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Some Dehalogenation Reactions of 1,4-Dibromobutane[1]

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The dehalogenation of 1,4-dibromobutane under a variety of conditions has been found to lead to a mixture of ethylene, butane, 1-butene, *trans* and *cis* 2-butenes, 1,3-butadiene, and cyclobutane. A free radical mechanism accounting for the formation of each of the above is proposed.

A literature survey of the metal dehalogenation reactions of 1,4-dibromobutane reveals a wide divergence of reported products. While it does not follow that all metal dehalogenations must proceed *via* a common mechanism, it is only through a thorough study of the reaction products that such a question can really be answered. Such a study is reported here.

The reaction of sodium vapor with 1,4-dibromobutane at 300° has been reported by Bawn and Milstead[2] to give ethylene (41%) and butylene (51%). The mechanism proposed by these authors involves the formation of a 1,4-butyl diradical and its subsequent reactions to give the observed products. Cason and Way[3] carried out essentially the same reaction in refluxing toluene and observed butane and cyclobutane (12%) as products. While they suggested no reaction mechanism, the further observation that cyclobutane formation was less in boiling benzene was interpreted as meaning that this was a process of relatively high activation energy.

Demjanow[4] reported the treatment of 1,4-dibromobutane with zinc in ethanol to give butyl bromide; while Hamonet[5] obtained butane under the same conditions. When the dehalogenation was carried out with zinc and refluxing dioxane, Grob and Bauman[6] identified ethylene, butylene, and butyl bromide as reaction products. They proposed the initial formation of an organozinc halide which then decomposed by an ionic process.

$$\mathrm{Br{-}Zn{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Br} \longrightarrow \mathrm{CH_2{=}CH_2 + CH_2{=}CH_2 + ZnBr_2}$$

$$\mathrm{Br{-}Zn{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Br} \xrightarrow{\mathrm{H_2O}} \mathrm{CH_3CH_2CH_2CH_2Br}$$

In this laboratory the treatment of 1,4-dibromobutane with a variety of metals in refluxing xylene and in butyl ether has been found to produce the same gaseous products in each case (Table I); ethylene, butane, 1-butene, *trans*- and *cis*-2-butene, 1,3-butadiene, and cyclobutane. Analysis of the complex reaction products was carried out by means of gas chromatography (Fig. 1). Direct comparison of yields between reactions conducted in xylene and in butyl ether is complicated by the fact that butyl ether itself undergoes some cleavage when heated with the metals used in this study. The treatment of boiling butyl ether with sodium produced a large amount of propane and small amounts of C-2 and C-4 hydrocarbons. With the less active metals listed in Table I, the production of propane was negligible.

While the distribution among the products observed on metallic dehalogenation of 1,4-dibromobutane varied considerably with the reaction conditions, the over-all consistency of products strongly supports the supposition of a common mechanism for all of these reactions. In order to

(1) Presented in part before the April 19, 1957, meeting of the Ohio Academy of Sciences, Bowling Green, Ohio.

(2) C. E. H. Bawn and J. Milstead, *Trans. Faraday Soc.*, **35**, 889 (1939).

(3) J. Cason and R. L. Way, *J. Org. Chem.*, **14**, 31 (1949).

(4) N. J. Demjanow, *Ber*, **28**, 22 (1895).

(5) J. Hamonet, *Compt. rend.*, **132**, 789 (1901).

(6) C. A. Grob and W. Bauman, *Helv. Chim. Acta*, **38**, 594 (1955).

TABLE I

DEHALOGENATION REACTIONS OF 1,4-DIBROMOBUTANE (0.01 MOLE)

Reagent	Solvent	Yield, Ml.	Products, Mole %					
			C_2H_4	C_4H_{10}	1-C_4H_8	2-C_4H_8	1,3-C_4H_6	Cyclo C_4H_8
Na	Xylene	80	63	16	5	2	3	11
Li	Xylene	80	16	46	15	5	5	13
Mg	Xylene	90	14	51	12	4	6	13
Na	Bu_2O[a]	200	High	s.a.	s.a.	s.a.	s.a.	0
Mg	Bu_2O[a]	190	31	24	19	6	2	9
Zn	Bu_2O[a]	260	34	28	16	11	1	0
Zn	dioxane	60	27	47	13	13	0	0
Mg + $CoBr_2$	Bu_2O[a]	200	8	24	46	13	3	1
Mg + $CoBr_2$	Et_2O	70	8	33	42	17	0	0
CH_3MgBr + $CoBr_2$	Xylene[b]	..[c]	21	3	8	5	4	2
CH_3MgBr + $CoBr_2$	Bu_2O	..[c]	23	17	15	30	0	8
CH_3MgBr + $CoBr_2$	Et_2O	..[c]	6	3	51	17	0	0

[a] The high yields in butyl ether were due to the secondary reaction of the metal with the solvent; the other product being propane. Small amount is abbreviated s.a. [b] In addition, 53% ethane and 4% propane were found. [c] No yield of reaction products was measured here due to the large dilution by methane.

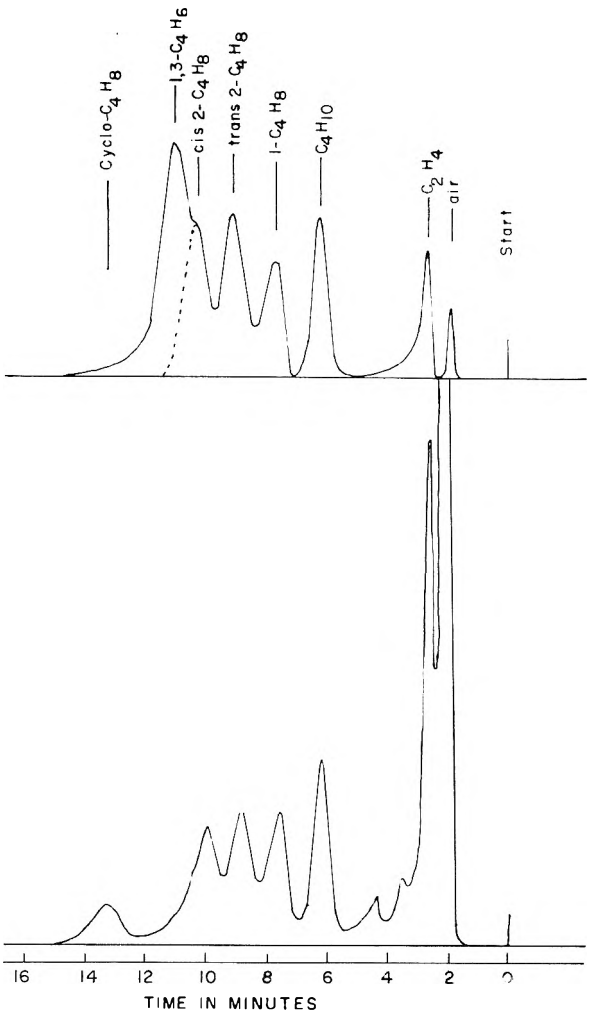

Fig. 1. Gas chromatography tracings for a standard mixture of hydrocarbons (upper curve) and the reaction product of 1,4-dibromobutane with methylmagnesium bromide and cobaltous bromide in butyl ether (lower curve)

further clarify the question of whether the dehalogenations are free radical or ionic in nature, the reaction was carried out under conditions which would favor radical formation.

Kharasch and co-workers[7] have carried out a number of reactions using a Grignard reagent and cobaltous halides as a source of free radicals in solution. It was proposed that radical formation takes place according to the following scheme.

$$RMgX + CoX_2 \longrightarrow RCoX + MgX_2$$

$$RCoX \longrightarrow R\cdot + \cdot CoX$$

When a mixture of 1,4-dibromobutane and cobaltous bromide was treated with methylmagnesium bromide in a high boiling solvent, it was found that the same group of gaseous reaction products was observed as in the metal dehalogenation reactions. The results of this series of reactions are also listed in Table I. At the lower temperature of refluxing ethyl ether, no cyclobutane was formed; a not unexpected result in view of the observations of Cason and Way.[3]

The experimental results of this study support the view that the metal dehalogenation reactions of 1,4-dibromobutane are free radical in nature. However, it should be born in mind that in any reactions as complex as these there is no difficulty in finding explanations of the experimental facts, but only in defending a preferred explanation selected from many. One reasonable reaction scheme which will accommodate the above observations is as follows:

$$Br{-}(CH_2)_4{-}Br \xrightarrow{M} Br(CH_2)_4\cdot(A) + MBr \quad (1)$$

$$(A) \longrightarrow \text{cyclo-}C_4H_8 + Br\cdot \quad (2)$$

$$(A) \longrightarrow 2C_2H_4 + Br\cdot \quad (3)$$

$$2(A) \longrightarrow Br{-}CH_2{-}CH_2{-}CH{=}CH_2 + n\text{-}C_4H_9Br \quad (4)$$

$$C_4H_9Br \xrightarrow{M} C_4H_9\cdot(B) + MBr \quad (5)$$

(7) M. S. Kharasch, R. D. Mulley, and W. Nudenberg, *J. Org. Chem.*, **19**, 1477 (1954).

TABLE II

REACTIONS OF *n*-BUTYL BROMIDE AND 4-PHENOXYBUTYL BROMIDE

Reagents	Solvent	Yield, Ml.	Product, Mole %					
			C_2H_4	C_4H_{10}	1-C_4H_8	2-C_4H_8	1,3-C_4H_6	Cyclo C_4H_8
n-Butyl bromide, 0.02 mole								
Mg + $CoBr_2$	Et_2O	490	0	55	21	24	...	...
CH_3MgBr + $CoBr_2$	Et_2O	...[a]	6	11	20	..	...	...
4-Phenoxybutyl bromide, .0052 mole								
Mg + $CoBr_2$	Xylene	25	5	3	79	10	1	2

[a] No yield of reaction products was measured due to the high dilution with methane. The other major product (63%) was pentane.

$$2(B) \longrightarrow C_4H_{10} + 1\text{-}C_4H_8 \quad (6)$$

In the same fashion the 4-bromo-1-butene (Equation 4) may decompose to form 1,3-butadiene and 1-butene. The 4-bromo-1-butyl radical (*A*) may be generated either by the direct abstraction of the halogen by the metal or by the thermal decomposition of a metal alkyl intermediate.[8]

The formation of cyclobutane as envisioned in Equation 2 above is a displacement of bromine atom from carbon by an attacking radical. The experimental evidence regarding radical displacement reactions has been summarized by Steacie.[9] The formation of a 1,4-butyl diradical as suggested by Bawn and Milstead[2] is also a possibility. In order to test the proposal of the 4-bromo-1-butyl radical (*A*) as a reaction intermediate, the decomposition of 4-phenoxybutyl bromide with magnesium and cobaltous bromide in refluxing xylene was carried out. Again a complex mixture of gaseous products was formed (Table II). Analysis of this mixture showed the same products as observed in the reactions of 1,4-dibromobutane. Cyclobutane was formed to the extent of 2 mole percent. Kharasch, Stampa, and Nudenburg[10] have reported that treatment of 4-phenoxybutyl bromide with phenylmagnesium bromide and cobaltous bromide in ether gave predominantly butyl phenyl ether and butenyl phenyl ether.

Both *trans* and *cis* 2-butene (the ratio *trans*/*cis* varied from two to five) were formed in each of the reactions studied. Kharasch, Lambert, and Urry[11] noted the formation of 2-butene when 1-chloro-3-phenylpropane was treated with butylmagnesium bromide and cobaltous bromide. Their suggestion of the rearrangement of a *n*-butyl radical to a *sec*-butyl radical *via* a hydrogen atom migration has not received further experimental support. However, should such a migration occur then the formation of 2-butene may be postulated as follows:

$$(B) \xrightarrow{\sim H} CH_3{-}CH_2{-}\dot{C}H{-}CH_3 \xrightarrow{\text{disproportionation}} C_4H_{10} + 1\text{-}C_4H_8 + 2\text{-}C_4H_8 \quad (7)$$

When butylbromide is allowed to react with magnesium and cobaltous bromide in ether, the yields of 1-butene and 2-butene were essentially the same (Table II). In another experiment butyl bromide and cobaltous bromide were allowed to react with methylmagnesium bromide. There was no observable yield in 2-butene under these conditions (Table II) and the high yield of pentane suggests that the recombination of methyl and butyl radicals is a faster reaction than any process leading to 2-butene formation.

One referee has suggested that the metal salts present in the reaction mixture may serve as Lewis acids catalyzing the rearrangement of 1-butene to 2-butene. While there is a real possibility of such an isomerization occurring in the reactions at lower temperatures, it would be dubious that 1-butene would have a sufficiently long residence time in the reaction vessel at the temperatures of refluxing butyl ether and xylene for such a rearrangement to occur.

Finally, with regard to the balance of product yields predicted by the above proposed mechanistic scheme, it should be born in mind that no mention has been made of the interactions of the various radicals proposed with each other or with the solvents employed. Such factors undoubtedly play an important role in determining the yields of reaction products. Thus, it is not to be expected that the above scheme should account quantitatively for the products but rather for the spectrum of products observed.

EXPERIMENTAL

Reagents. Eastman Kodak White Label 1,4-dibromobutane was carefully distilled through a Widmer column. After a slight forerun, the major fraction was taken; b.p. 74.5°/11 mm.

Butyl ether was washed with dilute potassium hydroxide and water. While still wet it was treated with an excess of

(8) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **21**, 93 (1956).

(9) E. W. R. Steacie, *Atomic and Free Radical Reactions*, Reinhold Publishing Corp., New York, N. Y., Vol. II, p. 743; Vol. I, p. 269.

(10) M. S. Kharasch, G. Stampa, W. Nudenburg, *J. Org. Chem.*, **18**, 575 (1953)

(11) M. S. Kharasch, F. L. Lambert, W. H. Urry, *J. Org. Chem.*, **10**, 298 (1945).

calcium hydride and then distilled from the excess hydride; b.p. 141°.

n-Butyl bromide was Eastman Kodak White Label carefully distilled through a Todd column; b.p. 106.6°.

The magnesium used in this study was Fisher Grignard Reagent magnesium.

Method of gas analysis. The gases produced in the following reactions were analyzed by means of a Fisher Gulf Partitioner using the standard column provided with the instrument (tricresyl phosphate on firebrick). The eluting gas was helium. The peaks produced by an unknown sample were identified by comparison with those produced by a standard known mixture of light hydrocarbon gases (Fig. 1). The cyclobutane band was identified by inference from the products formed by the treatment of 1,4-dibromobutane with sodium in refluxing toluene.[3]

The mole percent of each component was calculated by the expression:

$$\text{mole } \%\ \text{A} = \frac{\text{area under A}}{\text{total area}} \times 100$$

Apparatus. The apparatus consisted of a 100-ml., three-necked flask fitted with a dropping funnel and a condenser. All reactions were stirred by means of a magnetic stirrer. All gases were collected, after passing through the condenser, in a gas collection bottle filled either with mercury or a saturated salt solution.

Reaction of 1,4-dibromobutane with various metals. To a refluxing mixture of 2 g. of the appropriate metal and 20 ml. of solvent was slowly added 2.16 g. (0.01 mole) of 1,4-dibromobutane. The mixture was usually allowed to reflux overnight. The evolved gases were then measured and analyzed according to the above procedure. The metals, solvents, and reaction products are tabulated in Table I.

Reaction of 1,4-dibromobutane with methylmagnesium bromide and cobaltous bromide in various solvents. To a refluxing mixture of 2.16 g. (0.01 mole) of 1,4-dibromobutane and 2 g. of cobaltous bromide in 20 ml. of solvent, was added *ca.* 0.03 mole of methylmagnesium bromide in the same solvent. The solvents used were ethyl ether, butyl ether, and xylene. In the latter two solvents, the addition reagent was formed by mixing the solvent with the appropriate amount of methylmagnesium bromide in ethyl ether and then removing as much of the ethyl ether as possible by evacuating to water pump pressure. In xylene and butyl ether, the Grignard reagent was added in the form of a slurry. The gases produced were collected and analyzed as described previously.

Reactions of n-butyl bromide. (*a*) A mixture of 2.74 g. of *n*-butyl bromide (0.02 mole), 4.36 g. of cobaltous bromide (0.02 mole), and 1 g. of magnesium was refluxed in 15 ml. of ethyl ether for three hours. The reaction gas was collected and analyzed as before. The results are recorded in Table II.

(*b*) To a refluxing mixture of 2.74 g. of *n*-butyl bromide and 1 g. of cobaltous bromide in 15 ml. of ethyl ether was slowly added 25 ml. of *ca.* 1*M* methylmagnesium bromide. The yield of gas was quantitative based on the amount of methylmagnesium bromide. The analytical results are given in Table II.

