, and J. L. Willans, *J. Chem. Soc.*, 4670 (1956).

(3) V. L. Bell, Jr., and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 4901 (1953).

(4) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951).

lating the desired acid are described in the Experimental section.

We also were able to obtain *o*-benzyloxyphenylphosphonic acid by the reaction between *o*-bromophenylphosphonic acid, benzyl alcohol, and anhydrous potassium carbonate. The desired compound was obtained in only 10% yield. However, we were able to isolate from the reaction mixture a second phosphonic acid in 32% yield. The analysis and ultraviolet absorption spectrum (*cf.* Table I) of this unknown phosphonic acid indicated that it was either 2,2′-diphosphonodiphenyl ether[5] or a hydrate of 2,2′-biphenylenediphosphonic acid. The second possibility was effectively eliminated when we found that the compound lost no weight when heated to 200° for 1 hr. When the compound was heated to 240°, it decomposed to give a 69% yield of diphenyl ether (identified by its b.p. and ultraviolet absorption spectrum) and a residue of inorganic phosphate.[6] There seems little doubt, therefore, that the unknown phosphonic acid must be 2,2′-diphosphonodiphenyl ether.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

Compound	λ_{max}, mμ	ϵ_{max}
Phenyl ether[a]	221–225[b]	10,000
	265	1,570
	271	1,850
	278	1,630
o-Phenoxyphenylphosphonic acid[c]	229	9,110
	278.5	3,410
o-Biphenylylphosphonic acid[d]	237	8,220
	274.5	2,030
Unknown phosphonic acid[e]	235.5	7,840
	278.0	3,920

[a] Reagent grade material (Eastman Kodak Co. 104). [b] Shoulder. [c] Prepared as described by L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **23**, 769 (1958). [d] Taken from L. D. Freedman, *J. Am. Chem. Soc.*, **77**, 6223 (1955). [e] Shown to be 2,2′-diphosphonodiphenyl ether (see text). The ε values were calculated on this basis.

o-Hydroxyphenylphosphonic acid at a concentration of 0.01*M* showed significant activity (*i.e.*, at least 50% inhibition compared to the controls) *in vitro* against one strain of *Escherichia coli* and three strains of pathogenic *Staphylococcus aureus:* slight activity at this concentration was found against one strain of *Aerobacter aerogenes.*[7]

EXPERIMENTAL[8]

o-Benzyloxypherylphosphonic acid. A. From the diazonium fluoborate and phosphorus trichloride. *o*-Nitrophenyl benzyl ether[9] (23.0 g.) was dissolved in 200 ml. of 95% ethanol and shaken for about 2 hr. with Raney nickel and hydrogen at 40 lb. pressure. After the catalyst was removed by filtration, the amine was isolated by evaporating the filtrate to about 20 ml. and cooling in the deep freeze at −25°. The crystals obtained were washed with 5 ml. of petroleum ether and dried *in vacuo*. The yield of *o*-benzyloxyaniline was 87%; m.p. 36.5–37° (lit.[9] 39–40°).

A mixture of 0.2 mol. of the above amine and 150 ml. of 6*N* hydrochloric acid was boiled, with stirring, for about 5 min. to form the amine hydrochloride. The resulting suspension was quickly cooled to 0° and then diazotized with a solution of sodium nitrite. During this reaction, the temperature was kept below 5°. The diazonium fluoborate was then precipitated with a cold solution of sodium fluoborate.[10] The yield was 87%, decomposition temperature about 135°.

o-Benzyloxybenzenediazonium fluoborate (149 g., 0.5 mol.) was suspended in dry ethyl acetate and treated with phosphorus trichloride and cuprous bromide in the usual manner.[4] No evolution of nitrogen occurred until the mixture was warmed to about 55°. After nitrogen evolution had ceased, the reaction mixture was cooled to 5° and hydrolyzed by the dropwise addition of 200 ml. of water. The solution was then concentrated to 400 ml. *in vacuo* at a temperature below 45° and extracted with four 200-ml. portions of ether. The combined ether solutions were then extracted with 1 l. of 10% sodium carbonate solution. The aqueous alkaline solution was then treated with Darco and acidified with concentrated hydrochloric acid to *p*H 0.4, whereupon crude *o*-benzyloxyphenylphosphonic acid crystallized from solution. After recrystallization from aqueous acetone, the yield was 21%; m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{13}PO_4$: C, 59.10; H, 4.96; P, 11.72. Found: C, 59.11; H, 5.25; P, 11.97.

B. From o-bromophenylphosphonic acid and benzyl alcohol. An intimate mixture of 10.0 g. of *o*-bromophenylphosphonic acid,[11] 20 ml. of redistilled benzyl alcohol, 10.0 g. of anhydrous potassium carbonate, and 0.2 g. of copper powder was heated under reflux for a period of 16 hr. The reaction mixture was then diluted with about 35 ml. of water, and the excess benzyl alcohol was removed by steam distillation. The residual liquid[12] from the steam distillation was treated with Darco and then acidified to *p*H 0.4 to obtain crude *o*-benzyloxyphenylphosphonic acid. The yield of the pure acid, after recrystallization, was 1.1 g. (10%).

The original filtrate from the crude *o*-benzyloxyphenylphosphonic acid was acidified further with 10 ml. of concentrated hydrochloric acid and then evaporated to dryness on a steam bath. The residue was further dried in a desiccator over sodium hydroxide. The solid thus obtained was pul-

(5) This possibility was first suggested to us by Professor Robert L. McKee of the University of North Carolina.

(6) It has been known for a long time that heating phosphonic acids at relatively high temperatures may result in splitting of the carbon-phosphorus bond. Thus, A. Michaelis and C. Mathias [*Ber.*, **7**, 1070 (1874)] found that phenylphosphonic acid decomposes at 250° into benzene and metaphosphoric acid. More recently, H. Z. Lecher, T. H. Chao, K. C. Whitehouse, and R. A. Greenwood [*J. Am. Chem. Soc.*, **76**, 1045 (1954)] have reported that 2-naphthylphosphonic acid, when heated in a sealed tube at 275° for 24 hr., gives naphthalene and metaphosphoric acid. Unpublished work from this laboratory indicates that phenylphosphonic acids containing alkyl, aryl, alkoxy, phenoxy, or halogen substituents undergo a similar type of decomposition at 240°.

(7) We are grateful to Dr. J. D. Thayer, Chief of the Biology Section of our laboratory, for testing this compound.

(8) Melting points were taken as previously described; *cf.* ref. 4. Phosphorus was determined by the method of B. C. Stanley, S. H. Vannier, L. D. Freedman, and G. O. Doak, *Anal. Chem.*, **27**, 474 (1955).

(9) A. Sieglitz and H. Koch, *Ber.*, **58B**, 78 (1925).

(10) A. Roe, *Org. Reactions*, **V**, 203 (1949).

(11) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 683 (1953).

(12) Bromide ion analyses on aliquots of this liquid showed that all the bromine had been split from the ring.

verized and then extracted for several hours with 250 ml. of ether in a Soxhlet apparatus.[13] The material in the thimble was then extracted for 8 hr. with 250 ml. of absolute ethanol. The alcoholic solution was evaporated to dryness, and the residue was recrystallized from 6*N* hydrochloric acid. The yield of pure *2,2'-diphosphonodiphenyl ether* was 2.0 g. (32%); m.p. 233–235°.

Anal. Calcd. for $C_{12}H_{12}O_7P_2$: C, 43.65; H, 3.66; P, 18.76; neut. equiv. (for two ionizable hydrogens per molecule), 165.1. Found: C, 43.46; H, 3.96; P, 18.50; neut. equiv. (to *p*H 4.3), 168.2.

o-Hydroxyphenylphosphonic acid. A solution of 5.28 g. of *o*-benzyloxyphenylphosphonic acid in 50 ml. of 95% ethanol was shaken with 5.0 g. of 10% palladium-on-carbon[14] under an initial hydrogen pressure of 40 lb. After the uptake of hydrogen ceased, the catalyst was removed by filtration and the solvent distilled off under vacuum. The resulting sirup solidified when dried in a desiccator over calcium chloride. The crystals obtained were further dried *in vacuo* at 100°. The yield was quantitative, m.p. 124–127°.

Anal. Calcd. for $C_6H_7O_4P$: C, 41.39; H, 4.05; P, 17.79. Found: C, 41.17; H, 4.27: P, 17.51.

Absorption spectra measurements. The ultraviolet absorption spectra were determined in 95% ethyl alcohol by the procedure previously described.[15]

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(13) This step served to remove a small amount of colored material.

(14) R. Mozingo, *Org. Syntheses*, Col. Vol. III, 687 (1955).

(15) H. H. Jaffé and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 1069 (1952).