Reaction of 4-phenoxybutyl bromide with magnesium and cobaltous bromide. 4-Phenoxybutyl bromide was prepared by the method of Kharasch, *et al.*;[10] m.p. 40–41.5°. A mixture of 1.2 g. (5.2 mmole) of 4-phenoxybutyl bromide, 1 g. of cobaltous bromide, and 2 g. of magnesium was refluxed for three days in 25 ml. of xylene. The rather small gas yield (25 ml.) was collected and analyzed as before. The results are recorded in Table II.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY]

Synthesis of Tribenzocycloheptatriene and Related Compounds

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From the adduct (III) of butadiene and cinnamaldehyde, 4,5-tetramethyleno-2,3-benzosuberone (VI) has been prepared. Condensation of its 7-formyl derivative with the methiodide of β-diethylaminoethyl methyl ketone gave the tetracyclic hydroxyketone (X) from which by dehydration and dehydrogenation tribenzocycloheptatriene (II) has been obtained. The corresponding heptafulvene (XIV) does not differ in its physical properties from triphenylethylene; it has no "fulvenic" properties. Some other reactions of the adduct (III) and the ketone (VI) have also been explored.

The failure of the properties of the dibenzoheptafulvenes (I) to agree with those predicted by the theory, based on the linear combination of atomic orbitals (LCAO),[1–3] made it interesting to synthesize heptafulvenes derived from tribenzocycloheptatriene (II). The preparation of this compound started from the adduct (III) of butadiene and cinnamaldehyde, 2-phenyl-1,2,3,6-tetrahydrobenzaldehyde. The *trans*-structure of this aldehyde follows from the configuration of cinnamaldehyde[4] and from its oxidation to the known[5] 2-phenyl-1,2,3,-6-tetrahydrobenzoic acid, by means of silver oxide.[6]

(1) E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman, and B. Pullman, *Bull. soc. chim. France*, 18, 684 (1951).

(2) G. Berthier and B. Pullman, *Trans. Faraday Soc.*, 45, 484 (1949).

(3) See, however, A. Julg and B. Pullman, *J. chim. phys.*, 52, 481 (1951).

(4) M. Bourguel, *Bull. soc. chim. France* [4], 45, 1086 (1929); G. Gomboni, V. Thens, and H. Schmitz, *Helv. Chim. Acta*, 38, 255 (1955); H. Schinz, *Chem. Abstr.*, 49, 6874 (1956).

(5) J. W. Cook, C. L. Hewett, and A. M. Robinson, *J. Chem. Soc.*, 168 (1939); G. Blumenfeld, *Ber.*, 74, 524 (1941); C. D. Gutsche, *J. Am. Chem. Soc.*, 70, 4150 (1948); K. Alder, H. Vagt, and W. Vogt, *Ann.*, 565, 135 (1945); N. V. Organon, Brit. Patent 674,177 [*Chem. Abstr.*, 47, 7540 (1953)].

(6) The isomeric 2-phenyl-1,2,5,6-tetrahydrobenzaldehyde has been prepared by E. Lehmann and W. Paasche, *Ber.*, 68, 1146 (1935), and K. Alder, H. Vagt, and W. Vogt, ref. 5.

Condensation of III with malonic acid gave β-(2-phenylcyclohex-4-enyl)acrylic acid (IV); however, a pure product (m.p. 129°) could only be obtained after a number of recrystallizations, and the yield did not exceed 50%. It appears that a second product (a geometric isomer or, more likely, a compound with different location of the double bond) is formed, which, however, could not be isolated in pure form. The acid IV was characterized by its crystalline methyl ester and benzylisothiuronium salt.[7]

Hydrogenation of the acid (IV) gave the well known[8] *trans*-2-phenylcyclohexylpropionic acid (V) in 86% yield, which was also obtained in somewhat better over-all yield by the following alternative route: the diethyl acetal of (III) was hydrogenated and the hydrogenation product hydrolyzed to *trans*-2-phenylcyclohexanaldehyde. The latter condensed with malonic acid to yield the dihydro-analog of IV, which could be hydrogenated to V.

Cyclization of V with polyphosphoric acid gave in good yield 4,5-tetramethyleno-2,3-benzosuberone (VI) the key substance in the present synthesis.[9] It gave a 7-bromo derivative which, however, did not lend itself to further transformation. Reduction of the carbonyl group in VI with lithium aluminum hydride and dehydration of the secondary alcohol so formed gave 3,4-benzo-5,6-tetramethylenocyclohepta-1,3-diene (VII). This was dehydrogenated by means of palladium to a mixture of two hydrocarbons which could be separated by fractional distillation: 9-methylphenanthrene and the dihydro derivative (IX) of the expected 3,4,5,6-dibenzocyclohepta-1,3-5-triene (VIII), which did not give a picrate and had the same principal maximum (247 mμ; log ε 4.12) as 2-methyl-3,4,5,6-dibenzocyclohepta-3,5-diene (248 mμ; log ε 4.14) and the corresponding 2,4,7-trimethyl derivative (250 mμ; log ε 4.14), hydrocarbons which have only recently been described by Hall *et al.*[10,11]

A more convenient method for the preparation of the desired tetracyclic system was found in the Michael reaction between the 7-formyl derivative of VI and the methiodide of β-diethylaminoethyl methyl ketone in the presence of sodium ethoxide. The reaction product had the formula of the hydroxyketone X; it was characterized by a *mono*-2,4-dinitrophenylhydrazone, which exhibited a band at 365 mμ (4.23), as expected for a *saturated* ketone. The infrared spectrum of the compound revealed the presence of the hydroxyl group (3400 cm.$^{-1}$), but the carbonyl band appeared at the unexpectedly low frequency of 1675 cm.$^{-1}$ in the solid state, whilst in chloroform solution a doublet at 1724 and 1689 cm.$^{-1}$ was observed. It may be that the ketone contains some of the dehydration product (XI), and that some more of the latter was formed in the preparation of the potassium bromide disk. Potassium hydroxide in aqueous-alcoholic dioxane at room temperature dehydrated X to the tetracyclic ketone XI with a yield of 50%. The ultraviolet absorption spectrum of the 2,4-dinitrophenylhydrazone showed a band at 394 mμ (4.35), and that of the ketone itself at 292 mμ (4.10), as expected for an α,β-unsaturated cycloalkenone in which the double band is also conjugated with a phenyl group.[11a] Again, the infrared absorption of the carbonyl group had an unexpectedly low frequency, *viz.* 1650 cm.$^{-1}$ (in potassium bromide).

When XI was subjected to treatment with aluminum isopropoxide, not only was the keto group reduced to hydroxyl, but water was split off,[12] and the compound XII formed.

Dehydrogenation of XII gave II which both according to the analysis and the spectrum had the desired structure. Bromination of II with *N*-bromosuccinimide converted it into 1-bromo-2,3,4,5,6,7-tribenzocyclohepta-2,4,6-triene which was hydrolyzed to the corresponding secondary alcohol and oxidized further to the ketone XIII. This was characterized by its orange-red 2,4-dinitrophenylhydrazone and the infrared absorption band at 1667 cm.$^{-1}$.[13]

Reaction of XIII with benzylmagnesium chloride and subsequent dehydration gave the desired heptafulvene XIV, 1-benzylidene-2,3,4,5,6,7-tribenzocy-

(7) The route chosen in this investigation is somewhat similar to that of J. W. Cook, G. T. Dickson, J. Jack, J. D. London, J. McKeown, J. Macmillan, and W. F. Williams [*J. Chem. Soc.*, 139 (1950)], who condensed the fully aromatic 2-phenylbenzaldehyde with malonic acid. When the authors attempted to cyclize the resulting *o*-biphenylylpropionic acid (corresponding to V), they obtained not a seven-, but a five-membered ring.

(8) C. D. Gutsche, see ref. 5.

(9) The substance has been prepared before by a different route. C. D. Gutsche, *J. Am. Chem. Soc.*, **73**, 786 (1951).

(10) D. M. Hall, J. E. Landburg, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 3475 (1956); *cf.* Cook and Turner, *J. Chem. Soc.*, 113 (1937); *cf.* also G. H. Beaven and E. A. Jonson, *J. Chem. Soc.*, 651 (1957), who have studied 2-methyl-3,4,5,6-dibenzocyclohepta-3,5-diene (248 mμ; log ε 4.18).

(11) The occurrence of hydrogenation in dehydrogenation reactions (hydrogen transfer) is not unusual, nor is the formation of phenanthrene compounds from dibenzocycloheptadiene derivatives unexpected; similar observations have been made in the colchicine series. See, *e.g.*, A. Windaus, *Ann.*, **439**, 59 (1924), and J. W. Cook *et al.*, *J. Chem. Soc.*, 746 (1947).

(11a) See, *e.g.*, 3-phenylcyclopent-2-en-1-one: 280 mμ (log ε 4.42). A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, T. C. Johnson, and C. H. Shunk, *J. Am. Chem. Soc.*, 69, 1985 (1947).

(12) Such a secondary reaction is rare, but not altogether unknown: J. Doeuvre and H. Perret, *Bull. soc. chim. France*, [5], 2, 298 (1935); W. G. Grubb and J. Read, *J. Chem. Soc.*, 242 (1934); A. G. Short and J. H. Read, *J. Chem. Soc.*, 1306 (1939); W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, **4**, 461 (1939).

(13) This compound has recently been obtained by the rearrangement of the diazonium salt of 9-(*o*-aminophenyl)-9-fluorenol (M. Stiles, A. J. Sisti, and A. J. Libbey, 131st Meeting, American Chemical Society, April 1957). We are grateful to the referee who informed us of this fact. See the paper by M. Stiles and A. J. Libbey, *J. Org. Chem.*, **22**, 1243 (1957).

clohepta-2,4,6-triene. The absorption spectrum of this compound shows practically no structure; maxima are observed at 230 mμ (4.65) and at 262 mμ (4.38) (Fig. 1). The analogous dibenzoheptafulvene (I, R. = C_6H_5) absorbs at 284 mμ (4.40).[1]

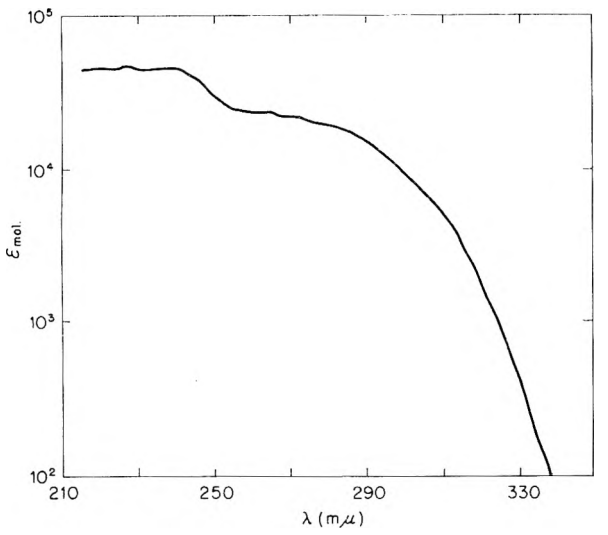


Fig. 1. Ultraviolet spectrum of 1-benzylidene-2,3,4,5,6-tribenzocyclohepta-2,4,6-triene (XIV) in ethanol

It follows, therefore, that XIV exactly as I is a fulvene only in name; its properties are not those one would have expected. One will have to assume that the incorporation of the double bonds of the cycloheptatriene system into aromatic rings deprives the system of its pseudo-aromatic character. The hypsochromic effect of the anellation of benzene rings to the system of the fulvenes derived from cyclopentadiene and the concomitant decrease in the polarity of the semicyclic double bond in these fulvenes are phenomena of the same character.[14]

In the course of this investigation, another route was explored in which the third ring was to be created through a Diels-Alder reaction. The aldehyde III was condensed with acetone, the ketone XV reduced to the secondary alcohol, and the latter dehydrated to 1-butadienyl-2-phenyl-cyclohex-4-ene (XVI). The yields in the three steps were fair (74%, 57%, 52%, respectively), but the condensation of XVI with maleic anhydride proved disappointing, and the method was abandoned.

EXPERIMENTAL

trans-2-Phenyl-1,2,3,4-tetrahydrobenzaldehyde (III). A mixture of 150 g. of freshly distilled cinnamaldehyde, 180 g. of butadiene, 4 g. of hydroquinone, and 350 ml. of benzene was heated at 200° for 20 hr. (autoclave) and distilled through a Vigreux column. A quantity of about 20 g. of cinnamaldehyde was recovered and 130–150 g. (yield, 62–71%) of the desired aldehyde, b.p. 171–173° (30 mm.), m.p. 36–37°, was obtained.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.9; H, 7.5. Found: C, 84.0; H, 7.8.

Ultraviolet spectrum: λ_{max}^{EtOH} 290 mμ (log ε 2.78); several minor (benzene) bands between 250 and 270 mμ (2.50–2.68).

Phenylhydrazone, bright yellow needles, from ethyl alcohol; m.p. 127°.

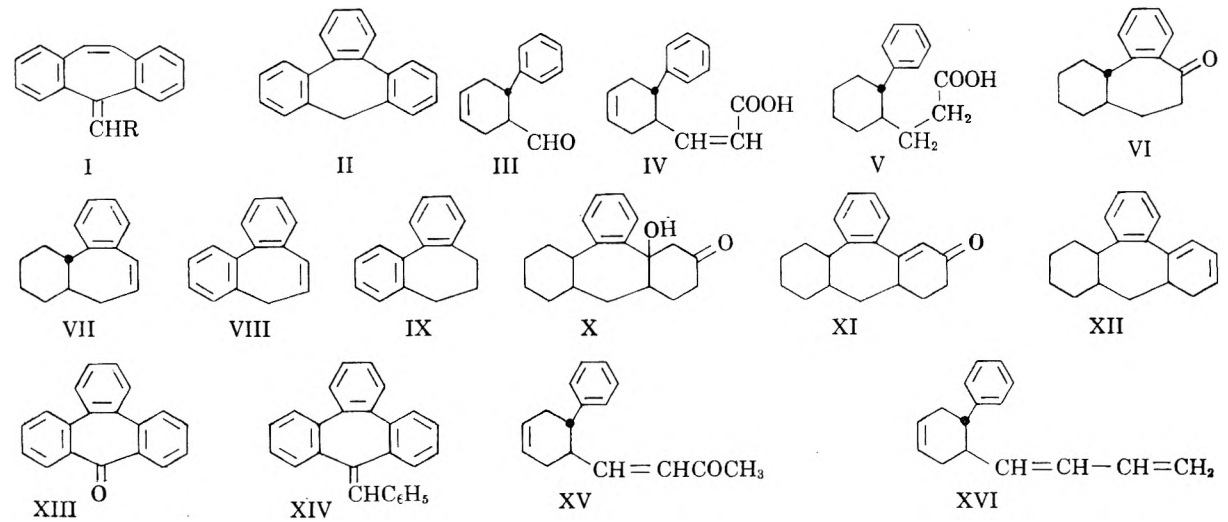
Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3. Found: C, 83.0; H, 7.3.

2-Nitrophenylhydrazone, yellow needles, from butyl alcohol, m.p. 180°. *Anal.* Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.0; H, 6.0; N, 13.1. Found: C, 71.0; H, 6.0, N, 12.9.

2,4-Dinitrophenylhydrazone, yellow needles, from alcohol; m.p. 161°.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.7; H, 5.1; N, 15.5. Found: C, 62.9; H, 5.0; N, 15.3.

trans-2-Phenyl-1,2,3,4-tetrahydrobenzoic acid. To a solution of 2.2 g. of sodium hydroxide in 50 ml. of water, silver oxide, prepared from 8.5 g. of silver nitrate, and 9 g. of the aldehyde (III) were added successively with stirring and cooling with ice. The product was kept at room temperature for 30 min., filtered, and acidified. The acid was recrystallized from ligroin and melted at 104° (lit.:[5] 107–108°); yield, 50%.



Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.9. Found: C, 77.2; H, 7.1.

β-(*2-Phenylcyclohex-4-enyl*)*acrylic acid* (IV). A mixture of 130 g. of the aldehyde (III), 143 g. of malonic acid, 280

(14) E. D. Bergmann, "The Fulvenes," in *Progress in Organic Chemistry*, Vol. 3, Butterworth's Scientific Publications, London, 1955, p. 81.

ml. of pyridine, and 5 ml. of piperidine was heated for 3 hr. at 100° and for 30 min. at 150°, and poured into ice cold hydrochloric acid. The product was extracted with ether and transferred again into 5% sodium carbonate solution. Acidification gave 150 g. (94%) of a yellowish product (m.p. 95–110°) which was recrystallized twice from cyclohexane and then melted at 126° (yield, 80–90 g.; 53%). Another recrystallization from benzene raised the m.p. to 129°. ν_{max}^{KBr} (in cm.$^{-1}$) 2950 (associated hydroxyl); 1685 (CO of an α,β-unsaturated acid); 1625 (C=C); 705 (CH wagging frequency in a *cis*-olefin).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.0. Found: C, 79.6; H, 6.8.

Methyl ester, prepared with diazomethane, b.p. 164–165° (3.5 mm.); m.p. 63° (from methanol).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4. Found: C, 79.5; H, 7.1.

The methyl ester (in ethanol) does not show a very characteristic ultraviolet absorption spectrum; at 262 mμ, an inflection (log ϵ 2.64) is observed. This may be due to steric influences.

Benzylisothiuronium salt, m.p. 161° (from ethanol).

Anal. Calcd. for $C_{23}H_{26}N_2O_2S$: C, 70.0; H, 6.6. Found: C, 70.0; H, 6.6.

β-(2-Phenylcyclohexyl)propionic acid (V). A solution of 63 g. of the acid IV in 250 ml. of glacial acetic acid was hydrogenated at ordinary temperature and pressure in the presence of 0.7 g. of 10% palladium-charcoal. The solvent was distilled off and the residue recrystallized from petroleum ether (60–90°), m.p. 85° (lit.:[8] 83.5–84.5°); yield, 54 g. (86%).

The same acid was obtained in almost quantitative yield, when β-(2-phenylcyclohexyl)acrylic acid (*vide infra*) was hydrogenated in ethanol solution and in the presence of 10% palladium-charcoal as catalyst. The hydrogenation proceeded rapidly at ordinary temperature and pressure.

Diethyl acetal of the aldehyde III. A mixture of 12.4 g. of the aldehyde (III), 8.3 g. of ethyl orthoformate, 30 ml. of anhydrous ethanol, and some drops of saturated alcoholic hydrochloric acid was kept at room temperature for 12 hr., neutralized by stirring with an excess of solid carbonate for 15 min., diluted with an equal volume of ether, filtered, and distilled, b.p. 120–122° (0.9 mm.). The yield was 15.2 g. (87%).

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.5; H, 9.2. Found: C, 78.4; H, 9.0.

With the dinitrophenylhydrazine reagent, the acetal gives the above-described 2,4-dinitrophenylhydrazone of III.

Diethyl acetal of 2-phenylhexahydrobenzaldehyde. The solution of 13.7 g. of the foregoing acetal in 50 ml. of ethanol was hydrogenated at ordinary temperature and pressure in the presence of 0.5 g. of 10% palladium-charcoal. The theoretical amount of hydrogen was absorbed in 40 min. The product distilled at 115–117° (0.7 mm.); and weighed, 12.7 g. (100%).

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.9; H, 10.0. Found: C, 78.0; H, 10.0.

2-Phenylhexahydrobenzaldehyde. The solution of 11 g. of the saturated acetal in 10 ml. of alcohol was heated on the water bath for 1 hr. with 50 ml. of 2% aqueous hydrochloric acid, and extracted with benzene. The product (7 g., 90%) distilled at 115–118° (1 mm.).

Anal. Calcd. for $C_{13}H_{16}O$: C, 83.0; H, 8.5. Found: C, 83.8; H, 8.7.

2,4-Dinitrophenylhydrazone, from butyl alcohol, m.p. 174°.

Anal. Calcd. for $C_{19}H_{20}N_4O_4$: C, 61.9; H, 5.4; N, 15.2. Found: C, 61.6; H, 5.3; N, 14.9.

β-(2-Phenylcyclohexyl)acrylic acid. In the manner described above, 37 g. of 2-phenylhexahydrobenzaldehyde, 40 g. of malonic acid, 80 ml. of pyridine, and 2 ml. of piperidine gave 31 g. (72%) of the desired acid, from ligroin, m.p. 113–114°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.3; H, 7.8. Found: C, 78.9; H, 8.0.

Benzylisothiuronium salt, m.p. 169° (from ethanol).

Anal. Calcd. for $C_{23}H_{28}N_2O_2S$: N, 7.1. Found: N, 6.9.

trans-4,5-Tetramethyleno-2,3-benzosuberone (VI). A mixture of 55 g. of the pure acid V and 900 g. of polyphosphoric acid[15] was heated at 100° for 3 hr., diluted with water, and extracted with benzene. The product boiled at 163–165° (1.5 mm.) and solidified spontaneously. Recrystallization from petroleum ether gave 32 g. (60%) of m.p. 55°.[9] $\bar{\nu}_{max}^{KBr}$ 1667 cm.$^{-1}$ This is a rather low carbonyl frequency, as benzosuberone has this band at 1690 cm.$^{-1}$; incidentally, in the Raman spectrum, the corresponding figure is 1676 cm.$^{-1}$.[16] In chloroform (40.9 mg.; 1 ml.) the carbonyl frequency was observed at 1690 cm.$^{-1}$ This extreme influence of the potassium bromide pellet is very unusual.

7-Bromo-4,5-tetramethyleno-2,3-benzosuberone. To a solution of 4.3 g. of the ketone VI in 20 ml. of carbon tetrachloride, there was added, over a period of 25 min., a solution of 3.2 g. of bromine in 30 ml. of carbon tetrachloride. After further 30 min., the solvent was evaporated *in vacuo* and the residue recrystallized from ligroin (b.p. 90–100°). The yield was 3.5 g. (60%) of colorless needles, m.p. 117–118°. $\bar{\nu}_{max}^{KBr}$ 1678 cm.$^{-1}$.[17]

Anal. Calcd. for $C_{15}H_{17}BrO$: C, 61.5; H, 5.8. Found: C, 61.6; H, 6.0.

4,5-Tetramethyleno-2,3-benzocyclohept-2-en-1-ol. To 0.5 g. of lithium aluminum hydride in 30 ml. of ether, there was added, during 30 min. and with stirring, a solution of 9 g. of the ketone VI in 50 ml. of ether. After 12 hr. at room temperature, the reaction product was decomposed and acidified. The product, a yellow-greenish oil boiled at 162–164° (0.1 mm.); yield, 7.5 g. (83%). It could not be obtained in analytically pure state; probably, even *in vacuo* some dehydration takes place. λ_{max}^{EtOH} 250 mμ (log ϵ 2.63); $\bar{\nu}_{max}^{liq.}$ 3500 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.3; H, 9.3. Found: C, 84.9; H, 9.8.

5,6-Tetramethyleno-3,4-benzocyclohepta-1,3-diene (VII). The foregoing alcohol (5 g.) was subjected to azeotropic distillation with 0.5 g. of *p*-toluenesulfonic acid in 80 ml. of xylene. After 90 min., the reaction mixture was washed with water and distilled; b.p. 105–110° (0.15 mm.); yield, 4.5 g. (quantitative). λ_{max}^{EtOH} 248 mμ (log ϵ 4.02).

Anal. Calcd. for $C_{15}H_{18}$: C, 90.9; H, 9.1. Found: C, 91.0; H, 9.4.

3,4,5,6-Dibenzocyclohepta-3,5-diene (*VIII*) *and 9-methylphenanthrene.* A mixture of 3.4 g. of VII and 1 g. of 10% palladium-charcoal was heated in a carbon dioxide atmosphere for 1 hr. at 310°, for 25 min. at 320°, and finally for 45 min. at 340°. The organic product was extracted with benzene and fractionated. Thus, two products were obtained: an oil (2 g.) of b.p. 156° (6 mm.) and a fraction (0.5 g.) of b.p. 170° (6 mm.) which solidified. This hydrocarbon was recrystallized from methanol, melted at 92°, gave the analytical figures required for, and exhibited an ultraviolet spectrum identical with that of, 9-methylphenanthrene. Also the mixture with an authentic specimen melted at 92°.

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(15) F. Uhlig, *Angew. Chem.*, **66**, 435 (1954).

(16) R. N. Jones and C. Sandorfy, *Chemical Application of Spectroscopy*, Interscience Publishers Inc., New York, N. Y., 1956, p. 449.

(17) It has been observed that a bromine atom α to a carbonyl either increases the frequency of the carbonyl absorption or leaves it practically unchanged, depending upon the conformation of the brominated product. In cycloheptanone, *e.g.*, α-bromination shifts the carbonyl band by 8 cm.$^{-1}$ *Cf.* E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); E. J. Corey and H. J. Burke, *J. Am. Chem. Soc.*, **77**, 5418 (1955); R. N. Jones *et al.*, *J. Am. Chem. Soc.*, **74**, 2828 (1952). G. Chiurdoglu, *Bull. soc. chim. France*, 1018 (1956); *Cf.* W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956); M. Josien, C. Castinel, and G. Chiurdoglu, *Compt. rend.*, **244**, 2383 (1957).

Anal. Calcd. for $C_{15}H_{12}$: C, 93.7; H, 6.2. Found: C, 93.4; H, 6.3.

Picrate, from methanol, m.p. and mixed m.p. with pure 9-methylphenanthrene picrate, m.p. 153°.

Anal. Calcd. for $C_{25}H_{15}N_3O_7$: C, 59.9; H, 3.6. Found: C, 60.2; H, 3.4. λ_{max}^{EtOH} 349 mμ (log ε 2.47); 341 mμ (2.28); 333 mμ (2.42); 326 mμ (2.28); 318 mμ (2.29); 296 mμ (4.02); 285 mμ (4.01); 253 mμ (4.66). The oily product gave an analysis corresponding to $C_{15}H_{14}$; it has the structure IX and shows a spectrum in accordance with this structure, 247 mμ (4.20) in ethanol.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.8; H, 7.2. Found: C, 92.6; H, 6.7.

4,5-Tetramethyleno-7-formyl-2,3-benzosuberone. To a suspension of dry sodium methoxide, freshly prepared from 1.4 g. of sodium metal[18] in 100 ml. of benzene, 4.8 g. of ethyl formate and then, at 0°, a solution of 6.4 g. of the ketone VI in 50 ml. of benzene were added. One stirred for 1 hr. at room temperature and for 1 hr. at reflux temperature, extracted the benzene solution with 5% sodium hydroxide solution, and isolated the product by acidification of the alkaline extract. From methanol, m.p. 117°; yield, 5.8 g. (80%).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4. Found: C, 79.6; H, 7.8.

Tetracyclic hydroxyketone (1a-hydroxy-8-keto-1,1a,2,3,4,-4a,6a,7,8,9,9a-dodecahydrotribenzo[a,c,e]cycloheptatriene) (X). To a solution of 0.7 g. of sodium in 50 ml. of ethanol, there were added, successively, 6.0 g. of the foregoing product and a solution of 4-diethylamino-2-butanone methiodide (prepared from 4 g. of the aminoketone and 4 g. of methyl iodide) in 40 ml. of ethanol. After 24 hr. at room temperature, water and benzene was added to the reaction mixture. The benzene solution was extracted with 5% sodium hydroxide solution from which 3 g. (50%) of the initial formyl compound was precipitated by acidification. (Prolongation of the reaction time to 48 hr. did not improve the conversion.) The benzene solution gave, upon distillation, an oil (3.1 g.; 46%) of b.p. 190° (0.1 mm.), which according to the analysis and the spectrum was the hydroxyketone X. It crystallized on standing and showed, after recrystallization from alcohol, the m.p. 82°. $\tilde{\nu}_{max}^{KBr}$ cm.$^{-1}$ 3400 (hydroxyl), 1670 (carbonyl); λ_{max}^{EtOH} 250 mμ (log ε 3.56); 282 mμ (log ε 3.10). In chloroform solution (45.0 mg. in 1 ml.), the carbonyl frequency is a doublet (1724; 1689 cm.$^{-1}$). It is assumed that the hydroxy-ketone contains a small amount of the unsaturated ketone (XI); in the preparation of the potassium bromide pellet, perhaps, some further dehydration takes place. Even so, the influence of the physical state on the carbonyl frequency is surprising.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 80.3; H, 8.4. Found: C, 80.0; H, 8.1. In accordance with formula X, the 2,4-dinitrophenylhydrazone was yellow; from butyl acetate, m.p. 168°. $\lambda_{max}^{CHCl_3}$ 365 mμ (log ε 4.36).

Anal. Calcd. for $C_{22}H_{28}N_4O_5$: C, 64.7; H, 6.1; N, 12.1. Found: C, 64.9; H, 6.5; N, 12.1.

Tetracyclic ketone (2-oxo-2,3,4,4a,6,6a,7,8,9,9a-decahydrotribenzo[a,c,e]cycloheptatriene) (XI). To a solution of 5 g. of (X) in 60 ml. of dioxan and 110 ml. of anhydrous ethyl alcohol, 110 ml. of a 10% aqueous solution of potassium hydroxide was added in an atmosphere of nitrogen and the mixture kept at room temperature for 48 hr. Dilute sulfuric acid was added and the product extracted with benzene. The product (2.5 g.; 50%) boiled at 207–210° (0.3 mm.) and solidified spontaneously. Recrystallization from alcohol yielded colorless crystals of m.p. 141°. $\tilde{\nu}_{max}^{KBr}$ 1650 cm.$^{-1}$ (carbonyl); λ_{max}^{EtOH} 287 mμ (log ε 4.15); 292 mμ (log ε 4.18).

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.8; H, 8.6. The red 2,4-dinitrophenylhydrazone was recrystallized from butyl acetate and melted at 250°. $\lambda_{max}^{CHCl_3}$ 268 mμ (log ε 4.20); 296 mμ (4.11); 394 mμ (4.52).

Anal. Calcd. for $C_{25}H_{26}N_4O_4$: C, 67.3; H, 5.8. Found: C, 68.1; H, 6.4.

Hydrocarbon (XII). *(4,4a,6,6a,7,8,9,9a-octahydrotribenzo-[a,c,e]cycloheptatriene).* During 5 hr., 1.4 g. of XI and 2 g. of aluminium isopropoxide in 70 ml. of anhydrous isopropyl-alcohol were distilled slowly in a Vigreux column. After cooling, ice and concentrated hydrochloric acid was added and the product isolated by extraction with benzene. The product distilled at 140–145° (0.01 mm.); yield, 1 g. (78%). λ_{max}^{EtOH} 234 mμ (log ε 4.00); 290 mμ (log ε 3.63).

Anal. Calcd. for $C_{19}H_{22}$: C, 91.2; H, 8.8. Found: C, 91.4; H, 8.6.

Tribenzocycloheptatriene (II). A mixture of the foregoing product (0.8 g.) and 10% palladium-charcoal (0.4 g.) was heated for 30 min. at 270–280°, for 20 min. at 290–310° and for 30 min. at 330°. 80% of the theoretical amount of hydrogen was collected. The product was extracted with benzene and the benzene residue triturated with ethanol, whereupon a white solid of m.p. 105–115° (0.3 g.; 40%) separated. Purification by chromatography on activated alumina with petroleum ether and recrystallization again from methanol raised the melting point to 121°. λ_{max}^{EtOH} 239 mμ (log ε 4.59); 256 mμ (4.26; inflection). $\tilde{\nu}_{max}^{KBr}$ (cm.$^{-1}$) 3100, 2900, 1475, 1441, 762, 758, 740.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.2; H, 5.8. Found: C, 94.6; H, 6.2.

1-Bromo-2,3,4,5,6,7-tribenzocyclohepta-2,4,6-triene. A mixture of 0.6 g. of tribenzocycloheptatriene (II), 0.3 g. of *N*-bromosuccinimide and 10 ml. of carbon tetrachloride was refluxed for 3 hr. in the presence of a trace of benzoyl peroxide. The filtered solution was evaporated and the residue triturated with petroleum ether and recrystallized from cyclohexane, m.p. 173–174°; yield, 0.5 g. (62%).

2,3,4,5,6,7-Tribenzocyclohepta-2,4,6-trien-1-one (XIII). A mixture of 0.3 g. of the foregoing compound in 10 ml. of acetone and of 4 ml. of a 5% aqueous solution of sodium carbonate was refluxed for 8 hr., the acetone evaporated and the residue extracted with benzene. The residue of the benzene solution was triturated with cyclohexane and the crude secondary alcohol (0.2 g.) oxidized as follows [the alcohol crystallized from aqueous methanol (80%) in white rods of m.p. 118°].

The solution of the product in 30 ml. of glacial acetic acid was refluxed for 1 hr. with a solution of 0.2 g. of sodium dichromate in 4 ml. of water. Water was added and the solid filtered and recrystallized from ethanol. M.p. 180° (lit.[13]: 178–179°); yield, 0.16 g. $\tilde{\nu}_{max}^{KBr}$ 1667 cm.$^{-1}$; $\tilde{\nu}_{max}^{CHCl_3}$ 1672 cm.$^{-1}$ (carbonyl): λ_{max}^{EtOH} 239 mμ (log ε 4.43); 323 mμ (log ε 3.27).

Anal. Calcd. for $C_{19}H_{12}O$: C, 89.1; H, 4.7. Found: C, 88.8; H, 4.7. The orange-colored 2,4-dinitrophenylhydrazone had m.p. 260°, after recrystallization from butyl alcohol.

Anal. Calcd. for $C_{25}H_{16}N_4O_4$: C, 68.8; H, 3.7. Found: C, 68.4; H, 3.8.

1-Benzylidene-2,3,4,5,6,7-tribenzocyclohepta-2,4,6-triene (XIV). To a solution of benzylmagnesium chloride, prepared from 1.25 g. of benzyl chloride and 240 mg. of magnesium, 500 mg. of the foregoing ketone XIII in 10 ml. of benzene was added; the mixture was refluxed for 1.5 hr. and worked up as usual. The crude product was dissolved in petroleum ether and chromatographed on activated alumina (40 g.). Elution of the adsorbate with benzene gave 1-benzyl-1-hyroxy-2,3,4,5,6,7-tribenzocyclohepta-2,4,6-triene; the benzene was evaporated, the residue heated in toluene for 2 hr. in the presence of 0.1 g. of *p*-toluenesulfonic acid and the solution evaporated. The product was chromatographed from petroleum ether on activated alumina (40 g.) and eluted with petroleum ether in 30-ml. fractions. The fifth and sixth fraction contained a colorless solid of m.p. 150–152°; the melting point was raised to 152–153° by recrystallization from ethanol. The yield was 0.4 g.