9-Substituted-9-hydroxy-Δ^{10}-ergolenes

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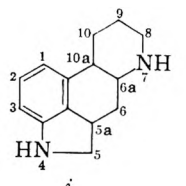
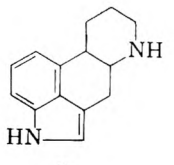
Numerous times during the course of our work on the total synthesis of lysergic acid[1] we found it appropriate to submit certain of the intermediates for pharmacological evaluation. On one such occasion we became interested in some 9-substituted-9-hydroxy-7-methyl-Δ^{10}-ergolenes (I).[2]



i



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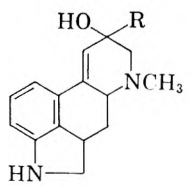

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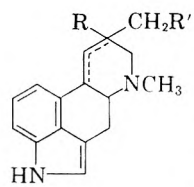

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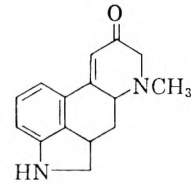
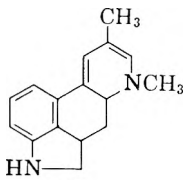


III

We were further intrigued by the possibility of synthesizing several new alkaloids which have been obtained by other workers during their studies on the fermentation of various strains of the ergot fungus.[3] Several members of this group of alkaloids are agroclavine (II, Δ^9, R′ = H), elymoclavine (II, Δ^9, R′ = OH), penniclavine (II, Δ^{10}, R = R′ = OH), and setoclavine (II, Δ^{10}, R = OH, R′ = H). The desired synthetic compounds, I (R = methyl, ethyl, allyl, phenyl), were prepared by the action of the appropriate organo-lithium compound or Grignard reagent on 9-keto-7-methyl-Δ^{10}-ergolene (III).[1] Except in the case of the phenyl substituted compound, it was necessary to employ an extremely large excess of reagent in order to obtain the product. Subsequent efforts to convert I (R = CH_3) to setoclavine by dehydrogenation were unrewarding.

The dehydration of I (R = CH_3) to 7,9-dimethyl-$\Delta^{8,10}$-ergoladiene (IV) was accomplished by the use



IV

of boron trifluoride. Evidence for the endocyclic position of the newly introduced double bond was the absence of terminal methylene absorption in the infrared spectrum.

Pharmacologically, these materials are characterized by their oxytocic, hypothermic, and central nervous system activity. Details of these studies will be published elsewhere.

(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956).

(2) In order to avoid the cumbersome nomenclature of this multi-ring system, we have assigned the generic name ergolane to 4, 5, 5a, 6, 6a, 7, 8, 9, 10,10a-decahydroindolo-[4,3-*fg*]quinoline (*i*). The name ergoline has been assigned to the corresponding Δ^5-compound (ii) by W. A. Jacobs and R. G. Gould, Jr., *J. Biol. Chem.*, **120**, 142 (1937).

(3) M. Abe, T. Yamano, Y. Kozu, and M. Kusumoto, *J. Agr. Chem. Soc. Japan*, **25**, 458 (1952); **29**, 364, 697 (1955); M. Abe, and S. Yamatodani, *J. Agr. Chem. Soc. Japan*, **28**, 501 (1954); *Bull. Agr. Chem. Soc. Japan*, **19**, 92, 94, 161 (1955); M. Pöhm, *Die Pharmazie*, **11**, 110 (1956); A. Stoll, A. Brack, H. Kobel, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **37**, 1815 (1954); A. Hofmann, R. Brunner, H. Kobel, and A. Brack, *Helv. Chim. Acta*, **40**, 1358 (1957).

EXPERIMENTAL

Melting points were determined in soft glass capillary tubes and are uncorrected.

9-Hydroxy-7,9-dimethyl-Δ^{10}-ergolene. Methyllithium in ether solution was prepared by dropwise addition of methyl iodide (148 g., 1.04 mol.) to a stirred suspension of 14.6 g. (2.08 mol.) of lithium ribbon in 350 ml. of dry ether. The solution was stirred for 0.5 hr. after the addition was complete and then with ice-bath cooling there was added slowly a solution of 10 g. (0.042 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole. The reaction mixture was stirred for several hours at room temperature, allowed to stand overnight, and then decomposed by slow addition of 150 ml. of ice water. Part of the product which was insoluble in both the organic and aqueous phases separated at this point and was removed by filtration and crystallized from methanol; yield, 3.72 g., m.p. 206–208°. Another crop was obtained from the ether-anisole layer by extraction with dilute hydrochloric acid, neutralization of the extract with sodium bicarbonate and extraction with chloroform. The chloroform extract on evaporation gave 0.63 g. of the methyl carbinol. The total yield was 4.35 g. (41%). A sample was recrystallized from methanol for analysis, m.p. 209–212°.

Anal. Calcd. for $C_{16}H_{29}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.01; H, 7.98; N, 10.82.

9-Ethyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. Ethylmagnesium bromide was prepared in the usual fashion in a 1 l. 3-necked flask using 113 g. of ethyl bromide, 25.4 g. of magnesium, and 350 ml. of ether. After addition of the ethyl bromide was complete, the solution was stirred for 30 min. and then cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 20 min. and the reaction mixture was allowed to stir for 2 hr. at room temperature and then to stand overnight. Decomposition of the complex was carried out by the addition of 140 ml. of saturated aqueous ammonium chloride solution at 0°. The organic layer was decanted and the sludge was extracted with chloroform. About 25 ml. of 50% aqueous sodium hydroxide was added and the sludge was again extracted with chloroform. The combined chloroform extract was washed with water and then extracted with three portions of dilute hydrochloric acid, each containing 5 ml. of the concentrated acid. The acid extracts were carboned and neutralized with an excess of sodium bicarbonate and then extracted with four 75 ml. portions of warm chloroform. The extracts were warmed to keep the product in solution, dried quickly over magnesium sulfate, and concentrated *in vacuo*. The residue was taken up in a little methanol, and the ethyl carbinol was filtered and washed with methanol and ether; yield, 2.67 g. (24%). A sample for analysis was recrystallized from methanol containing a little water, m.p. 204–206° (dec.).

Anal. Calcd. for $C_{17}H_{29}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.80; H, 8.77; N, 10.29.

9-Allyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. The allyl Grignard reagent was prepared in a 3 l. 3-necked flask by the addition during 5–6 hours of a solution of 126 g. (1.1 mol.) of allyl bromide in 625 ml. of dry ether to a stirred suspension of 76 g. (3.1 mol.) of magnesium in 250 ml. of ether. Stirring was continued for 15 min., after which the reaction mixture was cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 10 min. Stirring was continued at room temperature for 3 hr., and the mixture was allowed to stand overnight. It was then cooled and decomposed by addition of 140 ml. of saturated aqueous ammonium chloride solution. Ethyl acetate (300 ml.) was added and the organic layer was decanted. The sludge was extracted with ethyl acetate and then with chloroform. Fifty milliliters of 50% aqueous sodium hydroxide was then added, and the sludge was again extracted with chloroform. The chloroform extracts were combined and extracted five times with dilute hydrochloric acid (each portion containing 5 ml. of concentrated acid). The combined acid extract was neutralized with an excess of sodium bicarbonate and the allyl carbinol was extracted with three 200 ml. portions of chloroform. The combined extract was dried over magnesium sulfate and evaporated *in vacuo*. The product was digested with methanol, filtered and washed with methanol and ether; yield, 6.64 g. (62%). A sample was recrystallized from ethanol containing a little water, m.p. 198–202° (dec.).

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.75; H, 8.34; N, 9.59.

9-Hydroxy-7-methyl-9-phenyl-Δ^{10}-ergolene. Phenylmagnesium bromide was prepared in the usual way from 15.7 g. (0.1 mol.) of bromobenzene and 2.9 g. (0.12 mol.) of magnesium in 200 ml. of absolute ether. A solution of 4.8 g. (0.02 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 50 ml. of pure dioxane was then added with stirring during 10 min. Stirring was continued for 2 hr. and then the solution was allowed to stand at room temperature overnight. Saturated aqueous ammonium chloride solution (27 ml.) was added to decompose the complex and the ether layer was decanted. The residual sludge was extracted once with ether and twice with chloroform, and the combined extract was dried over magnesium sulfate and concentrated *in vacuo*. The residual phenyl carbinol, 0.7 g. (11%), was crystallized from ethanol, m.p. 219–220° (dec.).

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.12; H, 7.05; N, 8.67.

7,9-Dimethyl-$\Delta^{8,10}$-ergoladiene. 7,9-Dimethyl-9-hydroxy-Δ^{10}-ergolene, 0.5 g., was mixed with 20 ml. of acetonitrile and 5 ml. of boron trifluoride–etherate. The solution was allowed to stand at room temperature for 24 hr. and then poured into an excess of ice and water. The mixture was neutralized with sodium bicarbonate and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from methanol containing a little ethyl acetate; yield, 0.34 g. (74%), m.p. 122–126°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.21; H, 7.60; N, 12.09.

Ultraviolet absorption maxima are at 253, 293 and 306 mμ (neutral) and 213, 222, 230, 238, 288, and 309 mμ (acidic).

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Biologically Active 2,4-Dichlorophenoxyacetylated Amino Acids

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This report on amino acid derivatives of 2,4-dichlorophenoxyacetic acid, designated 2,4-D, is an extension of previous studies[2–8] which have dem-

(1) Present address, Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Md.

(2) W. A. Gentner and W. C. Shaw, 1957 Field Results, Crops Research Division, ARS, U. S. Dept. Agr., Beltsville, Md., Processed Rept. CR-25-58 (January 1958).

(3) W. A. Gentner and W. C. Shaw, 1958 Field Results, Crops Research Division, ARS, U. S. Dept. Agr., Beltsville, Md., Processed Rept. CR-6-59 (January 1959).

(4) C. F. Krewson, J. F. Carmichael, T. F. Drake, J. W. Mitchell, and B. C. Smale prepared for *J. Agr. Food Chem.*

TABLE I

PHYSICAL AND ANALYTICAL DATA OF AMINO ACID DERIVATIVES OF 2,4-DICHLOROPHENOXYACETIC ACID

N-(2,4-Dichlorophenoxyacetyl)-	M.P., °C. (Corr.)[a]	Yield, %		Formula	Analyses[b]					
					Cl, %		N, %		Optical rotation	
		Crude	Refined		Calcd.	Found	Calcd.	Found	$[\alpha]_D^{25}$	C, g./100 ml[c]
D-alanine	203.7 204.7	73.8	51.6	$C_{11}H_{11}Cl_2NO_4$	24.28	24.24	4.80	4.84	−12.8 ± 0.4	5.77
β-alanine	172.8–174.0[d]	82.5	72.6		24.28	24.27	4.80	4.79		
L-asparagine	186.4–187.4	73.2	57.1	$C_{12}H_{12}Cl_2N_2O_5$	21.16	21.14	8.36	8.27	+17.4 ± 0.5	4.46
D-asparagine	183.3–184.3	82.6	60.6		21.16	21.24	8.36	8.14	−18.5 ± 0.4	4.56
DL-asparagine	180.2 181.3[e]	82.8	47.1		21.16	21.21	8.36	8.11		
D-glutamic acid	184.0–185.0[f,g]	17.1	12.4	$C_{13}H_{13}Cl_2NO_5$	20.25	20.10	4.00	4.09	−12.5 ± 1.5	0.89
Glycylglycine	184.0–185.0[g]	74.4	48.8	$C_{12}H_{12}Cl_2N_2O_5$	21.16	20.80	8.36	8.11		
L-isoleucine	143.4–143.9	71.7	41.4	$C_{14}H_{17}Cl_2NO_4$	21.22	21.23	4.19	4.21	+10.0 ± 0.3	7.80
D-isoleucine	143.9–145.1	71.1	59.9		21.22	21.19	4.19	4.22	−10.1 ± 0.3	8.96
D-leucine	155.7–156.7	82.4	70.6		21.22	21.14	4.19	4.21	+16.0 ± 0.4	5.19
L-serine	180.0–183.0[h]		19.5	$C_{11}H_{11}Cl_2NO_5$	23.02	23.07	4.55	4.51	+22.2 ± 0.4	2.00[i]
D-serine	171.8–172.8[j]	58.7	13.6		23.02	22.38	4.55	4.67	−25.3 ± 0.4	5.29
L-threonine	131.0–132.5[k]		20.0	$C_{12}H_{13}Cl_2NO_5$	22.01	21.82	4.34	4.62	+13.8 ± 0.6	2.00
D-threonine	131.0–132.0[f]	62.2	42.6		22.01	21.92	4.34	4.32	−13.1 ± 0.4	5.47
L-tryptophane	152.2–153.4	98.9	70.1	$C_{19}H_{16}Cl_2N_2O_4$	17.40	17.32	6.88	6.88	−13.0 ± 0.3	8.22
D-tryptophane	177.2–178.2	89.2	79.2		17.40	17.41	6.88	6.86	+13.0 ± 0.3	9.09
L-valine	164.2–164.7	79.8	69.4	$C_{13}H_{15}Cl_2NO_4$	22.15	22.14	4.38	4.40	+13.8 ± 0.4	5.15
D-valine	164.2–164.7	80.0	70.6		22.15	22.15	4.38	4.39	−14.3 ± 0.4	5.33
N,*N*′-bis-(2,4-Dichlorophenoxyacetyl)-										
D-cystine	217.0–220.0[h]		32.8	$C_{22}H_{20}Cl_4N_2O_8S_2$	21.94	21.85	4.33	4.30	+109.2 ± 0.4	1.00[l]
DL-cystine	214.0–217.0[h]		40.0		21.94	21.64	4.33	4.35		

[a] Recrystallized twice from 50% ethanol unless otherwise indicated. [b] The authors are indebted to J. S. Ard of this laboratory for the analyses. [c] In 10% molar excess of sodium hydroxide. [d] Recrystallized once from 50% ethanol. [e] Sample sealed under nitrogen. [f] Recrystallized twice from ethyl acetate–hexane. [g] Prepared by C. H. H. Neufeld. [h] Prepared by J. F. Carmichael. [i] In pyridine. [j] Recrystallized twice from methyl ethyl ketone–hexane. [k] Prepared by T. F. Drake. [l] In dimethyl formamide.

onstrated that amino acid coupling can have a marked effect upon the growth-regulating properties of a compound. Such properties are also modified by combination with inexpensive protein hydrolyzates prepared from animal and vegetable sources.[9]

A previous report on the synthesis of 28 amino acid derivatives of 2,4-D appeared in 1952;[10] this note extends the 2,4-D series to 48 amino acid derivatives. The 20 new derivatives were prepared to elucidate further the mode of action and specificity of aryloxyalkylcarboxylic acids as plant growth regulators, as well as to investigate further the use of amino acids as bioactive formulating agents. Many of the compounds from the various series have been submitted to various cooperating agencies for evaluation as plant growth regulators, herbicides, fungicides, anticancer agents, insect repellents, and nematocides. One report[2] on herbicidal evaluation describes *N*-(2,4-dichlorophenoxyacetyl)-D-asparagine as effective in killing pigweed, mustard, and broadleaf weeds without effect on corn and gladiolus in postemergence sprays at $^1/_2$ to 1 pound per acre application rates. Details on the specific biological properties of these compounds will be reported elsewhere.

EXPERIMENTAL

The compounds listed in Table I were prepared by Schotten-Baumann techniques in accordance with descriptions outlined in previous publications. No special directives are necessary here in view of earlier descriptions and the absence of any particular preparative difficulties.

Some of the D-amino acids used in this work were obtained through the courtesy of the late Dr. Jesse P. Greenstein of the National Institutes of Health, Bethesda, Md.; others, and the 2,4-D used, were purchased from commercial sources and utilized without further purification. The 2,4-D was converted to its acyl chloride by the method of Freed[11] and also described by us.[10]

In general the yields of reaction products were fairly high but appreciably losses were taken in the purification processes because it was essential that traces of free acid be removed from the derivatives and that optical purity be obtained. The optical values received were essentially equal and opposite for the D- and L-isomeric compounds. The special variations used in the purification techniques are indicated in the footnotes of Table I.

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(5) C. F. Krewson, T. F. Drake, J. W. Mitchell, and W. H. Preston, Jr., *J. Agr. Food Chem.*, **4**, 690 (1956).

(6) C. F. Krewson, T. F. Drake, and C. H. H. Neufeld, T. D. Fontaine, J. W. Mitchell, and W. H. Preston, Jr., *J. Agr. Food Chem.*, **4**, 140 (1956).

(7) C. F. Krewson, C. H. H. Neufeld, T. F. Drake, T. D. Fontaine, J. W. Mitchell, and W. H. Preston, Jr., *Weeds*, **3**, 28 (1954).

(8) C. F. Krewson, E. J. Saggese, J. F. Carmichael, J. S. Ard, T. F. Drake, J. W. Mitchell, and B. C. Smale, *J. Agr. Food Chem.*, **7**, 118 (1959).

(9) C. F. Krewson, J. F. Carmichael, P. S. Schaffer, J. W. Mitchell, and B. C. Smale, prepared for *J. Agr. Food Chem.*

(10) J. W. Wood and T. D. Fontaine, *J. Org. Chem.*, **15**, 326 (1952).

(11) V. H. Freed, *J. Am. Chem. Soc.*, **68**, 2112 (1946).

The Structure of the Addition Product from Hydrogen Cyanide and a 2-Vinyldihydro-1,3-oxazine

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Received August 10, 1959

A recent article[1] described the preparation of several 2-alkenyl-4,6,6-trimethyldihydro-1,3-oxazines from unsaturated nitriles and 2-methyl-2,4-pentanediol and the reaction of one of these dihydro-1,3-oxazines with hydrogen cyanide. The heterocyclic bases were prepared according to the general method first described by Tillmanns and Ritter[2] who condensed a series of nitriles with 2-methyl-2,4-pentanediol in cold 92% sulfuric acid.

Treatment of I with hydrogen cyanide in glacial acetic acid yielded an addition product which could possess structure II or III as a result of either 1,4- or 3,4- addition, respectively. On the basis of the infrared spectrum of the adduct, II was concluded to represent the true structure. This reaction has now been re-examined and III is claimed to be the correct structure of the adduct. This claim is based upon an alternate synthesis of III, alkaline hydrolysis of the addition product, and a revised interpretation of the infrared spectrum in the light of recent studies.[3]

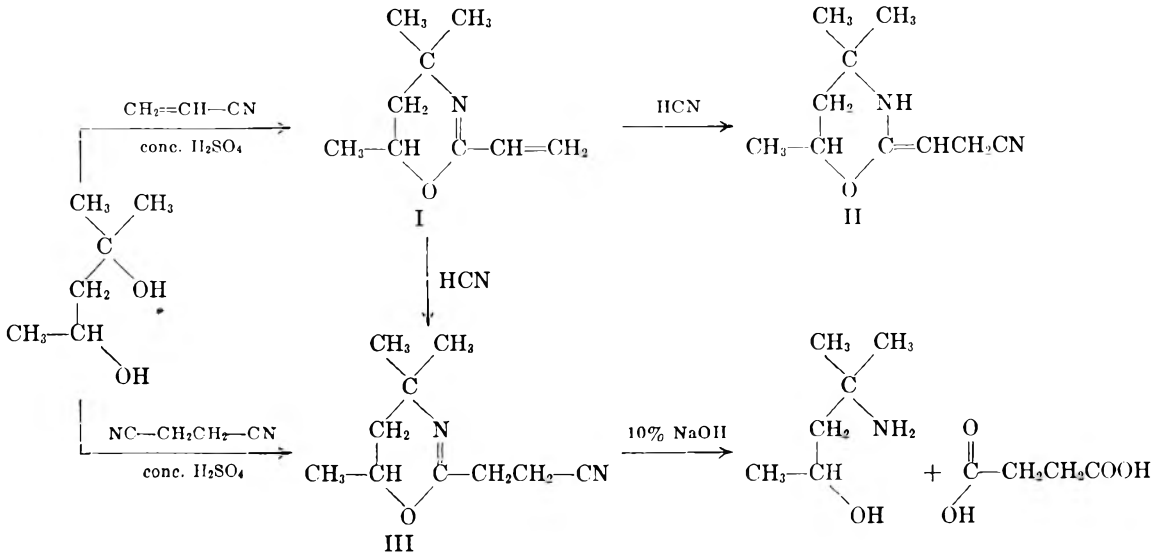
The alternate method of synthesis of the addition compound was accomplished by treating 2-methyl-2,4-pentanediol with succinonitrile in cold concentrated sulfuric acid. Comparison of this product with that obtained by treating I with hydrogen cyanide according to the method of Lynn[1] showed that both compounds were identical in every respect. This method of obtaining III is one which is currently under investigation in our laboratory for the preparation of a wide variety of *N*-heterocycles of the type, IV. It has been found possible, however, to limit the reaction of the dinitriles to only one of the nitrile groups, thus enabling the facile preparation of III. Other *N*-heterocycles such as 1-pyrrolines, 2-thiazolines, and dihydropyridines have already been reported.[4] Extension