Anal. Calcd. for $C_{25}H_{18}$: C, 94.3; H, 5.7. Found: C, 94.6; H, 5.6.

1-(β-Acetylvinyl)-2-phenylcyclohex-4-ene (XV). At −10°, a few drops of a solution of 1.4 g. of sodium in 45 ml. of

(18) A. S. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1715 (1946).

methanol were added to a solution of 19 g. of the aldehyde III in 150 ml. of anhydrous acetone. The temperature rose to 0°. When the temperature had fallen again to −10°, the balance of the sodium methoxide solution was added and the stirring continued for 30 min. at −10° and for 1 hr. at 25°. The mixture was neutralized with dilute sulfuric acid, diluted with water, and extracted with benzene to yield 17 g. (74%), b.p. 175–177° (1 mm.); λ_{max}^{EtOH} 292 mμ (log ε 3.40); $\tilde{\nu}_{max}^{liq.}$ 1675 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.9; H, 8.0. Found: C, 84.3; H, 8.2.

The 2,4-dinitrophenylhydrazone precipitated as an oil which crystallized on trituration with butyl alcohol. From the same solvent or from ethanol, orange-red crystals, m.p. 112–114°; $\lambda_{max}^{CHCl_3}$ 385 mμ (log ε 4.45).

1-Butadienyl-2-phenylcyclohex-4-ene (XVI). The ketone IX (14 g.) was reduced in the usual manner with 14 g. of aluminum isopropoxide and 100 ml. of isopropyl alcohol. The product, which boiled at 150–153° (2 mm.) (yield, 8 g., 57%) showed in the infrared no residual carbonyl absorption and the hydroxyl band at 3400 cm.$^{-1}$ It was heated with 1.5 g. of freshly fused potassium hydrogen sulfate at 140° *in vacuo*. The desired diene distilled at 130–132° (3 mm.); yield, 4.2 g. (52%). λ_{max}^{EtOH} 230 mμ (log ε 4.06); 292 mμ (log ε 2.72). $\tilde{\nu}_{max}^{liq}$ (cm.$^{-1}$) 1600; 1650 (substituted butadiene);[19] 660 (terminal=CH_2).[20]

Anal. Calcd. for $C_{16}H_{18}$: C, 91.4; H, 8.6. Found: C, 91.4; H, 8.4.

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(19) W. Bruegel, *Einfuehrung in die Ultrarotspektroskopie* Steinkopff, Darmstadt, 1954, p. 272.

(20) R. S. Rasmussen, R. R. Brattain, and P. S. Zucco, *J. Chem. Phys.*, 15, 135 (1947).

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

Attempts to Prepare Pyracylene. 1,2-Dihydropyracylene[1,2]

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The preparation of pyracene derivatives having eliminable functional groups on the five-membered rings and the attempted conversion of these to pyracylene is described. 1,2-Dihydropyracylene has been prepared by reaction of pyracene with chloranil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Since the initiation of the work on the synthesis of pyracene[3] one of the objectives has been to obtain the conjugate-unsaturated nonalternant hydrocarbon pyracylene (I).[4] Our interest in this compound arose from two considerations. First, it would have a total of 14 π-electrons associated with a cyclocondensed ring structure in which 12 of the electrons could be viewed as being in the planar perimeter and 2 in the ethylene core of the molecule.[5] The molecule would thus be an important addition to the type exemplified by pleiadiene (II) and acepleiadylene (III)[6] and provide a further test for the various theories of electronic structure of complex molecules.[7] Further, Brown[8] has calculated the resonance energy of pyracylene to be about 88 kcal./mole as compared to values of 61 and 36 for naphthalene and benzene obtained by the same method. The value for pyracylene is probably incorrect because of the neglect of strain considerations in the calculations (herewith).

(1) From the Ph.D. thesis of Robert G. Anderson.

(2) Support for a part of this work by contract DA-04-200-ORD-235 with the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

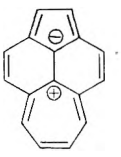
(3) A. G. Anderson, Jr. and R. H. Wade, *J. Am. Chem. Soc.*, 74, 2274 (1952).

(4) The only report indicating the existence of pyracylene is that of S. H. Hastings, B. H. Johnson, and H. E. Lumpkin, *Anal. Chem.* 28, 1243 (1956), who found that mass spectral data on a minor component of the aromatic fraction of virgin gas oil fit the molecular formula. Dibenzo[*a,g*]pyracylene and several of its derivatives are known; *cf.* E. Clar, *Ber.* 64, 2199 (1931); B. P. Federov, *Bull. Acad. Sci., U. S. S. R. Classe Sci. Chem.*, 397 (1947); C. Dufraisse and R. Girard, *Bull. soc. chim., France* (5) 1, 1359 (1934); C. Dufraisse, (5) 3, 1857 (1936); C. Dufraisse and R. Horelois, (5) 3, 1894 (1936); H. W. D. Stubbs and S. H. Tucker, *J. Chem. Soc.*, 2936 (1951).

(5) J. R. Platt, *J. Chem. Phys.*, 22, 1448 (1954); W. T. Simpson, *J. Chem. Phys.*, 17, 1218 (1949).

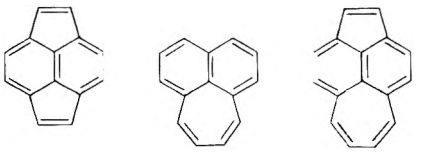
(6) V. Boekelheide, W. E. Langeland, and C.-T. Liu, *J. Am. Chem. Soc.*, 73, 2432 (1951); V. Boekelheide and G. K. Vick, *J. Am. Chem. Soc.*, 78, 653 (1956).

(7) For a theoretical interpretation of the pleiadienes see J. W. Sidman, *J. Am. Chem. Soc.*, 78, 1261, 4217 (1956). Profs. H. J. Dauben and W. T. Simpson have suggested (private communication) that an explanation based on the valence bond method which is consistent with the observed chemical and spectral properties and with the molecular orbital description may be advanced. This derives from a qualitative consideration of the reasonable valence bond structures with the inclusion of the dipolar sesquifulvalenoid structure shown. Since calculations [B. Pullman, A. Pullman, E. D.



Bergman, H. Berthod, E. Fischer, Y. Hirschberg, D. Lavie, and May Mayot, *Bull soc. chim. France*, 73 (1952)] indicate that the resonance stabilization of sesquifulvalene would be almost the same as that of naphthalene, the sesquifulvalenoid and naphthalenoid structures would be expected to contribute almost equally to the hybrid (strain will be the same in both types of structure).

(8) R. D. Brown, *J. Chem. Soc.*, 2391 (1951). The molecular orbital method with overlap was used.



I II III

From the molecular orbital treatment[8,9] the π-electron densities, free valencies and mobile bond orders and, consequently, the most probable positions for electrophilic, nucleophilic and homolytic attack have been predicted.

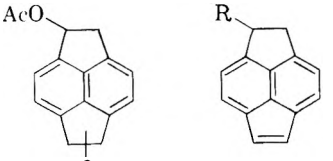
Second, the structure of pyracylene would classically be expected to have considerable strain[10] and a correlative study of its physical and chemical properties would be of importance in this respect. The existence of dibenz[*a*,*g*]pyracylene[4] shows that the strain is not prohibitive for a 1,2- and 5,6-bond distance of approximately 1.4 Å. Since these bonds are of the order of 1.64 Å as single bonds in pyracene,[11] perhaps pyracylene could exist with double bonds of about 1.4 Å. The enhancement of reactivity might, however, be much greater with the lengthening of double bonds and polymerization, for example, might occur very readily.

In the earlier work it was observed that liquid phase, catalytic (Pd-C) dehydrogenation of tetrahydropyracene at *ca.* 300° only gave pyracene.[3] Also, it has been observed by many workers that acenaphthylene polymerizes at temperatures above 200°. Accordingly, the usual catalytic reagents and conditions seemed unpromising and attention was directed to the introduction of unsaturation through elimination processes involving groups other than hydrogen. Any such scheme must involve the preparation of a pyracene (or hydropyracene) derivative having eliminable groups, preferably identical, in both *peri*-rings. Two approaches of this type were investigated.

The conversion of acenaphthene to acynaphthylene by a bromination-debromination sequence and also by acetoxylation followed by pyrolytic elimination of acetic acid had been accomplished.[12] When pyracene was treated with either four moles or an excess of *N*-bromosuccinimide, however, a mixture of bromides was obtained from which the desired tetrabromide could not be separated. Reaction of the mixture with zinc in tetrahydrofuran yielded zinc bromide plus a yellow polymeric material and it was not possible to determine whether or not pyracylene had been formed as an intermediate.

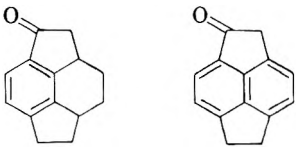
A test with acenaphthene showed that acetoxylation with even a large excess of lead tetraacetate formed only the monoacetate. Thus the diacetoxypyracene obtained from the corresponding reaction with pyracene was most probably the 1,5- or 1,6-compound (IV) or a mixture of these. Either product would yield pyracylene on the elimination of two molecules of acetic acid.

The ultraviolet spectrum of the pyrolysate from the diacetoxypyracene was very similar to that of acenaphthylene. The substance in the pyrolysate polymerized on attempted isolation but the polymer showed a band at 5.75μ which corresponded to absorption by the diacetoxypyracene. These findings suggested that 1-acetoxy-1,2-dihydropyracylene (V) was the initial product.



IV V, R = OAc VI, R = H

It was felt that the properties of 1,2-dihydropyracylene (VI) would provide better evidence concerning the identity of the pyrolysate product as V. As 2a,3,4,4a-tetrahydro-1-pyracenone (VII), a possible intermediate for the preparation of VI, was at hand,[3,13] an attempt was made to carry out the conversion. Liquid phase dehydrogenation of VII with Pd-C catalyst or with a Rh-C catalyst plus benzene gave only polymeric material. Vapor phase dehydrogenation with a Pd-C catalyst gave low ($\leq$4%) and erratic yields of pyracenone-1 (VIII).



VII VIII

Although VIII was apparently reduced to the corresponding alcohol with lithium aluminum hydride, the poor yields of VIII forced abandonment of the sequence.

The report by Braude and coworkers[14] of the dehydrogenation of acenaphthene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone led us to try this reagent and also chloranil with pyracene.

(9) J. I. F. Alonso and J. Mira, *Anales real soc. españ. fís. y quim.*, **50B**, 146 (1954).

(10) The introduction of double bonds in the peri-rings of pyracene would be expected to result in shortening of the 1,2- and 5,6-bonds. Prof. H. J. Dauben (Abstracts of Papers, 130th Meeting of the American Chemical Society, New York, September, 1956, p. 37-O) has calculated the strain energy of pyracylene to be *ca.* 52 kcal./mole. If the resonance energy value of Brown (ref. 8) is considered to be the delocalization energy then correction of this for strain would give 36 kcal./mole as a perhaps more realistic value for the resonance energy.

(11) A. I. Kitaigardoski, *J. Phys. Chem. (U. S. S. R.)*, **23**, 1036 (1949).

(12) A. G. Anderson, Jr. and R. G. Anderson, *J. Am. Chem. Soc.*, **77**, 6610 (1955).

(13) A. G. Anderson, Jr. and R. G. Anderson, *J. Org. Chem.*, **22**, 1197 (1957).

(14) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

The reaction with chloranil gave a 51% yield of a yellow crystalline material which was stable in the cold under a nitrogen atmosphere but decomposed at room temperature. Microanalysis, quantitative (one mole) hydrogenation to pyracene, the close similarity of the ultraviolet spectrum to that of acenaphthylene, and the characteristic (double bond) absorption at 6.20μ in the infrared established this product as 1,2-dihydropyracylene (VI).

A comparison of the spectra of VI and of the pyrolysate showed that the latter was not the acetoxy derivative (V). Thus the pyrolysis of the diacetoxypyracene must give a dimer, trimer, or some such species which can polymerize further; or pyracylene may be the unstable intermediate. Attempts to prepare pyracylene by altering the ratio of pyracene to chloranil, by treating the 1,2-dihydropyracylene with chloranil separately, or by the use of the dichlorodicyanoquinone were unsuccessful. The latter reagent gave a 42% yield of VI.

Efforts to achieve 1,6-disubstituted pyracene derivatives *via* the cyclization of 1-keto-2a,3,4,5-tetrahydroacenaphtheneacetic acid,[13] its oxime, or the acetate ester of the corresponding alcohol were unsuccessful with a variety of reagents and conditions. The ketal of the keto acid could not be formed by either direct or exchange reaction methods. The oxime resisted catalytic reduction with Raney nickel and treatment with sodium and alcohol.

EXPERIMENTAL[15,16]

Bromination—debromination of pyracene. A mixture of pyracene (0.196 g., 0.001 mole), *N*-bromosuccinimide (0.775 g., 0.0044 mole), 45 ml. of anhydrous carbon tetrachloride and a few crystals of benzoyl chloride was heated under reflux for 25 min. The product (0.31 g.) isolated as described elsewhere[12] and recrystallized three times from benzene, melted at 130–135° (dec.) and analyzed (C, 38.02; H, 2.86) as a mixture of bromides. Reaction of the mixture with zinc (2 equivalents based on tetrabromide) in tetrahydrofuran gave only a yellow polymeric material which was not characterized.

The use of an excess of *N*-bromosuccinimide in the procedure gave similar results.

1,5(1,6)-Diacetoxypyracene (IV). To a warm (60°) solution of pyracene[3,13] (0.43 g., 0.0024 mole) in 42 ml. of glacial acetic acid was added 4.0 g. (0.0058 mole) of red lead in 1 g. portions with stirring. The orange color produced by the red lead was allowed to disappear before the next portion was added. The mixture was stirred and kept at 60° until it no longer oxidized starch iodide paper and then poured into water (85 ml.). The aqueous solution was extracted with ether and the combined extracts washed with water, saturated sodium chloride solution, and finally dried (sodium sulfate). Removal of the solvent left a gummy residue which crystallized from methanol to give 0.53 g. (75%) of crude product, m.p. 162–180°. Sublimation and two further recrystallizations left 0.18 g. (25%) of pure material, m.p. 190–192°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.90; H, 5.45. Found: C, 72.60; H, 5.47.

Pyracenone-1 (VIII). 2a,3,4,4a-Tetrahydro-1-pyracenone[3,13] (0.47 g., 0.0023 mole) was sublimed in an oxygen-free nitrogen atmosphere through a column packed with a 5% Pd-C catalyst and maintained at 350–400° and a pressure of 20 mm.[17] over a period of 8 hr. The yellow solid in the receiver was washed out with acetone and when purified by crystallization from ethanol, sublimation, and recrystallization amounted to 0.018 g. (4%), m.p. 182–183°. The ultraviolet spectrum displayed maxima at 258mμ (log ϵ_{max} 1.75) and 346mμ (log ϵ_{max} 0.49).

Anal. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.48; H, 5.43.

1,2-Dihydropyracylene (VI). A solution of pyracene (0.210 g., 0.0012 mole) and chloranil (0.30 g., 0.0012 mole) in 10 ml. of xylene was refluxed under a nitrogen atmosphere for 24 hr. The brown reaction mixture was cooled to 0° and washed with 10% potassium hydroxide until the washings were colorless. The red organic layer was dried over magnesium sulfate and passed through a column (10 × 100 mm.) of activated, basic alumina. Removal of the solvent from the yellow effluent gave 0.108 g. (51%) of product, m.p. 145–150°. A portion recrystallized twice from hexane and sublimed at 80° and 0.3 mm. melted at 155–156°. The infrared spectrum showed a peak at 6.20μ. The ultraviolet absorption spectrum had maxima in mμ at 240 (log ϵ 4.28), 320 (log ϵ 4.00), 342 (log ϵ 3.78) and 357 (log ϵ 3.25). The substance was stable in the cold under nitrogen but decomposed at room temperature.

Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.13; H, 5.62.

The above procedure was also carried out with a 2:1 molar ratio of chloranil to pyracene and a 1:1 molar ratio of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The yields of VI were 45% and 42% respectively.

Treatment of VI with one molar equivalent of chloranil as above resulted in the recovery of the starting material (27%) as the only product which could be identified.

A solution of pure VI (0.053 g., 0.0003 mole) in ethanol took up 7.3 cc. (0.0003 mole) of hydrogen over a platinum catalyst at one atmosphere pressure and room temperature to give 0.052 g. (96%) of pyracene, m.p. 211–215°.[3]

1-Keto-2a,3,4,5-tetrahydro-5-acenaphtheneacetic acid oxime. A solution of the keto acid[13] (5.0 g., 0.022 mole) in 70 ml. of 10% potassium hydroxide was added to 30 ml. of an aqueous hydroxylamine hydrochloride solution and the mixture warmed on a steam bath for 30 min. Acidification of the cooled (0°) reaction mixture gave a precipitate which was washed with water and dried to yield 4.4 g. (82%) of tan product. A portion recrystallized several times from ethanol melted at 225–230°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16. Found: C, 68.67; H, 6.06.