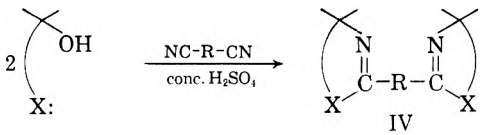
(1) J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

(2) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

(3) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

(4) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).





X = S, O, N; R = alkylene, arylene

of this ring closure reaction to dihydro-1,3-thiazines, dihydro-1,3-oxazines, and benzothiazines will be reported in the near future.

Additional proof in support of III was obtained by refluxing the hydrogen cyanide addition compound with 10% aqueous sodium hydroxide[5] for 24 hr. and isolating 4-methyl-4-amino-2-pentanol and succinic acid in quantitative yield. This mode of hydrolysis strongly supports the presence of the C=N link rather than the exocyclic C=C link in the molecule.

With regard to the infrared spectrum of the hydrogen cyanide addition compound, examination of the 6μ region reveals a single intense band at 6.00μ which had originally been assigned[1] to the stretching frequency of the C=C link. This intense band (not at all typical of the cyclic unconjugated C=C link) has recently been the subject of a study[3] on the spectral position of the C=N link in nitrogen heterocycles. It has been found, as a result of this study, that unconjugated 1-pyrrolines, 2-thiazolines, and more recently dihydro-1,3-thiazines[6] containing a 2-alkyl substituent exhibit a sharp intense band in the 6.00–6.10μ region. Two additional dihydro-1,3-oxazines containing a 2-alkyl substituent were prepared and their absorption in the 6μ region were compared (Table I). The moderately strong band in the 6.88–6.92μ region is due to —CH_2— deformation frequencies.[7] Examination of the 3μ region showed a weak band at 3.00μ which did not reappear when the oxazines were dried in benzene over potassium hydroxide pellets. Thus, it was concluded that a trace of water was responsible for the absorption in the 3μ region and not the presence of the N—H link. Furthermore, the structure of the 2-methyldihydro-1,3-oxazine, whose spectrum was used as a comparison, is well known.[5]

TABLE I

ABSORPTION OF 2-ALKYL-4,6,6-TRIMETHYLDIHYDRO-1,3-OXAZINES IN THE 6μ REGION

2-Alkyl Substituent	Absorption in 6μ Region (%T)
$-CH_3$	6.00 (4.0); 6.90 (39.4)
$-CH_2CH_3$	6.01 (4.0); 6.88 (42.6)
$-CH_2CH_2CN$	6.00 (3.5); 6.92 (27.0)

An additional study on the infrared spectra of *N*-heterocycles containing the C=N link is presently in progress and a communication in this respect is forthcoming.

EXPERIMENTAL[8,9]

The infrared spectra were performed in a Perkin-Elmer Model 21 recording spectrophotometer employing a sodium chloride prism. The samples were studied in a 5–6% carbon tetrachloride solution utilizing a cell with 0.48 mm. spacing.

2-(2-Cyanoethyl)-4,6,6-trimethyldihydro-1,3-oxazine (III). (a). Prepared by the addition of hydrogen cyanide in glacial acetic acid to 2-vinyl-4,6,6-trimethyldihydro-1,3-oxazine according to the method of Lynn.[1]

(b). To 40 g. (0.50 mol.) of succinonitrile in 100 ml. of concentrated sulfuric acid previously cooled to 3° in an ice bath was added with stirring 39.6 g. (0.25 mol.) of 2-methyl-2,4-pentanediol during a 3-hr. period. The temperature during the addition was maintained between 7–10°. The orange mixture was stirred for an additional hour at 3–5° and then poured over 300 g. of chipped ice. The aqueous

(5) M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, 60, 407 (1938).

(6) A. I. Meyers, unpublished observation.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 20.

(8) All melting points and boiling points are uncorrected.

(9) Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim (Ruhr), West Germany.

acid solution was extracted with three 75-ml. portions of chloroform and then cautiously neutralized by the addition of a sufficient amount of 35% sodium hydroxide solution. The red oil that appeared was taken up in ethyl ether and the alkaline solution further extracted with three 75-ml. portions of ether. The ethereal extracts were combined and dried over potassium carbonate. After the ether was removed at atmospheric pressure, the residual oil was distilled *in vacuo*. There was obtained 17.8 g. (40%) of a colorless oil b.p. 104–106°/3.5 mm., n_D^{30} = 1.4544 (lit.[1] b.p. 87°/1.3 mm.; n_D^{30} = 1.4542). Picrate (from ethanol) m.p. 282° dec.

Alkaline hydrolysis of III. Ten g. (0.055 mol.) of III were added to 100 ml. of 10% aqueous sodium hydroxide and refluxed for 24 hr. The colorless oil which was present was taken up in ether and the remaining aqueous layer was saturated with sodium chloride and extracted twice with an equal volume of ether. The ether extracts were combined and dried over anhydrous sodium carbonate. After removal of the ether, distillation of the residue yielded 6.3 g. of 4-amino-4-methyl-2-pentanol, b.p. 71–72°/12 mm., n_D^{20} = 1.4345 (lit.[5] b.p. 74–75°/15 mm., n_D^{20} = 1.4335).

Acidification of the alkaline aqueous solution yielded succinic acid, m.p. 272–274° dec. Admixture with an authentic sample of succinic acid showed no depression in the melting point.

2,4,4,6-Tetramethyldihydro-1,3-oxazine. This compound was prepared according to the method of Tillmanns and Ritter.[2] B.p. 58°/25 mm., n_D^{25} = 1.4355.

2-Ethyl-4,6,6-trimethyldihydro-1,3-oxazine. Prepared in the same manner as the 2-methyl derivative. B.p. 67°/20 mm., n_D^{25} = 1.4385.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.67; H, 10.96. Found: C, 69.62; H, 10.91.

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Synthesis of 5-Alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles and 3,3′-Ethylenebis-(6-iminohexahydro-*s*-triazine-1-carbonitrile)

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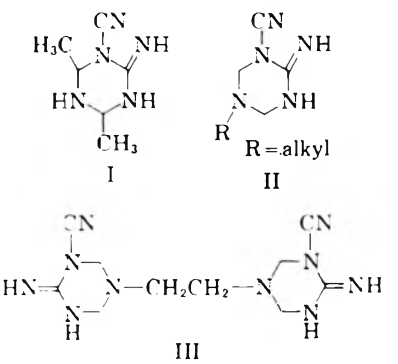
Received August 5, 1959

The condensation of primary alkylamines with one mol. of urea or thiourea and 2 mol. of formaldehyde to give 5-alkylhexahydro-*s*-triazinones and 5-alkylhexahydro-*s*-triazinethiones[1] suggested that cyanoguanidine might react in a similar fashion to form a cyclic derivative.

Pohl[2] showed that cyanoguanidine condenses with acetaldehyde-ammonia to give 2-imino-4,6-dimethylhexahydro-*s*-triazine-1-carbonitrile (I). This reaction has not been reported with any aldehyde-ammonia above C_2. This, together with the fact that the higher aliphatic aldehydes are not readily available, somewhat limits the scope of Pohl's reaction.

Cyanoguanidine reacted readily with one mol. of alkylamine and 2 mol. of formaldehyde to give high yields of 5-alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles (II), a new series of colorless, solid hexahydro-*s*-triazine derivatives. With 0.5 mol. of ethylenediamine and 1 mol. of formaldehyde cyanoguanidine yielded the expected 3,3′-ethylenebis(6-iminohexahydro-*s*-triazine-1-carbonitrile) (III). This condensation appears to be quite general in nature.



EXPERIMENTAL

The cyanoguanidine used was American Cyanamid Company's commercial grade (purity 99%+). All other compounds used were Eastman White Label grade. All melting points are uncorrected.

Typical procedure for 5-alkyl-2-iminohexahydro-s-triazine-1-carbonitriles: 5-Butyl-2-iminohexahydro-s-triazine-1-carbonitrile. To 400 ml. water, there were added 43 g. cyanoguanidine, 37 g. *n*-butylamine, and 81 ml. formalin while stirring vigorously. The temperature rose to 54°. Stirring was continued for 1 hr. after the addition was complete. A colorless oil deposited which crystallized on standing overnight. This product was collected by filtration and recrystallized from 95% ethanol. The yield was 80% of theory and consisted of colorless platelets having a melting point of 149–150°.

Anal. Calcd. for $C_8H_{15}N$: C, 53.01; H, 8.34; N, 38.64. Found: C, 52.89; H, 8.45; N, 38.80.

3,3′-Ethylenebis(6-iminohexahydro-s-triazine-1-carbonitrile). To a solution of 43 g. cyanoguanidine in 200 ml. water, there were added 20 g. ethylenediamine and 81 ml. formalin while stirring vigorously. The temperature rose to 72°. The hot, clear solution was stirred, and white crystals of the product, m.p. 225–226°, deposited within 1 hr. in 75% yield.

Anal. Calcd. for $C_{10}H_{16}N_8$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.54; H, 6.47; N, 45.11.

(1) Burke, W. J., *J. Am. Chem. Soc.*, **69**, 2136 (1947); U. S. Patent **2,304,624** (1942); *cf.* also Paquin, A. M., *Angew. Chem.*, **A60**, 267 (1948).

(2) Pohl, F., *J. prakt. Chem.*, **77**, 538–539 (1908).

TABLE I

5-ALKYL-2-IMINOHEXAHYDRO-*S*-TRIAZINE-1-CARBONITRILES

Alkyl	Yield, %	M.P., °C.	Analysis					
			Calculated			Found		
			% C	% H	% N	% C	% H	% N
Methyl	92	196–197	43.15	6.52	50.33	43.20	6.58	50.30
Butyl	80	149–150	53.01	8.34	38.64	52.89	8.45	38.80
Isobutyl	88	177–178	53.01	8.34	38.64	52.96	8.35	38.71
Allyl	86	172–173	50.89	6.71	42.40	51.00	6.69	42.30
Cyclohexyl	84	172–173	57.94	8.28	33.79	57.91	8.29	33.69
n-Decyl	94	160–161	63.36	10.25	26.39	63.27	10.29	26.35
n-Dodecyl	92	157–158	65.48	10.65	23.87	65.54	10.59	23.82
n-Octadecyl	92	132.3	69.97	11.48	18.55	69.94	11.42	18.51

Acknowledgment. The author wishes to thank the Microanalytical Laboratory of the Stamford Laboratories for the microanalyses and Stanley E. Polchlopek for the infrared curves and their interpretation.

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Studies in Purine Chemistry. VII. An Improved Synthesis of Hypoxanthine[1,2]

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The desulfurization of a mercapto or alkylmercapto substituent is often a critical step in heterocyclic synthesis, particularly in pyrimidine and purine chemistry. The most commonly employed desulfurization method is to reflux the compound with an excess of Raney nickel under what are commonly termed "Mozingo conditions,"[3] and this procedure[4] has been employed in syntheses of both hypoxanthine[5] and adenine[6–8] derivatives. Other methods for replacement of the mercapto group by hydrogen include oxidation with nitric acid[9] or with hydrogen peroxide in acidic solution.[9–11]

An attractive alternative has more recently been described which involves oxidation of the mercapto group in alkaline solution with hydrogen peroxide to a sulfinic acid, followed by decomposition with strong acid, and has been applied to the synthesis of 4,5,6-triaminopyrimidine from 2-mercapto-4,5,6-triaminopyrimidine[12,13] and of 4,6-diaminopyrimidine from 2-mercapto-4,6-diaminopyrimidine.[13] By application of this method to the preparation of 4-hydroxy 5,6-diaminopyrimidine from 2-mercapto-4-hydroxy-5,6-diaminopyrimidine, and by means of certain other modifications, we have been able to effect significant improvements in the conventional synthesis of hypoxanthine from thiourea and ethyl cyanoacetate. Details are given in the Experimental.

Evans *et al.*[13] pointed out that the decomposition of 4,6-diaminopyrimidine-2-sulfinic acid to 4,6-diaminopyrimidine required much stronger acid than the analogous decomposition of 4,5,6-triaminopyrimidine-2-sulfinic acid to 4,5,6-triaminopyrimidine and that weaker acid led predominately to the 2-hydroxy derivative. This was attributed to the weaker basicity of the former pyrimidine, coupled with the requirement that diprotonation precede heterolytic cleavage of the C—S bond. We have found that oxidation of 2-mercapto-4-hydroxy-6-aminopyrimidine, a still weaker base, leads directly to 2,4-dihydroxy-6-aminopyrimidine; the 2-sulfinic acid could not even be isolated.

(1) This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For the previous paper in this series, see E. C. Taylor and C. C. Cheng, *Tetrahedron Letters*, No. 12, 9 (1959).

(3) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1945).

(4) For examples of the utilization of this method, see M. P. V. Boarland, J. F. W. McOmie, and R. N. Timms, *J. Chem. Soc.*, 4691 (1952); M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 4942 (1952); L. F. Cavalieri and A. Bendich, *J. Am. Chem. Soc.*, **72**, 2587 (1950); E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3143 (1956); R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 973 (1956); E. C. Taylor, *J. Am. Chem. Soc.*, **74**, 2380 (1952); C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 852 (1958); D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950); H. Getler, P. M. Roll, J. F. Tinker, and G. B. Brown, *J. Biol. Chem.*, **178**, 259 (1949).

(5) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(6) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

(7) G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 556 (1945).

(8) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(9) W. Traube, *Ann.*, **331**, 64 (1904).

(10) H. Andersag and K. Westphal, *Ber.*, **70**, 2035 (1937).

(11) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 574 (1943).

(12) M. Hoffer, "Jubilee Volume Dedicated to Emil C. Barrell," Basel, 1946, p. 428.

(13) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

EXPERIMENTAL

2-Mercapto-4-hydroxy-6-aminopyrimidine.[14] To a solution of sodium ethoxide (prepared by dissolving 9 g. of sodium in 200 ml. of ethanol) was added 22.6 g. of ethyl cyanoacetate. A white precipitate formed immediately. After 15 min., 15.2 g. of thiourea was added with shaking, and the mixture was allowed to stand at room temperature for 1 hr. with occasional shaking. It was then heated under reflux for 2 hr., cooled and filtered. The collected solid was dissolved in boiling dilute potassium hydroxide and reprecipitated by the addition of glacial acetic acid to give 28.4 g. (99%) of white crystals.

2-Mercapto-4-hydroxy-5-nitroso-6-aminopyrimidine.[14] To a solution of 20 g. of 2-mercapto-4-hydroxy-6-aminopyrimidine in 500 ml. of water containing 5.5 g. of sodium hydroxide and 10 g. of sodium nitrite and maintained at room temperature was added dropwise 15 g. of glacial acetic acid. The reaction mixture was stirred overnight and then filtered to give a brownish-red solid in 90% yield. The crude product was extracted with boiling acetone and then with boiling ethanol (thus removing a small amount of colorless impurity) and was then suitable for further reaction.

2-Mercapto-4-hydroxy-5,6-diaminopyrimidine. The procedure used was essentially the same as previously described by Albert *et al.*,[15] except that the temperature of the reduction mixture was maintained below 30° rather than below 50°, and the sodium hydrosulfite was added very slowly rather than all at once. Furthermore, the reduction mixture was stirred for 20 hr. at room temperature following addition of all of the hydrosulfite and was then decolorized with charcoal. The diaminopyrimidine was obtained in 96.5% yield.

4-Hydroxy-5,6-diaminopyrimidine-2-sulfinic acid. To a solution of 1 g. of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine in 90 ml. of water containing 0.6 g. of sodium hydroxide and precooled to −3° was added dropwise 1.8 ml. of 30% hydrogen peroxide in 17 ml. of water. During the addition the temperature was carefully maintained below 0°. The reaction mixture was allowed to stir for 1.5 hr. following addition of the peroxide and was then acidified with glacial acetic acid. Filtration yielded 0.8 g. of a colorless solid, m.p. 188–190°.

4-Hydroxy-5,6-diaminopyrimidine hydrochloride. A mixture of 1.5 g. of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid and 30 ml. of ethanolic hydrogen chloride was stirred at room temperature for 20 hr. in a flask protected from atmospheric moisture by a calcium chloride tube. The reaction mixture was evaporated to dryness, the residue dissolved in water, filtered and the filtrate again evaporated to dryness to give 1.3 g. of a colorless solid, m.p. 249–251°d., identical in all respects with an authentic sample of 4-hydroxy-5,6-diaminopyrimidine hydrochloride prepared by Raney nickel desulfurization of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine.[16]

Decomposition of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid with concentrated hydrochloric acid yielded 2,4-dihydroxy-5,6-diaminopyrimidine hydrochloride rather than the desired product.

Hypoxanthine. A mixture of 2 g. of 4-hydroxy-5,6-diaminopyrimidine hydrochloride and 30 ml. of an equimolar mixture of ethyl orthoformate and acetic anhydride was heated under reflux for 4 hr. and then evaporated to dryness. Recrystallization of the residual solid from aqueous ethanol gave 1.6 g. (95.5%) of pure hypoxanthine, identical in all respects with an authentic sample.

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(14) This preparation is a slight modification of the original method described by Traube (Ref. 9).

(15) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(16) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, 67, 290 (1945).

Potential Anticancer Agents.[1] XXVIII. Synthesis of 5-(Chloromethyl)uracil

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Both 5-fluorouracil[2] and 5-[bis(2-chloroethyl)-amino]uracil[3] have been shown to inhibit the growth of various tumors. Matthews[4] reported that all of the 5-halogenated uracils were incorporated into phage DNA, giving mutants. Hitchings *et al.*,[5] have shown 5-bromouracil to be a competitive thymine antagonist.