1-Hydroxy-2a,5,4,5-tetrahydro-5-acenaphtheneacetic acid. A solution of 1-keto-2a,3,4,5-tetrahydroacenaphtheneacetic acid (7.6 g., 0.033 mole) in 25 ml. of 10% potassium hydroxide and 100 ml. of methanol was added in 20-ml. portions with shaking over a period of 30 min. to a solution of sodium borohydride (5.8 g., 0.152 mole) in 150 ml. of methanol. After about 10 hr. the mixture was acidified slowly with 10% hydrochloric acid and most of the methanol removed with a stream of air while the solution was warmed on a steam bath. The precipitate which formed was collected and dried to give 7.6 g. (99%) of crude product. A portion recrystallized three times from ethanol melted at 215–220° and had a

(15) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ultraviolet spectra were taken on a Cary Model 11S Recording Spectrophotometer or (ϵ values) on a Beckmann Model DU Spectrophotometer in ethanol. Infrared spectra were obtained with a Perkin Elmer Recording Spectrophotometer with sodium chloride cells.

(16) Microanalyses were performed by B. Nist and C. H. Ludwig.

(17 A. G. Anderson, J. A. Nelson, and J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953); H. L. Pan, M. S. Thesis, Univ. of Wash., 1953.

neutral equivalent of 232 (calcd. N.E. 232). The ultraviolet spectrum displayed maxima in mμ at 267 (log ε 2.92) and 274 (log ε 2.90).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C 72.11; H, 7.12.

1-Acetoxy-2a,3,4,5-tetrahydroacenaphthyleneacetic acid. To a solution of the above hydroxy acid (2 g., 0.0086 mole) in 20 ml. of anhydrous pyridine was added with shaking 8 ml. of acetic anhydride. The mixture was heated under reflux for 15 min., cooled, and poured into 100 ml. of ether. The resulting solution was washed with 10% hydrochloric acid, then water, and finally with saturated sodium chloride solution. The organic layer was dried (magnesium sulfate) and the solvent removed to give an orange solid which melted at 172–186° and amounted to 2.1 g. (79%) after crystallization from ethanol. A portion recrystallized twice more from ethanol melted at 179–188° and showed absorption maxima in mμ at 274 (log ε 2.96) and 267 (log ε 2.95).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.01; H, 6.79.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Aromatization of the Diels-Alder Adduct of Tetraphenylcyclopentadienone and Fumaronitrile[1]

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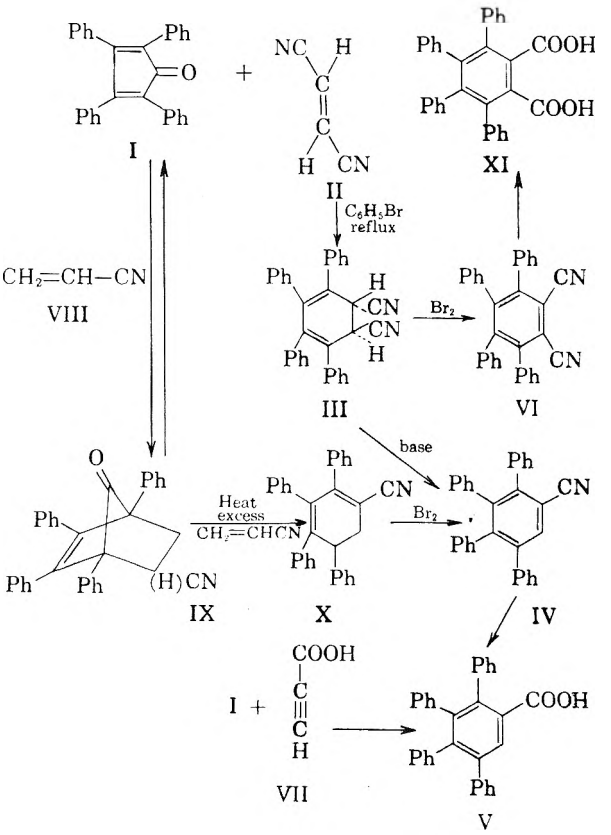
The reaction of tetraphenylcyclopentadienone (I) and fumaronitrile (II) in bromobenzene gave *trans*-1,2-dihydrotetraphenyl-*o*-phthalonitrile (III). Bromine converted III to tetraphenyl-*o*-phthalonitrile (VI). Alkali dehydrocyanates III to give 2,3,4,5-tetraphenylbenzonitrile (IV).

When tetracyclone (tetraphenylcyclopentadienone) (I) was refluxed with fumaronitrile (II) in bromobenzene, *trans*-1,2-dihydro-3,4,5,6-tetraphenyl-*o*-phthalonitrile (III) was formed. The trans configuration is assumed by analogy with other Diels-Alder reactions. Bromine aromatized III to tetraphenyl-*o*-phthalonitrile (VI). In turn VI was hydrolyzed to tetraphenylphthalic acid (XI), a known compound. Somewhat unexpected was the thermal behavior of III.

Heating III above its melting point gave a poor yield of a colorless compound whose analysis corresponded to that of 2,3,4,5-tetraphenylbenzonitrile (IV). Thus, the central ring of III had been aromatized by elimination of hydrogen cyanide, an infrequently observed reaction.[4] The same dehydrocyanation was effected by means of an alkaline alumina during an attempted chromatographic purification of III in 89% yield and by refluxing III in bromobenzene with diethylenetriamine in over 90% yield.

The structures of these compounds were proved by alternate syntheses. The synthesis of V via the reaction of I with propiolic acid went smoothly in 62% yield.[5] An attempt to prepare tetraphenylbenzoic acid (V) by hydrolysis of IV gave only a small quantity of V. The two acids agreed in their physical properties but the poor yield in the hydrolysis prompted a search for a more elegant proof for the structure of IV.



(1) Presented in part at the Meeting-in-Miniature of the Metropolitan-Long Island Subsection of the American Chemical Society, February 20, 1953.

(2) Taken from the B.S. thesis of R.F.D. (1951), the M.S. thesis of R.S.M., Jr., (1953) and from a portion of the Ph.D. dissertation of L.R.

(3) To whom inquiries should be sent.

(4) For a recent reference see A. Treibs and R. Derra, *Ann.*, **589**, 176 (1954).

(5) It is interesting to note the difference in the behavior of phenylpropiolic acid with tetracyclone. Dilthey, *et al.*,[6,7] have pointed out that decarboxylation occurs when phenylpropiolic acid reacts with tetracyclone to give pentaphenyl-

I reacted smoothly with acrylonitrile (VIII) in the latter as solvent to give 7-keto-1,4,5,6-tetraphenylbicyclo[2.2.1]-5-heptene-2-carbonitrile (IX). Carbon monoxide was eliminated from IX by heating it with VIII in either *p*-cymene or nitrobenzene solution. Excess VIII appeared to be necessary since on heating IX it dissociated into its congeners. The 2,3-dihydro-3,4,5,6-tetraphenylbenzonitrile (X) so formed[9] was dehydrogenated by bromine in bromobenzene to give IV. A mixture melting point of this sample with that prepared previously was not depressed.

EXPERIMENTAL[11]

trans-1,2-Dihydro-3,4,5,6-tetraphenyl-o-phthalonitrile (III). A solution of 12.0 g. (0.031 mole) of I and 2.8 g. (0.036 mole) of II in 12 ml. of bromobenzene was refluxed for 5.25 hr. Cooling to room temperature gave crystals which were filtered and recrystallized from benzene to give 10.09 g. (0.023 mole, 74%) of colorless crystals, m.p. 230–232° (gas evolved upon melting).

Anal. Calcd. for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.41; H, 5.18; N, 6.36.

Tetraphenyl-o-phthalonitrile (VI) was prepared directly from I and II without isolation of III (Procedure A) or from III (Procedure B).

Procedure A. A solution of 8.5 g. (0.11 mole) of II and 38.4 g. (0.10 mole) of I in 75 ml. of bromobenzene was refluxed until the effluent gases would no longer reduce a 0.02% solution of palladium(II) chloride—about 2 hr. The reaction mixture was allowed to cool and then 24 g. (0.15 mole) of bromine in 25 ml. of bromobenzene was slowly added down the condenser and followed by refluxing for 3 hr. Cooling gave a crop of crystals which was filtered and washed with 20 ml. of cold benzene and the 20 ml. of cold petroleum ether (b.p. 90–100°). The residue (23 g.) was recrystallized three times from toluene and three times from benzene to constant melting point affording colorless crystals, 265.3–265.4°, 13.4 g. (0.031 mole, 31%).

Anal. Calcd. for $C_{32}H_{20}N_2$: C, 88.86; H, 4.66; N, 6.48. Found: C, 89.14; H, 4.78; N, 6.64.

Procedure B. To a refluxing solution of 0.10 g. (0.23 mmole) of III in 2 ml. of bromobenzene was added dropwise a solution of 0.156 g. (0.98 mmole) of bromine in 2 ml. of bromobenzene. After refluxing for 3.5 hr., the solution was distilled to dryness. Extraction of the residue with 5 ml. of petroleum ether (b.p. 60–70°) left a residue of flat platelets, 0.050 g. (0.12 mmole, 50%), melting at 256–258° to a dark brown melt.

Tetraphenyl-o-phthalic acid (XI). One gram of VI was refluxed for 12 hr. with an excess of 10% alcoholic potassium hydroxide. Cooling gave crystals which were washed with two 10-ml. portions of 6*N* HCl and two 10-ml. portions of water. Four recrystallizations of the residue from benzene gave a nitrogen-free product, m.p. 289–290° (uncorr.), which did not depress the melting point of known tetraphenylphthalic anhydride, m.p. 288.3–289.0° (uncorr.).[12]

7-Keto-1,4,5,6-tetraphenylbicyclo[2.2.1]-5-heptene-2-carbonitrile (IX). IX was prepared by refluxing a solution of I and VIII in benzene or by refluxing I in VIII alone; the latter procedure is preferable and is described.

A solution of 1.0 g. (2.6 mmoles) of I in 2.4 g. (0.045 mole) of acrylonitrile was refluxed for 4.5 hr. during which time the red-purple color of I was discharged. Upon cooling to room temperature, colorless crystals separated which were filtered and dried *in vacuo* at 65–70° for 5 hr. to give 0.63 g. (1.44 mmoles, 55%), m.p. 204–206° (dec.).

Anal. Calcd. for $C_{32}H_{23}NO$: C, 87.84; H, 5.30; N, 3.20. Found: C, 87.51; H, 5.26; N, 3.18.

Reversible dissociation of IX. A solution of 0.5 g. of IX in 3 ml. of bromobenzene was slowly heated to reflux. The color changed from colorless initially to pink and then to deep purple at reflux. No evidence of evolution of gas was noted. At reflux 3 ml. of acrylonitrile was added in one portion and the reflux continued for 5 hr. The purple color was completely discharged and distillation of the solution to dryness gave 0.48 g. (96%) of white microcrystals of recovered IX, m.p. 203.4–204.8° (dec.).

2,3-Dihydro-3,4,5,6-tetraphenylbenzonitrile (X). Decarbonylation of IX was effected in either nitrobenzene or in *p*-cymene with about equal facility. The use of nitrobenzene is described.

A solution of 2.0 g. crude (IX), m.p. 188–194°, and 5 ml. of acrylonitrile in 90 ml. of nitrobenzene was refluxed (165°) for 10 hr. At first a red-purple color (I) appeared and then it disappeared on further heating. Removal of the solvent at reduced pressure and recrystallization (charcoal) of the residue from a mixture of benzene and petroleum ether (b.p. 30–60°) afforded 0.78 g. (42%) of colorless product, m.p. 192.5–194°.

Anal. Calcd. for $C_{31}H_{23}N$: C, 90.92; H, 5.66; N, 3.42. Found: C, 90.47; H, 5.78; N, 3.63.

2,3,4,5-Tetraphenylbenzonitrile (IV). (A) A solution of 0.56 g. (1.4 mmoles) of X and 0.4 g. (2.5 mmoles) of bromine in 30 ml. of bromobenzene was refluxed for 6 hr. Distillation of the solvent at reduced pressure and recrystallization of the residue from a mixture of benzene and petroleum ether (b.p. 30–60°), and then from absolute alcohol gave 0.49 g. (1.2 mmoles, 86%) of IV, m.p. 216–217°. The melting point of IV was depressed upon admixture with X.

(B) A benzene solution of 0.197 g. (0.45 mmole) of III passed through a column of Merck alumina (which was basic to *p*H paper). The eluant was evaporated to yield 0.162 g. (0.40 mmole, 88%) of IV, m.p. 215.5–217°. A mixture melting point between III and this product was depressed.

(C) III was heated at 240–250° (uncorrected) for 15 min. The material melted and a gas was evolved. After cooling, the product was recrystallized from ligroin (b.p. 65–90°) to give a poor yield of IV, m.p. 215–216°.

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benzene if the reaction mixture is heated "too high." They have also pointed out that under the same conditions phenylpropiolic acid itself decarboxylates. Dudkowski and Becker[8] have verified these facts for the reaction in boiling toluene (110°) and in boiling *p*-cymene (177°). With propiolic acid and tetracyclone no decarboxylation was observed since the Diels-Alder reaction went more rapidly and was complete before 100° was reached.

(6) W. Dilthey, I. Thewalt, and O. Trösken, *Ber.*, **67B**, 1959 (1934).

(7) W. Dilthey, S. Henkels, and A. Schaefer, *Ber.*, **71B**, 974 (1938).

(8) J. J. Dudkowski and E. I. Becker, *J. Org. Chem.*, **17**, 201 (1952).

(9) The position of the double bonds is not certain; however, the band at 2230 cm.$^{-1}$ indicates a conjugated nitrile.[10] The named compound is one of several possible structures.

(10) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).

(11) Melting points have been corrected unless otherwise indicated. Infrared spectra were obtained on a Perkin Elmer Recording Infrared Spectrophotometer, Model 21. In the combustion analyses of the highly arylated compounds, obtaining correct results was facilitated by raising the temperature of the combustion furnace from the customary 700° to about 1000°.

(12) The acid and the anhydride have the same melting point.[13]

(13) G. W. Thielcke and E. I. Becker, *J. Org. Chem.*, **21**, 1003 (1956).

(D) A solution of 1.02 g. (2.35 mmoles) of III and 0.0109 g. (0.106 mmole) of diethylenetriamine in 10 ml. bromobenzene was refluxed for 1 hr. The evolution of hydrogen cyanide was detected by the formation of a copious precipitate in a 5% silver nitrate solution, connected to the system by a vent-line trap. The solvent was removed at reduced pressure to give 0.95 g. (2.37 mmoles, 99%) of IV, which sintered at 214.5° and melted at 215.5–216.5°. The product was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–40°) to give 0.87 g. (2.13 mmoles, 91%) of IV, m.p. 215–216°. Recrystallization from absolute alcohol gave the analytical sample which sintered at 215.5° and melted at 216–217°.

Anal. Calcd. for $C_{31}H_{21}N$: C, 91.37; H, 5.19; N, 3.44. Found: C, 91.19; H, 5.35; N, 3.57.

Mixed melting points between samples of IV prepared from III and from X showed no depression, m.m.p. 216–217°.

2,3,4,5-Tetraphenylbenzoic acid (V). (A) A solution 3.0 g. (7.8 mmoles) of tetracyclone and 1.48 g. (0.021 mole) of propiolic acid[14] in 10 ml. of bromobenzene was slowly heated. The color of tetracyclone was almost completely discharged within 10 min. and before the solution reached 100°. The evolution of carbon monoxide was detected by the reduction of dilute aqueous permanganate in a vent-line trap. The solution was refluxed (156°) for 8 hr. Removal of the solvent at reduced pressure gave 3.1 g. of light tan crystals. One gram of this material was recrystallized four times from acetone to give 0.66 g. (1.54 mmoles, 62%), of colorless crystals of V, m.p. 327.5–328.5°.

Anal. Calcd. for $C_{31}H_{22}O_2$: C, 87.30; H, 5.20. Found: C, 87.10; H, 5.34.

(B) A mixture of 0.38 g. (0.93 mmoles) of tetraphenylbenzonitrile, 1.0 g. of potassium hydroxide, 10 ml. of 3A[15] ethanol and 0.4 ml. of water was refluxed 12.25 hr. An additional 50 ml. of water was added, the mixture was digested on the steam bath 24 hr. longer, cooled, and then 10 ml. of concentrated hydrochloric acid was added (acid to Congo paper), and the mixture was digested 4 hr. longer. Filtration, washing with water until acid free, and drying afforded 0.36 g. (0.85 mmole, 90%) of colorless V, m.p. 270–286°. Recrystallization from acetone gave only 10% of material, m.p. 297–300°. Admixture with authentic V raised the melting point to 309.5–310.5°. The infrared spectra coincided except for the presence of a band at 3455 $cm.^{-1}$ No improvement was achieved by digestion of this material on the steam bath for 7 hr. in a mixture of 20 ml. of 3A ethanol and 20 ml. of 6*N* H_2SO_4, isolation, and subsequent recrystallization.