Efforts to find new anticancer agents could, therefore, be logically directed toward the preparation of various thymine derivatives such as 5-(fluoromethyl) uracil, 5-[bis(2-chloroethyl)aminomethyl]uracil, and other uracil derivatives containing potential alkylating groups attached to a 5-methyl grouping. The key intermediate to the synthesis of these agents would be 5-(chloromethyl)-uracil (IV). This compound has now been synthesized in 57% yield by the choromethylation of uracil (I).

Early attempts in this laboratory to prepare IV by the chlorination of thymine using *N*-chlorosuccinimide and benzoyl peroxide, as reported by West and Barrett,[6] failed to yield IV. Instead, a compound melting at 224.5–225.5° was obtained. West reported a similar melting point of 222–224° and an empirical formula of $C_5H_5ClN_2O_4$. The failure of this compound to react with alcoholic silver nitrate solution upon heating, its stability toward water (being recrystallized without change from hot water), its lack of absorption in the ultraviolet, and its liberation of iodine from an acetic acid solution of potassium iodide, are convincing

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) C. Heidelberger, L. Greisbach, B. J. Montag, D. Mooren, O. Cruz, R. J. Schnitzer, and E. Grunberg, *Cancer Res.*, 18, 305 (1958); R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, 79, 4559 (1957).

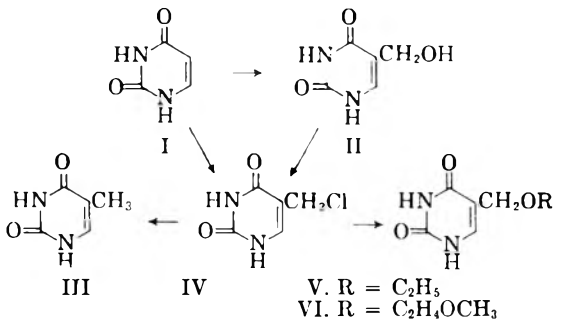
(3) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, 80, 6459 (1958).

(4) R. E. F. Matthews, *Pharm. Reviews*, 10, No. 3, 359 (1958).

(5) G. H. Hitchings, E. A. Falco, and M. B. Sherwood, *Science*, 102, 251 (1945).

(6) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, 76, 3146 (1954).

evidence that it was not IV. The absence of absorption in the ultraviolet would suggest that the uracil ring had been either ruptured or else saturated. The iodide test indicates *N*-chlorination.



I II III IV V. R = C_2H_5 VI. R = $C_2H_4OCH_3$

Efforts were shifted to the chlorination of 5-(hydroxymethyl)uracil (II), which was prepared by the method of Cline *et al.*[7] Attempts to chlorinate II in pyridine with thionyl chloride resulted in the formation of a compound that appeared to be the quaternary salt formed from IV and pyridine. When chlorination in dichloromethane with thionyl chloride was attempted, no reaction occurred, probably due to the limited solubility of II in that solvent.

Crude IV was prepared in 37% yield by heating 5-(hydroxymethyl)uracil (II) in concentrated hydrochloric acid. Although an analytical sample of IV could not be obtained by this procedure, the infrared absorption spectrum and paper chromatographic[8] behavior indicated that a product different from thymine (III), uracil (I), and 5-(hydroxymethyl)uracil (II) had been obtained. This crude IV was reduced to thymine in 62% yield by means of tin and hydrochloric acid. The thymine produced was identical with that of an authentic sample in its infrared absorption and paper chromatographic behavior.

Schmeds[9] reported the chloromethylation of 3,6-dimethyluracil to yield 3,6-dimethyl-5-(chloromethyl)uracil by heating the former in aqueous formaldehyde with excess concentrated hydrochloric acid. Attempts to prepare IV from uracil (I) using that procedure resulted in only a 13% yield of crude 5-(chloromethyl)uracil (IV). It was found, however, that extraction of crude IV with warm 1,2-dimethoxyethane and concentration of the extracts yielded a more pure sample of IV, as evidenced by paper chromatographic[8] behavior (disappearance of spots near the origin) and chloride analyses (closer to theoretical for IV).

It was then found that the best conditions for the synthesis of IV were continuous passage of hydrogen chloride through a solution of uracil and paraformaldehyde in concentrated hydrochloric acid while heating to 70–80°. The product was isolated in 57% yield and analyzed closely to the theoretical chlorine value for IV without extraction with 1,2-dimethoxyethane. Only a trace spot still remained at the origin on paper chromatographic[8] investigation. Proof that chloromethylation had occurred at the 5-position of uracil was shown by reduction of IV to thymine (III) in 82% yield by means of tin and hydrochloric acid. The thymine was characterized by the identity of its infrared absorption spectrum and paper chromatographic behavior[8] with those of an authentic sample of thymine. In addition, IV differs from West's compound[3] in that IV gives an immediate precipitate of silver chloride on treatment with alcoholic silver nitrate solution, and 5-(hydroxymethyl)-uracil (II) is produced upon reaction with water. The identity of II was proven by its agreement in behavior on paper[8] (R_f 0.19) and by its identical infrared absorption spectrum with that of II prepared by the method of Cline.[7]

5-(Chloromethyl)uracil (IV) also reacted readily with alcohols to yield ethers. A similar reaction has been reported by Cline[7] to occur with 5-(hydroxymethyl)uracil (II) and alcohols under somewhat more vigorous reaction conditions. The product obtained by heating IV with 2-methoxyethanol was isolated as a crystalline solid, m.p. >300°, and shown by analysis to be 5-[(2-methoxyethoxy)-methyl]uracil (VI). This material was homogeneous on paper chromatography,[8] showing only one spot, R_f 0.39.

EXPERIMENTAL

5-(Chloromethyl)uracil (IV). A suspension of 40 g. (0.36 mol.) of uracil (I) and 13.4 g. (0.44 mol.) of paraformaldehyde in 350 ml. of concentrated hydrochloric acid was stirred while gaseous hydrogen chloride was passed through the reaction mixture, which was then heated to 80°. When that temperature was reached, complete solution had been attained. The heat source was removed; the reaction temperature remained spontaneously at 80° for 0.5 hour, then subsided. After 4 hr. total time, the now heterogeneous reaction mixture was filtered through a glass sintered funnel and the precipitate dried over phosphorus pentoxide at 1 mm. pressure; yield, 32.6 g. (57%), m.p. >300°; λ_{max}^{Nujol} (μ) 3.05, 3.20 (NH), 5.70, 5.98 (uracil C=O), 6.70, 6.96, 8.24, 8.48 (uracil ring). The compound moved as two spots (R_f 0.70, 0.18)[8] provided the compound was dissolved in 1,2-dimethoxyethane for spotting on the paper. Uracil has R_f 0.28; thymine, R_f 0.42; and 5-(hydroxymethyl)uracil, R_f 0.19 in this system.[8] When IV was spotted in warm ethanol, the compound had R_f 0.53, and in warm methyl Cellosolve, R_f 0.39, corresponding to V and VI, respectively. In warm 1-butanol an R_f of 0.70 was obtained due to the formation of 5-(butoxymethyl)uracil.

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.5; H, 3.14; Cl, 22.1. Found: C, 37.7; H, 3.54; Cl, 21.1.

The compound is very sensitive to moisture, fuming in air, thus making an accurate analysis difficult.

5-[(2-Methoxyethoxy)methyl]uracil (VI). Crude IV (1 g.; Cl, 13.2%), prepared from uracil (I), was extracted with 2-methoxyethanol by heating to 70° and filtering hot.

(7) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, 81, 2521 (1959).

(8) Paper chromatograms were run by the descending technique on Whatman No. 1 paper with 1-butanol–water, unless otherwise indicated. Spots were detected by their ultraviolet absorption.

(9) K. Schmeds, *Ann.*, 441, 192 (1925).

The filtrate upon concentration *in vacuo* yielded 0.46 g. of VI, m.p. >300°, silver nitrate test negative; λ_{max}^{Nujol} (μ) 3.12, 3.25 (NH), 5.72, 5.44 (C=O of uracil), 9.00, 9.10 (C—O—C of ether).

Anal. Calcd. for $C_5H_{12}N_2O_4$: C, 48.0; H, 6.05; N, 14.0. Found: C, 47.7; H, 6.00; N, 14.0.

Reduction of 5-(chloromethyl)uracil (IV) *to thymine* (III). A suspension of 5.00 g. (0.03 mol.) of 5-(chloromethyl)uracil (IV), prepared by chloromethylation of uracil, in 150 ml. of concentrated hydrochloric acid was heated to 60°. The reaction mixture was kept at 60° and 35.0 g. of tin was added over a period of 20 min. with stirring. After being stirred and heated for 3 hr., the reaction mixture was decanted to remove the excess tin. The solution was evaporated to one third its volume under reduced pressure on a water bath at 60°. The solution was diluted with 750 ml. of hot, distilled water and filtered. The filtrate was treated with hydrogen sulfide for 15 min., then heated for 30 min. at 80°, the mixture cooled to room temperature, and the tin sulfide removed by filtration. The filtrate yielded 3.49 g. of white crystals when concentrated *in vacuo*. This crude thymine was recrystallized from dilute aqueous ethanol to give 3.2 g. (82%) of thymine; λ_{max}^{Nujol} (μ) 3.15 (NH), 5.68, 5.94 (C=O of uracil), 6.65, 7.00 (ring). The spectrum was identical with that of an authentic sample of thymine.