A mixture of 0.27 g. of IV (0.66 mole), 4.5 g. of concentrated sulfuric acid and 3.3 ml. of water was refluxed for 12.25 hr., diluted, filtered, washed, and recrystallized from acetone to give 0.015 g., (5%) of V, m.p. 316–319°. A mixture melting point with authentic V was 317.0–320.5°. Infrared spectra were superimposable.

BROOKLYN 1, NEW YORK

(14) C. Moureu and J. C. Bongrand, *Ann. chim.*, **14**, 47 (1920).

(15) "Lange's Hand Book of Chemistry, 9th Edition," Handbook Publishers, Inc., Sandusky, Ohio, 1956, p. 1781.

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

Unsymmetrical Tetraalkylmethanes. II.[1] Syntheses from 2-(β-Cyanoethyl)-2-ethylhexanal

NORMAN RABJOHN AND H. H. FARMER[2,3]

Received October 22, 1957

Two unsymmetrical tetraalkylmethanes, 5-ethyl-5-methyldecane (III) and 5-ethyl-5-methyltetracosane (IV), have been prepared from 2-(β-cyanoethyl)-2-ethylhexanal. A common intermediate, 4-ethyl-4-methyloctanoic acid (I), was converted to the hydrocarbons by the action of an organocadmium reagent on the corresponding acid chloride, followed by a Wolff-Kishner reduction of the resulting ketone, or by electrolytic coupling with stearic acid.

In a previous investigation[4] it was shown that the readily available 2-(β-cyanoethyl)-2-ethylhexanal could be converted to an unsymmetrical tetraalkylmethane by treatment with a Grignard reagent, followed by reduction of the intermediate dihydropyran to a tetrahydropyran. The latter was cleaved with hydrogen bromide to a dibromide which was reduced then to a hydrocarbon. The over-all process gave poor yields and left much to be desired.

The present study describes the satisfactory syntheses of two unsymmetrical tetraalkylmethanes from 2-(β-cyanoethyl)-2-ethylhexanal. The reactions employed are summarized in the following equations.

The cyanoethylated aldehyde was converted readily to the γ,γ,γ-trisubstituted propionic acid (I) by concurrent reduction and hydrolysis during the Wolf-Kishner reaction. This acid in the form of its chloride, was then transformed into the ketone (II) in approximately 60% yield by the use of diethylcadmium. A further Wolf-Kishner reduction led to the desired hydrocarbon (III).

The branched acid (I) was electrolyzed in methanol–petroleum ether solution in the presence of stearic acid by the Kolbe process to give a mixture of *n*-tetracosane and the unsymmetrical tetraalkylmethane (IV). The latter resulted in approximately 30% yield.

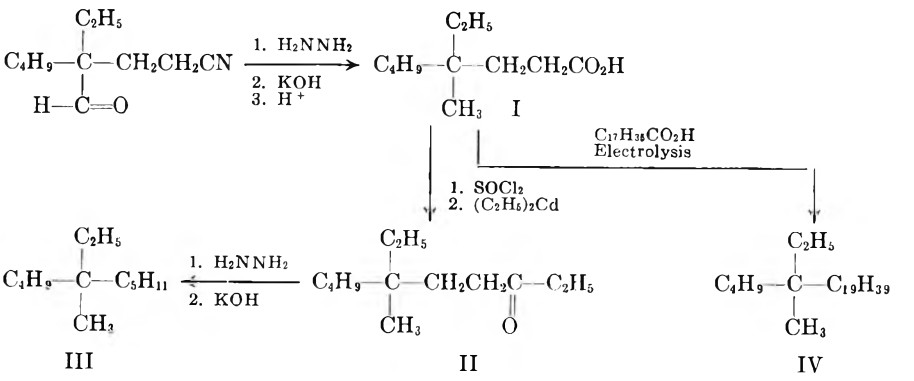
Infrared absorption spectra of compounds III and IV indicated that they were free of unsatura-

(1) Part I: Norman Rabjohn and M. J. Latina, *J. Am. Chem. Soc.*, **76**, 1389 (1954).

(2) Supported in part by the Petroleum Research Fund of the American Chemical Society.

(3) Abstracted from the Ph.D. thesis of H. H. Farmer, 1955.

(4) Norman Rabjohn, M. J. Latina, and L. V. Phillips, *J. Org. Chem.*, **21**, 285 (1956).



tion or oxygen containing intermediates. The former has a solidification point below −70° while the latter melts at 10–11°. The boiling points of both are about 30° below the corresponding straight chain isomers.

EXPERIMENTAL[5]

4-Ethyl-4-methyloctanoic acid (I). A mixture of 83 g. (0.46 mole) of 2-(β-cyanoethyl)-2-ethylhexanal,[6] 50 ml. of 85% hydrazine hydrate, and 500 ml. of diethylene glycol was heated under reflux for 1 hr. Then 200 g. of a 50% potassium hydroxide solution was added and the reaction mixture was caused to reflux for a further 2 hr. The mixture was distilled through an alembic column until the temperature in the flask reached 200°, and the residue was heated at this temperature for 5 hr. It was cooled, diluted to 3 l. with water, and acidified with hydrochloric acid. The layers were separated and the water solution was extracted with ether. The organic layers were combined, concentrated, and distilled. There was obtained 53 g. (63%) of 4-ethyl-4-methyloctanoic acid, b.p. 109–110°/0.7 mm., n_D^{25} 1.4459.

Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90; neut. equiv., 186. Found: C, 71.22; H, 11.68; neut. equiv., 187.

4-Ethyl-4-methyloctanoyl chloride. A mixture of 25 g. (0.13 mole) of 4-ethyl-4-methyloctanoic acid and 50 ml. (0.7 mole) of thionyl chloride was heated under reflux for 30 min. after the initial reaction had subsided. The excess thionyl chloride was removed and the residue was distilled to give 25 g. (91%) of the desired acid chloride; b.p., 88–91°/1 mm.

It was identified by means of its anilide; m.p. 72–73°.

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 78.33; H, 10.38.

6-Ethyl-6-methyl-3-decanone (II). A Grignard reagent was prepared from 3.4 g. (0.14 g.-atom) of magnesium and 15.3 g. (0.14 mole) of ethyl bromide in 100 ml. of dry ether. This was treated with 12.8 g. (0.07 mole) of cadmium chloride and the ether was replaced with anhydrous benzene in the usual manner. The reaction mixture was stirred while a solution of 22.8 g. (0.11 mole) of 4-ethyl-4-methyloctanoyl chloride in 30 ml. of benzene was added. The reaction mixture was caused to reflux for 1 hr. and then was decomposed by pouring onto ice and sulfuric acid. The layers were separated and the water solution was extracted with benzene. The organic layers were combined, and washed successively with water, sodium bicarbonate solution, saturated sodium chloride solution, and water. The benzene solution was dried over anhydrous sodium sulfate, concentrated, and distilled. There was obtained 12.1 g. (58%) of ketone; b.p., 90–91°/0.5 mm., n_D^{25} 1.4412.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.67; H, 13.43.

A hydantoin derivative was prepared by the method of Henze and Speer;[7] m.p., 143–144°.

Anal. Calcd. for $C_{15}H_{28}N_2O_2$: C, 67.12; H, 10.52. Found: C, 67.03; H, 10.28.

5-Ethyl-5-methyldecane (III). A mixture of 22.8 g. (0.116 mole) of 6-ethyl-6-methyl-3-decanone, 15 ml. of 85% hydrazine hydrate, 100 ml. of diethylene glycol, and 25 g. of potassium hydroxide in a 50% aqueous solution was heated under reflux for 2 hr. Water was removed by distillation until the temperature of the reaction mixture reached 200°. The mixture was heated then at this temperature for 4 hr. during which time a layer separated. The mixture was cooled and the upper layer was taken up in ether and separated from the reaction mixture. The diethylene glycol solution was extracted with two portions of ether which then were combined with the original ether solution of the hydrocarbon. This was washed with water, dried over calcium chloride, and concentrated. The residue was distilled to give 7.5 g. (35%) of product. This was purified further by shaking with three 20-ml. portions of cold concentrated sulfuric acid, then with water, 5% sodium bicarbonate solution, and again with water. It was dried over anhydrous calcium sulfate and distilled; b.p., 101–103°/18 mm., n_D^{25} 1.4291.

Anal. Calcd. for $C_{13}H_{28}$: C, 84.69; H, 15.31. Found: C, 84.83; H, 15.32.

5-Ethyl-5-methyltetracosane (IV). The mixed Kolbe reaction was carried out in a 2-l. resin flask fitted with a copper cooling coil and a mechanical stirrer and immersed in a water bath. The platinum electrode assembly consisted of an outer platinum cylinder 10 cm. long and 3 cm. in diameter, an inner platinum cylinder 6 cm. long and 2.5 cm. in diameter, and a coil of platinum wire 5 cm. long and 1 cm. in diameter placed inside the inner cylinder.

A mixture of 69 g. (0.37 mole) of 4-ethyl-4-methyloctanoic acid, 315 g. (1.1 moles) of stearic acid, 500 ml. of petroleum ether (b.p., 60–68°), and a solution of 2 g. of sodium in 1200 ml. of methanol was placed in the flask. All of the solid could not be brought into solution; however, at the temperature (55–60°) attained during the electrolysis, the mixture became homogeneous. At the beginning of the reaction at 110 volts only 1 amp. of current passed through the solution. This value increased over the first 4 hr. to 3.5 amps., rose to 4.5 amps. during the next 7 hours, and then dropped off rapidly as the reaction neared completion.

The reaction mixture was concentrated by distillation to about one-half volume, and a solution of 56 g. of potassium hydroxide in 500 ml. of water was added. Distillation was continued then to remove most of the solvent. The residue was diluted with 2 l. of petroleum ether (b.p. 60–68°), the mixture was shaken thoroughly and the layers separated. The petroleum ether solution was washed with warm water, filtered, and cooled. There precipitated from solution 65.4 g. of a white, crystalline solid; m.p. 73–75°. This was pre-

(5) All melting points are uncorrected. The authors are indebted to R. L. Elliott and R. E. Bolin for the semimicro carbon and hydrogen analyses. They also would like to thank Dr. E. E. Pickett for the infrared data.

(6) H. A. Brusen and T. W. Riener, *J. Am. Chem. Soc.*, 66, 56 (1944).

(7) H. Henze and R. Speer, *J. Am. Chem. Soc.*, 64, 522 (1942).

sumed to be tetratriacontane; lit.[8] m.p., 72–73°. The filtrate was concentrated and the residue was distilled to give 40.5 g. of material which boiled at 200–218°/1 mm. This was shaken with four 25-ml. portions of concentrated sulfuric acid, washed with water, 5% potassium carbonate solution, again with water, and dried over anhydrous calcium sulfate. There was obtained 32.2 g. (23%) of product; b.p., 208–210°/1 mm., n_D^{25} 1.4511, m.p. 10–11°.

Anal. Calcd. for $C_{27}H_{56}$: C, 85.17; H, 14.83. Found: C, 85.07; H, 14.57.

COLUMBIA, MO.

(8) G. Egloff, *Physical Constants of Hydrocarbons*, Vol. V, Reinhold Publishing Corp., New York, 1953, p. 270.

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

Synthesis of Heterocyclic Compounds from Aryl Azides. IV. Benzo-, Methoxy-, and Chloro-carbazoles[1,2]

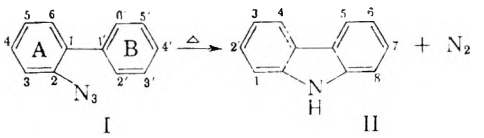
PETER A. S. SMITH, JOHN M. CLEGG,[3] AND J. H. HALL

Received September 3, 1957

1,2-Benzocarbazole(III) has been prepared in high yield from both 2-(2′-azidophenyl)naphthalene(IV) and 1-azido-2-phenylnaphthalene(V). The isomeric 2,4-benzocarbazole has been prepared from 1-(2′-azidophenyl)naphthalene. 1,4-Dimethoxycarbazole has been prepared from (*o*-azidophenyl)hydroquinone dimethyl ether, and 2-methoxy-, 2-hydroxy-, and 3-chloro-carbazole have been prepared from *o*-azidobiphenyls. 2-Azido-2′-cyanobiphenyl has been found to cyclize to tetrazolophenanthridine instead of to 4-cyanocarbazole, and 4-azidofluorene and 4-azidofluorenone to decompose on heating without apparent cyclization, to give intractable products.

o-Azidobiphenyl has been prepared from *o*-hydrazinobiphenyl and N^{15}-labeled potassium nitrite. Thermal decomposition gave carbazole with normal isotope content, while all the excess N^{15} was found in the evolved nitrogen.

The thermally or photochemically induced cyclization of *o*-azidobiaryls (I) to give carbazole derivatives has been shown in previous papers[2] to be a synthetically useful route to bromo- and nitrocarbazoles, and to certain heterocyclic analogs. From these studies, little could be concluded regarding the generality of the reaction or its mechanism, particularly since the substituents studied were all electron-withdrawing. In the work reported in this paper, an attempt has been made to fill some of these gaps in the knowledge of the reaction.



I II

The loss of nitrogen from the azido group might occur as the first stage in the reaction, unassisted by any sort of preliminary cyclization. In such a case, the ease with which nitrogen is lost should depend on the electronic condition of the ring holding the azido group, and be independent of the nature of the ultimate cyclization point on ring B, except insofar as ring B influences the condition of ring A. Furthermore, the outer two nitrogen atoms of the azido group would be those that appear as molecular nitrogen.

Alternatively, loss of nitrogen might accompany or follow cyclization to ring B. In such a case, the nature of the site of cyclization on ring B should profoundly influence the ease with which nitrogen is released from the azide. Furthermore, the structure of this cyclic intermediate or transition state, as the case may be, would determine which of the azide nitrogen atoms would be released.

o-Azidobiphenyls substituted in ring B with a hydroxy or methoxy group in the 4′-position, and with two methoxy groups in the 3′,6′-positions, have now been prepared. All give the expected carbazoles on heating. Qualitatively, no difference in ease of decomposition large enough to clearly show a concerted reaction was noticed, either among these compounds, or between them and the azidobiphenyls previously reported.[4] It thus appears that the synthesis of carbazoles by this reaction may be expected to succeed with most types of substituents.

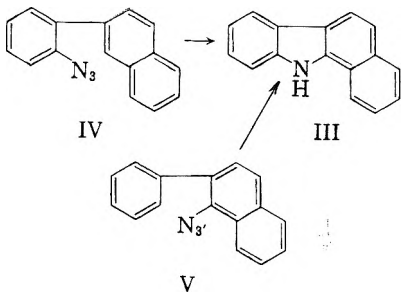
A similar comparison is provided by the reactions leading to benzocarbazoles. 1,2-Benzocarbazole(III) was prepared from β-(*o*-azidophenyl)-naphthalene(IV), involving cyclization to the α-position of the naphthalene, and from β-phenyl-α-azidonaphthalene(V), involving cyclization to a simple benzene ring. The high yields were similar for the two cyclization paths, but the ease of nitrogen release was noticeably different, the azidophenyl isomer requiring at least a 10° higher temperature for comparably rapid decomposition. Complete selectivity was shown in cyclization to the naphthalene ring; cyclization to the 3-position, which would have led to 2,3-benzocarbazole, did not occur to a detectable extent. Another example

(1) The larger part of this work was supported by the Office of Ordnance Research, U. S. Army (D.O.R. Project No. 965).

(2) Part III, *J. Am. Chem. Soc.*, **75**, 6335 (1953).

(3) In part from the doctoral thesis of John M. Clegg.

(4) P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2438 (1951).

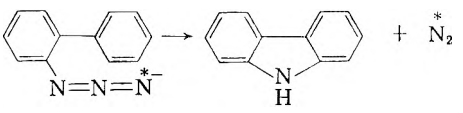


IV III V

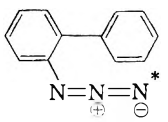
of internal selectivity is given by the example of α-(*o*-azidophenyl)naphthalene, which cyclized entirely to the 2-position, giving 3,4-benzocarbazole, and not to a detectable extent to the 8-position, which would have given a benzacridine. β-(*o*-Azidophenyl)pyridine, reported previously,[5] shows little selectivity, however, and cyclizes to both the α- and the γ-positions, but in this case the two sites are electronically similar.

These observations are insufficient to determine the mechanism of the reaction, but they do imply that regardless of whether the loss of nitrogen is concerted or not, the formation of the new bond to nitrogen can be a highly selective process. Therefore, if the rate-determining step is the unassisted breakdown of the azido group to give molecular nitrogen and an arylnitrogen, Ar-N:, the latter species either has a half-life appreciably longer than the time for rotation about the aryl-aryl bond, or it is able by polarization to accelerate such rotation in a selective manner. To help resolve these questions, kinetic investigations have recently been begun.