The compound had the following R_f values as compared with thymine: in benzene-methanol-water (2:1:6) on Schleicher and Schuell No. 2043B acetylated paper, R_f 0.64 (thymine, 0.64); in 1-butanol–water on Whatman No. 1 paper, R_f 0.45 (thymine, 0.45); in isopropanol–ammonium hydroxide–water (70:5:25), R_f 0.79 (thymine, 0.79); in isopropanol–2*N* hydrochloric acid (65:35), R_f 0.85 (thymine, 0.83).

Acknowledgments. The authors wish to thank Dr. Peter Lim for interpetation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry.

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New Di- and Tetrahydropyran Derivatives

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In connection with another study, certain di- and tetrahydropyran dibasic acids and amino acids were desired whose preparation is described below.

The dibasic acids were obtained through the addition of phosgene to the requisite 2,3-dihydro-4*H*-pyran derivative, followed by the elimination of the elements of hydrogen chloride, saponification of the acid chloride and, if desired, by hydrogenation. Alternatively, the acid chlorides were converted into amides which, on dehydration, yielded nitriles. An amino acid derivative was also prepared through the addition of *N*-substituted 2-aminoethanol to 5-carbethoxy-2,3-dihydro-4*H*-pyran.

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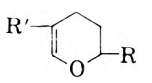
It is known that when a mixture of 2,3-dihydro-4*H*-pyran and phosgene is allowed to react and the resulting addition product is subsequently heated under reduced pressure, hydrogen chloride is eliminated and 2,3-dihydro-4*H*-pyran-5-carbonyl chloride is formed.[2] By adapting this method, Ia was obtained in 42% yield. Attempts to add phosgene to 2-formyl-2,3-dihydro-4*H*-pyran failed to produce an acid chloride, the phosgene reacting instead with the formyl group. However, acid chloride Ig was obtained from compound Ii in which the aldehyde function was masked through formation of the acetal derivative. In the absence of interfering substituents, the addition of phosgene may be a general method for the introduction of a carbonyl chloride group into the dihydropyran nucleus.

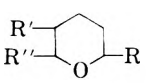
With Raney nickel catalyst, dihydropyran derivatives show a wide variation of susceptibility to hydrogenation, ranging from ready reactions at room temperature[3] to slow hydrogenations at elevated temperatures and pressures.[4,5] 2,5-Dicarbethoxy-2,3-dihydro-4*H*-pyran (Id) was difficult to reduce over Raney nickel at 150° and at 300 atm. pressure. However, over rhodium or palladium catalysts in glacial acetic acid, hydrogenation of Id could be effected with ease at room temperature and ordinary pressure.

Substituted 2,3-Dihydro-4*H*-pyran



Ia. R = $COOC_2H_5$, R′ = COCl; Ib. R = $COOC_2H_5$, R′ = COOH; Ic. R = R′ = COOH; Id. R = R′ = $COOC_2H_5$; Ie. R = $COOC_2H_5$, R′ = $CONH_2$; If. R = R′ = $CONH_2$; Ig. R = $CH(OC_2H_5)_2$, R′ = COCl; Ih. R = $CH(OC_2H_5)_2$, R′ = $COOC_2H_5$; Ii. R = $CH(OC_2H_5)_2$, R′ = H; Ik. R = $CONH_2$, R′ = H; Il. R = CN, R′ = H; Im. R = R′ = CN; In. R = $COOC_2H_5$, R′ = CN.

Substituted Tetrahydropyrans



IIa. R = R″ = H, R′ = $COOC_2H_5$; IIb. R = R″ = H, R′ = COOH; IIc. R = R′ = $COOC_2H_5$, R″ = H; IId. R = CHO, R′ = H, R″ = OC_2H_5; IIe. R = $OCH_2CH_2NHCOCH_3$, R′ = R″ = H; IIf. R = $OCH_2CH_2NHCOCH_3$, R′ = H, R″ = $COOC_2H_5$; IIg. R = $OCH_2CH_2NHCOC_6H_4NO_2$, R′ = R″ = H.

The replacement of the carbethoxy by a carboxamide group occurred easily when dihydropyran derivative Ia was treated with ammonium hydroxide at 0°. The carboxamides were converted to the nitriles by *p*-toluenesulfonyl chloride and

(2) P. A. Hawkins and N. Bennett, British Patent 570,974.

(3) M. Delépine and A. Horeau, *Bull. soc. chim. France*, (5) 5, 339 (1938).

(4) J. G. M. Bremner and D. G. Jones, British Patent 612,314.

(5) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, 73, 5280 (1951).

pyridine at 60 to 130°.[6] Several other methods[7] resulted either in the recovery of the starting material or in complete destruction of the molecule.

Owing to its basicity, 2-aminoethanol, not unexpectedly, failed to add to the double bond of dihydropyran under conditions similar to those usually employed for the addition of alcohols.[8] The *N*-acetyl and *N*-nitrobenzoyl derivatives of 2-aminoethanol underwent the desired addition reaction in the presence of catalytic amounts of hydrochloric acid, resulting in compounds IIe, IIf, and IIg, respectively.

EXPERIMENTAL[9]

2-Carbethoxy-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ia). A mixture of 24 g. (0.154 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran[5] and 34 g. (0.342 mol.) of phosgene was maintained for 7 days at 40° in a sealed glass tube. Vacuum distillation of the mixture yielded 9.4 g. (39%) of the initial ester, contaminated with hydrogen chloride, followed by 14.1 g. (42% yield) of compound Ia, b.p. 155–156° (8 mm.). When the reaction was conducted at 15° most of the starting material was recovered unchanged. In the presence of BF_3 the only product obtained was a clear resin.

2-Carbethoxy-5-carboxy-2,3-dihydro-4H-pyran (Ib). Acid chloride Ia was hydrolyzed with water at 5° to give Ib, (m.p. 127–128° from water). Saponification with 10% NaOH under reflux for 1 hr. gave the dicarboxylic acid Ic, (m.p. 237° from water).

Anal. Calcd. for $C_9H_{12}O_5$ (Ib): C, 54.2; H, 6.0; OC_2H_5, 22.5. Found: C, 53.8; 54.3; H, 6.2, 6.3; OC_2H_5, 22.2, 22.2.

2,5-Dicarbethoxy-2,3-dihydro-4H-pyran (Id). Acid chloride Ia, (28 g., 0.128 mol.), was added at 5° with stirring to 50 ml. of ethanol. After 1 hr., 130 ml. of water was added and the diester was extracted with ether (82%, b.p. 161–163° [11 mm.]).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 58.1; H. 7.1; OC_2H_5, 39.4. Found: C, 58.0; H, 7.3; OC_2H_5, 38.8.

2-Carbethoxy-5-carboxamide-2,3-dihydro-4H-pyran (Ie). Acid chloride Ia, (22 g., 0.1 mol.), was slowly added with stirring at −20° to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 110 ml. of benzene (65%, m.p. 150–151.5° [from water]).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.8; H, 6.6; N, 7.1; OC_2H_5, 22.5. Found: C, 54.8; H, 6.7; N, 7.1; OC_2H_5, 22.1.

2,5-Dicarboxamide-2,3-dihydro-4H-pyran (If). Acid chloride Ia, (8 g., 0.037 mol.), was slowly added with stirring at ordinary temperature to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 40 ml. of benzene (48%, m.p. 256–257° dec.).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.3; H, 5.9; N, 16.4; OC_2H_5, 0.0. Found: C, 49.6, 49.1; H, 6.4, 6.1; N, 16.3, 16.4; OC_2H_5, 0.0, 0.0.

2-Diethoxymethylene-2,3-dihydro-4H-pyran (Ii). Using the method of Fischer and Baer,[10] 44.8 g. (0.4 mol.) of 2-formyl-2,3-dihydro-4*H*-pyran[11] was treated with 72 g. (0.48 mol.) of ethyl orthoformate, 15 ml. of ethanol and 1.5 g. of NH_4NO_3. The yield was 50%, b.p. 94° (12 mm.).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.8; H, 9.7; OC_2H_5, 48.3. Found: C, 64.2, 63.7; H, 10.3, 9.9; OC_2H_5, 49.1, 47.5.

Only 2-formyl-5-ethoxy-tetrahydropyran (IId) was obtained when a few drops of alcoholic HCl were added at −5° to a mixture of 2-formyl-2,3-dihydro-4*H*-pyran and ethanol. The yield was 40%, b.p. 85° (12.5 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 8.9; OC_2H_5, 28.5. Found: C, 60.4; H, 9.1; OC_2H_5, 28.6.

2-Diethoxymethylene-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ig). Phosgene, 10 g. (0.101 mol.), was condensed into 17 g. (0.092 mol.) of Ii and the mixture kept at ordinary temperature in a closed Erlenmeyer flask for 4 days. Vacuum distillation yielded 4 g. (22%) of unchanged acetal, 6 g. (24%) of acid chloride Ig, b.p. 164° (16 mm.), and 4 g. of resinous residue. When the reaction was run with 2-formyl-2,3-dihydro-4*H*-pyran, the only product was a clear resin.

2-Diethoxymethylene-5-carbethoxy-2,3-dihydro-4H-pyran (Ih). Acid chloride Ig, (3.9 g., 0.0157 mol.), was added with stirring to 7.5 ml. of ethanol. After 1 hr. water was added and the acetal-ester extracted with ether. Vacuum distillation of the ether extract gave Ih (88%, b.p. 162–165° [12 mm.]).

Anal. Calcd. for $C_{13}H_{21}O_5$: C, 60.5; H, 8.5; OC_2H_5, 52.3. Found: C, 60.4; H, 8.9; OC_2H_5, 53.3.

3-Carbethoxytetrahydropyran (IIa). (a) 2,3-Dihydro-4*H*-pyran-5-carboxylic acid,[2] (32 g., 0.250 mol.), in 100 ml. of ethanol was hydrogenated over 5 g. of Raney nickel for 10 hr. at 150° and 200 atm. IIa (18 g., b.p. 89–91° [13 mm.]) and saturated acid IIb (b.p. 142–145° [12 mm.], *p*-bromophenacyl ester, m.p. 98–99° [lit.[4] m.p. 96°]) were obtained.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9. Calcd. for $C_6H_{10}O_3$: C, 55.3; H, 7.7. Found: C, 55.7; H, 7.9.

(b) Ester IIa was obtained in 25% yield when 32 g. of 5-carbethoxy-2,3-dihydro-4*H*-pyran[2] was hydrogenated over 4 g. of Raney nickel for 4 hr. at 110° and 150 atm.

2,5-Dicarbethoxytetrahydropyran (IIc). (a) Id, (20 g., 0.088 mol.), in 30 ml. of ethanol was hydrogenated over 3 g. of Raney nickel for 3 hr. at 150° and 300 atm. (82%, b.p. 158–158.5° [12 mm.]).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; OC_2H_5, 39.1. Found: C, 56.4; H, 8.1; OC_2H_5, 38.3.

(b) Id, (5 g., 0.022 mol.) in 25 ml. of glacial acetic acid was hydrogenated at ordinary temperature and pressure over rhodium and palladium catalyst. With 3 g. of Rh catalyst (5% Rh on charcoal), the theoretical amount of hydrogen was taken up after 1 hr.; with 0.5 g. of Pd catalyst (10% Pd on asbestos), 48 hr. were required for complete hydrogen uptake. In both cases hydrogenation was considerably slowed in an ethanol medium. The saturated diester was saponified with 10% aqueous NaOH. The free acid, very water soluble, was isolated as the silver salt and as the *p*-bromophenacyl ester, m.p. 163–165°.

Anal. Calcd. for $C_{15}H_{15}BrO_6$ (monoester): C, 48.5; H, 4.1; Br, 21.53. Calcd. for $C_{23}H_{20}Br_2O_7$ (diester): C, 48.6; H, 3.5; Br, 28.2. Found: C, 48.5; 49.1; H, 3.9, 4.0; Br, 26.9.

2-Carboxamide-2,3-dihydro-4H-pyran (Ik). 2-Carbethoxy-2,3-dihydro-4*H*-pyran (76 g., 0.487 mol.), and 50 ml. of liquid ammonia were heated in an autoclave for 8 hr. at 150° under 50 atm. hydrogen (76%, m.p. 117° [from water and benzene]).

Anal. Calcd. for $C_6H_9NO_2$: C, 56.8; H, 7.1; N, 11.0. Found: C, 57.4; H, 7.4; N, 11.4.

2-Carbonitrile-2,3-dihydro-4H-pyran (Il). Amide Ik, (12.7 g., 0.1 mol.), pyridine, (18 ml., 0.22 mol.) and *p*-toluenesulfonyl chloride (19.1 g., 0.1 mol.) were heated to 60°. The homogeneous solution which formed solidified on cooling. The solid was pulverized and extracted with ether. Vacuum distillation of the ether extract gave the nitrile (40%, b.p. 99–101° [14 mm.]).

Anal. Calcd. for C_6H_7NO: C, 66.0; H, 6.4; N, 12.9. Found: C, 65.4; H, 6.6; N, 12.9.

2,5-Dicarbonitrile-2,3-dihydro-4H-pyran (Im). Diamide If, (3.2 g., 0.019 mol.), pyridine (10 ml., 0.124 mol.) and *p*-toluenesulfonyl chloride (10 g., 0.053 mol.) were heated to

(6) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).

(7) D. T. Mowry, *Chem. Revs.*, **42**, 257 (1948).

(8) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. 1, p. 344.

(9) All melting points are uncorrected.

(10) H. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 576 (1935).

(11) K. Alder and E. Rüden, *Ber.*, **74**, 920 (1941).

130°. After cooling, the solid residue was crushed and extracted with ether, m.p. 46–48°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.1; H, 4.9; N, 20.6.

2-Carbethoxy-5-carbonitrile-2,3-dihydro-4H-pyran (In). Amide-ester Ie (5 g., 0.025 mol.), pyridine (6.3 ml., 0.078 mol.), and *p*-toluenesulfonyl chloride (4.71 g., 0.025 mol.) were heated to 80°, and treated further as under Im. On concentration of the ethereal extract 3 ml. of an oil was obtained.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 60.0; H, 6.1; N, 7.8; OC_2H_5, 24.8. Found: C, 59.5; H, 6.1; N, 8.0; OC_2H_5, 24.7.

2-(2-Acetaminoethoxy)tetrahydropyran (IIe). Equimolecular quantities of 2-acetamino-ethanol[12] and 2,3-dihydro-4*H*-pyran[13] were heated with stirring in the presence of 3 drops of conc. HCl. When the mixture became homogeneous, the solution was cooled, neutralized with aqueous Na_2CO_3, extracted with ether and distilled, (b.p. 180–182° [12 mm.]).

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.8; H, 9.1; N, 7.5. Found: C, 57.8; H, 9.4; N, 7.4.

2-(2-Acetaminoethoxy)tetrahydro-6-carbethoxypyran (IIf). A mixture of 10.3 g. (0.1 mol.) of 2-acetaminoethanol,[12] 15.6 g. (0.1 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran,[5] and 3 drops of conc. HCl was heated with stirring until a homogeneous solution was formed. It was purified as above (31%), b.p. 150–170° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.6; H, 8.1; N, 5.4; OC_2H_5, 17.3. Found: C, 54.4; H, 8.0; N, 5.9; OC_2H_5, 18.0.

2-(2-p-Nitrobenzaminoethoxy)tetrahydropyran (IIg). A mixture of 4.5 ml. (0.05 mol.) of 2,3-dihydro-4*H*-pyran,[13] 10 g. (0.05 mol.) of 2-(*p*-nitrobenzamino)-ethanol,[14] 2 drops of conc. HCl and 50 ml. of xylene was heated on a water bath. After cooling, the crystals which formed were filtered, dried, and recrystallized from benzene and ethanol, m.p. 103–106°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.2; H, 6.1; N, 9.5. Found: C, 56.5; H, 6.4; N, 9.9.

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(12) G. F. D'Alelio and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 111 (1937).

(13) R. L. Sawyer and D. W. Andrus, *Org. Syntheses*, Coll. Vol. III, 276 (1955).

(14) H. Brintzinger and H. Koddebusch, *Ber.*, **82**, 201 (1949).

Communications TO THE EDITOR

Synthesis of Tetrakistriphenylstannoxytitanium

Sir:

In recent years several reports have appeared on the isolation of trialkylsiloxy and triarylsiloxy derivatives of titanium.[1-4] However, tetrakistriphenylstannoxytitanium (I) prepared herein appears to be the first compound containing a tin-oxygen-titanium linkage. This was synthesized by an ester interchange between tetra-*n*-butyl titanate and triphenyltin hydroxide:

$$4(C_6H_5)_3SnOH + (C_4H_9O)_4Ti \longrightarrow [(C_6H_5)_3SnO]_4Ti + 4C_4H_9OH$$

I

A 20% yield was obtained. Side reactions may occur in the following manner:

$$2(C_6H_5)_3SnOH \longrightarrow (C_6H_5)_3SnOSn(C_6H_5)_3 + H_2O$$

$$(C_4H_9O)_4Ti + H_2O \longrightarrow (C_4H_9O)_3TiOH + C_4H_9OH$$

$$2(C_4H_9O)_3TiOH \longrightarrow (C_4H_9O)_3TiOTi(OC_4H_9)_3 + H_2O$$

No attempt was made to increase the yield of final product by azeotropic distillation of the water and alcohol or by purification of the triphenyltin hydroxide.

Tetrakistriphenylstannoxytitanium melts at 215–216° and is quite soluble in benzene. In comparison tetrakistriphenylsiloxytitanium melted[2] at 460–470° and was very slightly soluble in benzene.

Tetra-*n*-butyl titanate was obtained from Matheson, Coleman & Bell and purified by fractional distillation (b.p. 156–157° at 2.5 mm.). Triphenyltin hydroxide (Practical Grade) was obtained from Anderson Chemical Co.

Preparation of tetrakistriphenylstannoxytitanium, I. A 0.0125-mol. sample of triphenyltin hydroxide was added to 100 ml. of hot benzene and filtered; 0.0030 mol. of tetra-*n*-butyl titanate in 50 ml. benzene was added slowly with stirring to the triphenyltin hydroxide solution. A small amount of light brown residue was obtained on filtration. The supernatant liquid was evaporated by use of a Rinco evaporator leaving a light yellow solid residue. Upon recrystallization from benzene and then washing with petroleum ether a white solid was isolated, m.p. 215–216° (hot stage melting point apparatus). *Anal.* Calcd. for $[(C_6H_5)_3SnO]_4Ti$: C, 57.20; H, 4.00; Sn, 31.40; Ti, 3.17. Found: C, 57.43, 57.55; H, 4.25, 4.35; Sn, 31.10; Ti, 2.95, 3.03.

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(1) W. D. English and L. H. Sommer, *J. Am. Chem. Soc.*, **77**, 170 (1955).
(2) V. A. Zeitler and C. A. Brown, *J. Am. Chem. Soc.*, **79**, 4616 (1957).
(3) D. C. Bradley and I. M. Thomas, *J. Chem. Soc.*, 17, (1958).
(4) B. N. Dolgov and N. F. Orlov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* 1395 (1957).