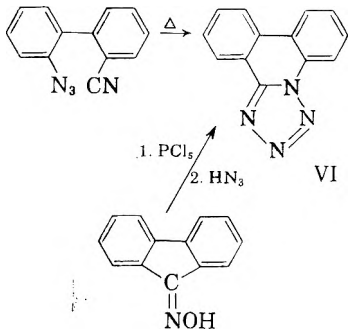
Further information about the nature of the breakdown of the azido group was obtained from *o*-azidobiphenyl in which the terminal nitrogen was isotopically labeled. This was obtained by treatment of the hydrazine with isotopic nitrite, according to the method developed by Clusius.[6] On heating, all of the excess isotopic nitrogen was found in the evolved gas, which showed that it is almost certainly the carbon-attached nitrogen atom that is retained in the carbazole (retention of the central nitrogen can be safely ignored on the grounds of mechanistic improbability). A cyclic



intermediate or transition state involving the outer azide nitrogen is therefore very unlikely.



2-Azido-2′-cyanobiphenyl, prepared in a series of steps through the half-nitrile of diphenic acid, was studied in order to see whether the difficultly accessible carbazole-4-carbonitrile could be made by this reaction, and if it could not, to learn in what way the cyano group would interfere. This azide was found to undergo a change in melting point from 57° to 223.5° as a result of heating, but no loss of nitrogen occurred. The alteration product was found to be tetrazolophenanthridine(VI), whose structure was confirmed by independent synthesis in the form of the von Braun-Rudolph reaction applied to 9-chlorophenanthridine, obtained by the Beckmann rearrangement of fluorenone oxime.



VI

This is the first authenticated case of an azide other than hydrogen azide adding to a nitrile (an isolated patent claim of a similar reaction in the aliphatic series has been disputed).[7] Tetrazolophenanthridine was found to have exceptional stability to heat; unlike most tetrazoles, which lose nitrogen at slightly above 200°, this substance required 300° for decomposition, at which temperature it was converted to a black glass, from which nothing could be characterized.

4-Azidofluorene and 4-azidofluorenone were prepared from the amines obtained by degradation of the corresponding carboxylic acids, with the intention of seeing whether the energy of the azido group would enable them to be converted to the strained carbazoles with, respectively, a 4,5-methylene or 4,5-carbonyl bridge. Such cyclization of an azide between two benzene rings held coplanar by the bridging group might be feasible if the cyclization proceeded through abstraction of the 5-hydrogen by the aryl nitrogen, followed by N-C bond formation. If, on the other hand, it should be necessary for N-C bond formation to occur first, with subsequent hydrogen migration, the nitrogen would have to approach the 5-carbon partly from one side, to avoid having the 5-hydrogen between it and the carbon, and the coplanarity enforced by the bridging group should interfere with the cyclization. Furthermore, by either path followed, the final tetracyclic system would be highly strained, and ring closure might not occur for this reason alone.

(5) P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 2626 (1951).

(6) K. Clusius and H. R. Weisser, *Helv. Chim. Acta*, **35**, 1548 (1952).

(7) J. H. Boyer and F. C. Canter, *Chem. Revs.*, **54**, 44 (1954).

TABLE I

NEW AZIDOBIARYLS

	Yield, %	M.P., C.°	Empirical Formula	Anal. Calcd. C	Anal. Calcd. H	Anal. Found C	Anal. Found H
2-Azido-4′-hydroxybiphenyl	57.5	117–119.2	$C_{12}H_9ON_3$[13]	68.23	4.30	68.25	4.31
2-Azido-2′,5-dimethoxybiphenyl	61[a]	81.5–83.5	$C_{14}H_{13}O_2N_3$[14]	65.87	5.13	66.07	5.24
1-Azido-2-phenylnaphthalene	43[b]	44–45	$C_{16}H_{11}N_3$[16]	78.34	4.52	78.70	4.20
2-(2′-Azidophenyl)naphthalene	72[c]	46–47	$C_{16}H_{11}N_3$[16]	78.34	4.52	77.64	4.30
1-(2′-Azidophenyl)naphthalene	95[d]	101–102	$C_{16}H_{11}N_3$[16]	78.34	4.52	78.40	4.57
2-Azido-2′-cyanobiphenyl	16[e]	55.5–57	$C_{13}H_8N_4$[17]	70.89	3.66	70.84	3.72
4-Azidofluorenone	96.5[f]	118.5–120	$C_{13}H_7ON_3$[17]	70.58	3.19	70.77	3.32
4-Azidofluorene[g]	83.5	78–81	$C_{13}H_9N_3$[17]	75.34	4.38	75.41	4.42

[a] From 2-amino-2′,5′-dimethoxybiphenyl in aqueous hydrochloric acid. [b] From 2-phenyl-1-naphthylamine in aqueous hydrochloric acid. [c] From 2-(2′-aminophenyl)naphthylamine[15] in aqueous hydrochloric acid. [d] From 1-(2′-aminophenyl)-naphthalene with hydrochloric acid in water; crude product m.p. 98–101°. [e] From 2-amino-2′-cyanobiphenyl hydrochloride with hydrochloric acid in aqueous acetic acid; crude product m.p. 55.5–58°. [f] From 4-aminofluorenone,[18] with sulfuric acid in water-ethanol; crude product m.p. 110–115°. [g] From 4-aminofluorene with sulfuric acid in water-ethanol; crude product m.p. 75–79°.

The two azides lost nitrogen as usual, at about 180°, and gave solid products. However, the products were apparently amorphous and polymeric, having high, indefinite melting points and a general insolubility in organic solvents. It was apparent that cyclization did not take place, and one cannot conclude whether it is strain in the product of cyclization or the availability of only an unfavorable path that is responsible.

In the course of this work, the known 3-chlorocarbazole was prepared by the new route of cyclization of 2-azido-5-chlorobiphenyl. In connection with this synthesis, a route of synthetic value has been developed for 2-amino-5-chlorobiphenyl; direct chlorination of 2-benzamidobiphenyl gives the 5-chloro derivative in 65% yield, whereas attempts to chlorinate 2-acetamidobiphenyl are reported[8] to give tarry, nearly inseparable mixtures. In addition, the preparation of some biphenyl intermediates by synthetically practicable paths has been developed, in cases where the only published procedures are not of preparative value.

EXPERIMENTAL

2-Acetamido-4′-aminobiphenyl dihydrochloride. 2-Acetamido-4′-nitrobiphenyl (25.6 g., 0.1 mole) was hydrogenated[9] in 200 ml. of methanol with platinum oxide at an initial hydrogen pressure of 49 p.s.i. When the calculated amount of hydrogen had been absorbed, the mixture was filtered, concentrated, diluted with ether, and dried over magnesium sulfate. Passing in hydrogen chloride then precipitated 21.74 g. (71.2%) of 2-acetamido-4′-aminobiphenyl dihydrochloride as a white solid, m.p. 185° (dec.).

Anal.[10] Calcd. for $C_{14}H_{16}ON_2Cl_2$: C, 56.18; H, 5.39; Cl, 23.15. Found: C, 56.25; H, 5.38; Cl, 23.7.

2-Acetamido-4′-hydroxybiphenyl. A diazonium solution prepared from 19.42 g. (0.065 mole) of 2-acetamido-4′-aminobiphenyl dihydrochloride in 120 ml. of *N* sulfuric acid and 5.17 g. of sodium nitrite in 30 ml. of water was freed of excess nitrous acid with urea, and further acidified with 200 ml. of *N* sulfuric acid and overlaid with 75 ml. of toluene. The mixture was heated on a steam bath until the color lightened, chilled overnight, and the solid collected. The solid was dissolved in 150 ml. of 10% sodium hydroxide, decolorized with charcoal, and reprecipitated with hydrochloric acid, to give 11.56 g. (78%) of 2-acetamido-4′-hydroxybiphenyl, m.p. 177–182° (reported,[11] 185–186°).

2-Amino-4′-hydroxybiphenyl. 2-Acetamido-4′-hydroxybiphenyl (3.74 g.) was hydrolyzed by refluxing for 16 hr. with 30 ml. of concd. hydrochloric acid and 70 ml. of glacial acetic acid. Dilution with water and neutralization with sodium hydroxide precipitated 2.85 g. (93.5%) of 2-amino-4′-hydroxybiphenyl, m.p. 161–163.5°. Recrystallization from aqueous ethanol gave an analytical sample, m.p. 163.5–165.5° (reported,[12] 164–165°).

Anal.[10] Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99. Found: C, 77.70; H, 5.91.

Azides. The azides prepared are summarized in Table I. All were prepared from diazonium salts and sodium azide, with minor variations as noted, in a manner analogous to the following example.

2-Azido-4′-hydroxybiphenyl. A solution of 2.85 g. (0.0154 mole) of 2-amino-4′-hydroxybiphenyl in 40 ml. of water and 8 ml. of concd. sulfuric acid was diazotized at 0° with 1.17 g. (0.017 mole) of sodium nitrite, the excess nitrous acid was destroyed with urea, and a solution of 1.17 g. (0.018 mole) of sodium azide in 10 ml. of water was added. After two hours at 0°, the azide, wt. 1.87 g. (57.5%), m.p. 113–119°, was filtered off. Recrystallization from aqueous methanol gave an analytical sample, m.p. 117–119.2°.

2-Nitro-2′,5′-dihydroxybiphenyl. A diazonium solution prepared from 13.8 g. (0.1 mole) of *o*-nitroaniline in excess

(8) H. A. Scarborough and W. A. Waters, *J. Chem. Soc.*, 89 (1927).

(9) C. K. Bradsher and L. J. Wissow, *J. Am. Chem. Soc.*, **68**, 404 (1946).

(10) Analysis by Mrs. Anna Griffin, University of Michigan.

(11) F. C. Copp and L. P. Walls, *J. Chem. Soc.*, 313 (1950).

(12) W. H. von Glahn and B. W. Rottschaefer, U. S. Pat. **2,363,819**; *Chem. Abstr.*, **39**, 3675[4] (1945).

(13) Analysis by Clark Microanalytical Laboratories, Champaign, Ill.

(14) Analysis by Microtech Laboratories, Skokie, Ill.

(15) D. H. Hey and S. E. Lawton, *J. Chem. Soc.*, **374** (1940).

(16) Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(17) Analysis by Dr. Goji Kodama, University of Michigan.

(18) C. Graebe and P. Schestakow, *Ann.*, **284**, 312 (1895).

25% sulfuric acid was added dropwise with stirring to a solution of 22 g. (0.2 mole) of hydroquinone in 1100 ml. of water at room temperature. After several hours of stirring, the mixture was filtered and the filtrate extracted with ether. The extracts were in turn extracted with 10% sodium hydroxide solution containing some sodium bisulfite, and the alkaline extract was neutralized with hydrochloric acid and allowed to cool. The orange needles of 2-nitro-2′,5′-dihydroxybiphenyl that separated had m.p. 163–167° (reported,[19] 167°), and the yield varied between 11.5 and 13.5% in four trials.

2-Nitro-2′,5′-dimethoxybiphenyl. This compound was prepared by treating the foregoing substance with dimethyl sulfate in aqueous sodium hydroxide solution. It could be obtained more expeditiously, however, by evaporating the ether extracts containing the crude dihydroxy compound, dissolving the residue in 4% sodium hydroxide solution, and treating with a large excess (4 moles per mole of *o*-nitroaniline) of dimethyl sulfate at 60–70° with stirring. When the mixture is heated overnight, the contaminating hydroquinone dimethyl ether sublimes, and on cooling, 2-nitro-2′,5′-dimethoxybiphenyl separates as a brown solid, m.p. 100–105°, in 10.5% yield.

The crude product was purified by washing its ether solution with *N* sodium hydroxide until the washings were colorless, drying over magnesium sulfate, and evaporating to a small volume. There was obtained from 4.54 g. of crude material two crops of light yellow crystals: 3.18 g. of m.p. 100–102°, and 0.45 g. of m.p. 96–101°.

Anal.[14] Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05. Found: C, 65.17; H, 4.91.

2-Amino-2′,5′-dimethoxybiphenyl. In a Parr bottle was placed 3.33 g. (0.0128 mole) of 2-nitro-2′,5′-dimethoxybiphenyl with about 200 ml. of methanol and a small amount of platinum dioxide. It was shaken with hydrogen until the pressure reading on the gage was constant (about 16 hr.). The solution was filtered, the methanol evaporated, the residues taken up in acetone, and water added. The crude, brownish product weighed 1.60 g. (56.5%), m.p. 65–68°. It was recrystallized once from acetone-water, and once from methanol-water, to obtain an analytical sample as fine, white needles, m.p. 68–69°.

Anal.[14]: Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59. Found: C, 74.16; H, 6.54.

2-Benzamido-5-chlorobiphenyl. Chlorine was passed through a sintered glass inlet tube into a solution of 27.3 g. (0.1 mole) of 2-benzamidobiphenyl in 250 ml. of dry ether until the mixture was bright yellow and crystals began to form. The solvent was partially evaporated and the product, 20.1 g. (65.5%), m.p. 137–143°, was filtered off. 2-Benzamido-5-chlorobiphenyl prepared by benzoylation of the amine has reported m.p. 142–143°.[8]

2-Amino-5-chlorobiphenyl. Hydrolysis of 4.0 g. (0.013 mole) of 2-benzamido-5-chlorobiphenyl by refluxing for 12 hr. with 25 ml. of concentrated hydrochloric acid and 75 ml. of glacial acetic acid gave 2.0 g. (75.5%) of the amine, m.p. 47–50° (reported, 48°,[20] 54°[21]).

2-(2′-Nitrophenyl)naphthalene. A mixture of 2′- and 4′-nitro-2-phenylnaphthalene, b.p. 230–270°/0.8 mm., was prepared from 76.7 g. (0.415 mole) of 2-acetamidonaphthalene by the method of Hey and Lawton.[15] This mixture, a red sirup, was dissolved in 200 ml. of benzene and allowed to stand overnight. The crystals which separated melted at 167–175° and were primarily the 4′-nitro isomer. The filtrate was chromatographed on alumina using benzene for development and elution. Two bands were seen under ultraviolet light; the lower fluoresced deep purple and the upper fluoresced tan. The eluted lower band gave 12.2 g. (12%) of 2-(2′-nitrophenyl)naphthalene, m.p. 93–98° (m.p. 101° after recrystallization from ethanol); the upper band was found to contain the 4′-nitro isomer.

1-(2′-Nitrophenyl)naphthalene. Ten grams of copper-bronze powder was added over a period of 15 min. to a mixture of 14.9 g. (0.06 mole) of 1-iodo-2-nitrobenzene and 15.2 g. (0.06 mole) of 1-iodonaphthalene heated to 240°. After 3 hr. at 235–240°, the mixture was cooled and the mass extracted with three 30 ml. portions of benzene. Chromatography of the extracts on an alumina column, using benzene for development, gave three bands visible under ultraviolet light. The lowest fluoresced bright blue and contained α,α′-binaphthyl along with some other material, presumably 1-iodo-2-nitrobenzene. The middle band fluoresced grey-brown and contained 1-(2′-nitrophenyl)naphthalene and 1-iodonaphthalene. The upper band fluoresced purple and was 2,2′-dinitrobiphenyl. The middle band was washed out with benzene to give an oil after evaporation, which after crystallization from 70 ml. of 95% ethanol gave 3.41 g. (21%) of 1-(2′-nitrophenyl)naphthalene, m.p. 88–90° (reported m.p. 88–90°[22]). The upper band on similar treatment gave 2.70 g. of 2,2′-dinitrobiphenyl.

Carbazoles. The carbazoles prepared are summarized in Table II. All were prepared by heating dilute solutions of azides in kerosine, according to the method described for the following example.

3,4-Benzocarbazole from 1-(2′-azidophenyl)naphthalene. A solution of 0.5012 g. of 1-(2′-azidophenyl)naphthalene in 50 ml. of kerosine (washed by extraction with sulfuric acid) was quickly heated to 180–200°. After five minutes, the solution was allowed to cool and was eventually chilled to −10°. Filtration then gave 0.272 g. (61%) of 3,4-benzocarbazole, m.p. 132.5–134.5° after washing with petroleum ether (b.p. 30–40°). The filtrates were passed through an alumina column, the kerosine was removed by eluting with petroleum ether (b.p. 40–60°), and the column was devel-

TABLE II

CARBAZOLES PREPARED FROM AZIDOBIARYLS

	Yield	Crude M.P., C°.	Pure M.P., C.°
2-Hydroxycarbazole	87.5	255–260	266.5–269.5[a]
2-Methoxycarbazole	71.8[b]	227–234	234–235.5[c]
1,4-Dimethoxycarbazole	71	109–112	111.5–112.8[d]
3-Chlorocarbazole	60.5[e]	188–191	195.8–197[f]
1,2-Benzocarbazole[g]	94	226–228	229–230[h]
1,2-Benzocarbazole[i]	94	228–230	230–231
3,4-Benzocarbazole	100	132.5–134.5	135–136[j]

[a] Reported[24] m.p. 276°. *Anal.*[13] Calcd. for $C_{12}H_9ON$: C, 78.67; H, 4.95. Found: C, 78.78; H, 4.95. [b] Based on 2-amino-4′-methoxybiphenyl;[11] azide not isolated. [c] Reported[25] m.p. 235–236°. *Anal.*[14] Calcd. for $C_{13}H_{11}ON$: C, 79.6; H, 5.62. Found: C, 79.47; H, 5.73. [d] *Anal.*[14] Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77. Found: C, 74.03; H, 5.83. [e] From 2-amino-5-chlorobiphenyl; azide not isolated. [f] Reported[26] m.p. 199°. [g] From 1-azido-2-phenylnaphthalene. [h] Reported[27] m.p. 225°; undepressed when mixed with 1,2-carbazole from 2-(2′-azidophenyl) naphthalene. Picrate, m.p. 186–188° (reported 185°). [i] From 2-(2′-Azidophenyl)-naphthalene. [j] Reported[23] m.p. 134–135°.

(19) J. Dobáš, *Chem. listy*, **46**, 277 (1952); *Chem. Abstr.*, **47**, 8669d (1953).

(20) H. Hübner and H. Lüddens, *Ann.*, **209**, 349 (1881).

(21) Th. De Crauw, *Rec. trav. chim.*, **50**, 776 (1931).

(22) J. Forrest and S. H. Tucker, *J. Chem. Soc.*, 1137 (1948).

(23) F. R. Japp and W. Maitland, *J. Chem. Soc.*, **83**, 270 (1903).

(24) F. Baullauf, F. Muth, and A. Schmelzer, U. S. Patent **1,807,682**; *Chem. Abstr.*, **25**, 4412 (1931).

(25) C. K. Bradsher, F. C. Brown, and P. H. Leake, *J. Org. Chem.*, **22**, 500 (1957).

(26) O. Süs, *Ann.*, **557**, 240 (1947).

(27) S. H. Oakeshott and S. G. Plant, *J. Chem. Soc.*, 1843 (1928); W. Borsche, *Ann.*, **359**, 79 (1908).

oped with benzene. A single, bright blue, fluorescent band was visible under ultraviolet light. Elution with benzene gave 0.176 g. of a solid, m.p. 127–134°, which gave no m.p. depression with the 3,4-benzocarbazole first isolated; total yield 0.448 g. (100%). Recrystallization from 30 ml. of petroleum ether (b.p. 90–100°) raised the m.p. to 135–136° (reported,[23] 134–135°).

2-Methoxycarbazole from 2-Hydroxycarbazole. To a solution of 0.32 g. (0.00175 mole) of 2-hydroxycarbazole in 20 ml. of sodium hydroxide was added slowly 0.25 g. (0.002 mole) of dimethyl sulfate, and the resulting mixture was heated on the steam bath for one hour. The yield of crude 2-methoxycarbazole obtained upon filtration of the cooled solution was 0.28 g. (81%), m.p. 231.5–234.5°. Upon recrystallization from acetone-water, 0.15 g., m.p. 231.5–234.5°, and 0.06 g., m.p. 224–230° was obtained. A mixed melting point with material prepared from 2-azido-4′-methoxybiphenyl gave no depression.

2-Biphenylyl azide-3′-N^{15}. 2-Biphenylylhydrazine chlorostannite[28] (2.99 g., 0.00473 mole) was slurried with 7 ml. of concentrated hydrochloric acid in 25 ml. of water, and 1.00 g. of potassium nitrite (about 2% enriched in N^{15}) in 5 ml. of water was added dropwise to the solution at 0–5°. After 30 min., the precipitated azide was filtered off; wt. 1.77 g. (96%), m.p. 48–50°. It was recrystallized for use by chilling its solution in methanol to −20°.

Decomposition of labeled azide. The apparatus used for the collection of nitrogen from the decomposition of the N^{15}-labeled azide was that described by Vaughan, Boyd, McCane, and Sloan.[29] In the reaction vessel was placed 25 ml. of kerosine (extracted with sulfuric acid, sodium hydroxide solution, dried and distilled) along with 0.3–0.4 g. of the azide. The reaction vessel was connected to a nitrometer tube filled with 50% potassium hydroxide solution. Air was removed from the system by a stream of carbon dioxide, obtained from Dry Ice and found to contain only a slight trace of air. The reaction vessel was heated to 195° for 30 min. by means of an oil bath, and then cooled to room temperature. The nitrogen was swept into the nitrometer tube with carbon dioxide, and collected over 50% potassium hydroxide solution; the yield was quantitative. The nitrogen was drawn from the nitrometer through Ascarite and Dehydrite into an evacuated sample tube, and samples were analyzed on a Nier-type isotope-ratio mass spectrometer. (See Vaughan *et al.*[29] for details of the procedure.)

Assay of potassium nitrite. The labeled potassium nitrite was assayed by heating it with an equivalent of ammonium chloride in aqueous solution.[29] The nitrogen obtained was collected in the same way as described above.

TABLE III

RESULTS OF N^{15} EXPERIMENTS

Source of N_2	Isotope Ratio (29/28)	Atom % N^{15} in N_2	Excess Atom % N^{15} in N_2
"Pure" tank N_2	0.00735	0.365	0.000
$KN^*O_2 + NH_4Cl$	0.02617	1.291	0.926
Ordinary 2-azidobiphenyl	0.00738	0.368	0.003
Labeled 2-azidobiphenyl	0.02640	1.303	0.935

Atom % N^{15} in KN^*O_2, 2.217%.
Maximum possible atom percent of N^{15} in N_2 from labeled azide, 1.292%.
Maximum possible atom percent of N^{15} in N_2 from labeled azide over that from ordinary azide, 0.924%.

$$\frac{0.935}{0.924} \times 100 = 101\%$$

Thus, 101 ± 3% of the isotropic (terminal) nitrogen atoms of the azide appeared in the evolved nitrogen.

2-Carboxy-2′-cyanobiphenyl. Phenanthrenequinone monoxime was subjected to the Beckmann rearrangement "of the second kind" essentially according to Werner and Piguet,[30] except that the benzenesulfonyl chloride was added to the pyridine solution of the oxime at ice-bath temperature, followed by refluxing for 1.5 hr. The yield was 31%.

2-Amino-2′-cyanobiphenyl. A mixture of 13.5 g. (0.061 mole) of 2-carboxy-2′-cyanobiphenyl and 14.3 g. (0.12 mole) of thionyl chloride was heated under reflux on a steam bath for 2 hr., and the excess thionyl chloride was removed under aspirator vacuum. A solution of 7.8 g. (0.12 mole) of sodium azide in 30 ml. of water was added dropwise with stirring to the residual dark oil dissolved in 50 ml. of acetone, kept at 0–5° with an ice-salt bath. After several hours, 40 ml. of water was added and the suspension was allowed to stand overnight. The solid azide was collected, dissolved in toluene to a total volume of 294 ml., and dried over magnesium sulfate. The resulting amber solution was heated until nitrogen evolution ceased. A small portion of the resulting purple solution was reserved for other work, and the main portion, 245 ml., was cooled and added dropwise with stirring to 500 ml. of concentrated hydrochloric acid that had been additionally saturated with hydrogen chloride near 0°; some frothing occurred. The mixture was then allowed to come to room temperature overnight with continuous stirring, after which the layers were separated and the aqueous phase was neutralized with sodium carbonate. The mixture was extracted with ether, the extracts were dried over magnesium sulfate, and hydrogen chloride was passed in until precipitation appeared complete. There was obtained 4.41 g. (40%) of *2-amino-2′-cyanobiphenyl hydrochloride*, m.p. 307–310°, which, from the analytical figures, may have lost a small amount of hydrogen chloride during drying.

Anal.[18]: Calcd. for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81. Found: C, 67.90, 67.88; H, 5.25, 5.30.

The free base was obtained as a brown oil when the hydrochloride was dissolved in sodium carbonate solution. Taking it up in ether, drying over magnesium sulfate, concentration and crystallization from chilled aqueous ethanol gave fine, white needles, m.p. 61–63°.

Anal.:[13] Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19. Found: C, 80.12; H, 5.01.

The N-carboethoxy derivative was obtained from an experiment in which the hydrochloric acid hydrolysis step following the Curtius rearrangement was largely incomplete. From 14.13 g. of 2-carboxy-2′-cyanobiphenyl, there was obtained in the manner described only 0.396 g. (2.7%) of 2-amino-2′-cyanobiphenyl hydrochloride. Evaporation of the toluene layer and addition of ethanol to the residual oil gave 8.83 g. (33%) of 2-carboethoxyamino-2′-cyanobiphenyl, light tan solid from aqueous ethanol, m.p. 91–96°. An analytical sample from one further crystallization melted at 94.5–96.5°.

Anal.:[18] Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.74; H, 5.42; N, 10.44.

9,10-Tetrazolophenanthridine. A. From 2-Azido-2′-cyanobiphenyl. In an attempt to bring about cyclization to 4-cyanocarbazole, 0.1 g. of 2-azido-2′-cyanobiphenyl in 20 ml. of kerosine was heated near 180° for 0.5 hr. and allowed to cool; a few bubbles were noticed during the heating. The tan solid that formed was collected by centrifugation, washed with petroleum ether, and treated with charcoal in hot absolute alcohol. Dilution with water produced a crystalline solid, wt. 0.0718 g. (71.8%), m.p. 220–222°, which proved to be 9,10-tetrazolophenanthridine. An analytical sample recrystallized from ethanol had m.p. 221.5–223.5°.

(28) C. Graebe and A. Sc. Rateanu, *Ann.*, **279**, 267 (1894).

(29) W. R. Vaughan, W. T. Boyd, D. L. McCane, and G. J. Sloan, *Anal. Chem.*, **23**, 508 (1951).

(30) A. Werner and A. Piguet, *Ber.*, **37**, 4311 (1904).

Anal.:[10] Calcd. for $C_{13}H_8N_4$: C, 70.89; H, 3.66. Found: C, 70.65; H, 3.77.

B. From fluorenone oxime. To a mixture of 10 g. (0.05 mole) of fluorenone oxime and 15 g. (0.07 mole) of phosphorus pentachloride was cautiously added 100 ml. of phosphorus oxychloride; a vigorous reaction began at once. After two hours of refluxing, the mixture had turned black. The phosphorus oxychloride was removed by distillation after the addition of 25 ml. of xylene as diluent and chaser, and a solution of *ca.* 0.1 mole of hydrogen azide in 200 ml. of dry benzene was added to the cold residue. After one week at room temperature, the solution was heated for 0.5 hr., cooled and washed thoroughly with 20% sodium carbonate solution. The dried (magnesium sulfate) and filtered solution was concentrated to near dryness, heated with absolute alcohol, filtered from some insoluble matter, and crystallized by the addition of water to give 2.06 g. (18.4%), m.p. 208–218°. A sample recrystallized from aqueous ethanol gave no depression of melting point when mixed with the compound obtained from 2-azido-2′-cyanobiphenyl.

Pyrolysis of 4-Azidofluorenone. When 1.0 g. samples of 4-azidofluorenone were heated in kerosine or resorcinol dimethyl ether solution, nitrogen was evolved at about 175° and the solutions turned nearly black. On cooling, a brown, amorphous solid separated, insoluble in benzene or ethanol, but soluble in nitrobenzene. Attempts at crystallization, with and without chromatography, failed, as did attempts to prepare a picrate and an oxime.

4-Aminofluorene. A mixture of 5.00 g. (0.0238 mole) of fluorene-4-carboxylic acid[31] and 5.95 g. (0.05 mole) of thionyl chloride was heated on a steam bath for one hour and the excess thionyl chloride was distilled off. A solution of 3.25 g. (0.05 mole) of sodium azide in 15 ml. of water was added with stirring to a solution of the resulting acid chloride in 25 ml. of acetone. The light orange-brown, crude, solid azide was collected after the addition of 50 ml. of water, and was pressed dry and promptly dissolved in 60 ml. of benzene. After 0.5 hr. of refluxing, nitrogen evolution had stopped, and 25 ml. of 50% potassium hydroxide solution was added and the refluxing continued for several hours. Hydrogen chloride was passed into the separated and dried benzene layer, precipitating 3.28 g. (63.5%) of 4-aminofluorene hydrochloride, m.p. 240° (dec.). A purer sample was prepared by releasing the free base with aqueous ammonia, taking it up in benzene, and reprecipitating with hydrogen chloride, which gave a white solid, m.p. 283–288°.

Anal.[14]: Calcd. for $C_{13}H_{12}NCl$: C, 71.69; H, 5.56. Found: C, 71.82; H, 5.70.

The free base was obtained by decomposing the salt with aqueous ammonia and crystallizing from benzene. It formed pale yellow needles, m.p. 112.5–114°.

Anal.[14]: Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.12. Found: C, 86.02; H, 6.09.

Pyrolysis of 4-azidofluorene. Attempted thermal cyclization of 4-azidofluorene in the same manner as described for 4-azidofluorenone gave an amorphous, brown solid of similar characteristics, that resisted all attempts at crystallization.

ANN ARBOR, MICH.

(31) W. E. Bachmann and J. C. Sheehan, *J. Am. Chem Soc.*, 62, 2689 (1940).

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

Synthesis of Some 1,1-Dibenzylhydrazines[1]

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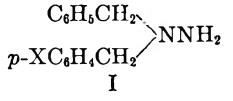
A series of unsymmetrically substituted dibenzylhydrazines, p-$XC_6H_4CH_2NCH_2C_6H_5$ (NH$_2$), where X = CH_3O—, $(CH_3)_2N$—, CH_3—, and Cl—, have been prepared by reduction of the corresponding nitrosamines with lithium aluminum hydride. 1-Benzyl-1-furfurylhydrazine was also prepared by this method. Attempts to prepare other hydrazines of this type are discussed.

In connection with a current investigation of the oxidation of 1,1-dibenzylhydrazines, it was necessary to prepare a number of disubstituted hydrazines of the general formula I.



I

The hydrazines were all prepared by the same general route. Benzylamine and a suitably substituted benzaldehyde (II) were condensed to give a Schiff base (III). III was reduced in absolute ethanol in the presence of platinum oxide to a secondary amine (IV) which was then nitrosated in dilute acetic acid solution to give a nitrosamine (V). The latter was reduced with lithium aluminum hydride to the corresponding 1,1-dibenzylhydrazine (I). The properties of the products are listed in Tables I–V.

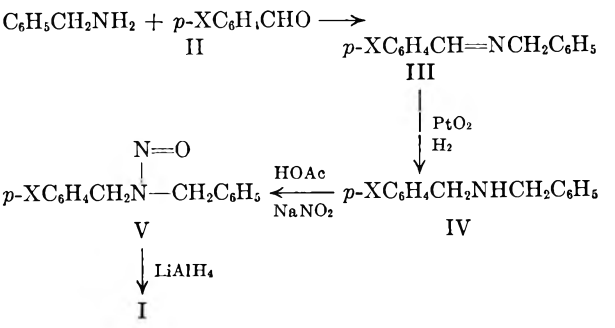


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TABLE I

SCHIFF BASES: RCH = $NCH_2C_6H_5$[a](III)

R	Yield, %	M.P., or B.P. Mm.	Lit. M.P., or B.P. Mm.
p-$(CH_3)_2NC_6H_4$[b]	63	76–77[c]	
p-$CH_3SO_2C_6H_4$[b]	66	72.5–74[d]	
p-$CH_3OC_6H_4$	77	39–40	42[e]
p-$CH_3C_6H_4$	76	207(24)	210(25)[f]
p-ClC_6H_4	81	34–36	34[f]
p-$NO_2C_6H_4$	70	55–57[g]	56[g]
2-furyl	60	158–159(12)	155(11)[h]
p-OHC_6H_4	93	202–204[i]	205–206[i]

[a] Prepared by heating benzylamine and the appropriate aldehyde in the absence of a solvent except where noted otherwise. [b] Recrystallized from ether. [c] Calcd. for $C_{16}H_{18}N_2$: C, 80.62; H, 7.63; N, 11.76. Found: C, 80.33; H, 7.58; N, 11.37. [d] Calcd. for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.54; N, 5.13. Found: C, 65.63; H, 5.46; N, 5.47. [e] Ref. 7. [f] C. Shoppee, *J. Chem. Soc.*, 1225 (1931). [g] This product was obtained only when an ethereal solution was allowed to stand for several hours [C. K. Ingold and H. Piggott, *J. Chem. Soc.*, **121**, 2381 (1922)]. The procedure of footnote *a* invariably yielded a light yellow solid, m.p. 193–195°, of unknown structure. [h] G. De Chamot, *Ann.*, **271**, 11 (1892). [i] A. Mason and G. Winder, *J. Chem. Soc.*, **65**, 192 (1894). [j] This value seems unusually high compared to the melting points of the other Schiff bases. The same compound was obtained using the method described in footnote *g*. The structure of the product is supported by its ultraviolet absorption spectrum (λ_{max} 273 mμ, log a_M 4.25) which shows a reasonable relationship to that reported for *N*-(*p*-methoxybenzylidene)benzylamine (λ_{max} 268 mμ, log a_M 4.30) [P. Grammaticakis, *Bull. soc. chim.*, (5), 427 (1941).]

also was attempted with sodium borohydride in the presence of aluminum chloride. In this case the reduction failed and 74% of the starting material was recovered. The reduction was then attempted employing lithium aluminum hydride in the manner suggested by Felkin[4] who had successfully reduced ester groups without affecting aromatic nitro groups. This method also failed and the starting material was again recovered along with a small amount of orange solid which was not the desired hydrazine.

The hydrazines were all colorless or light yellow liquids which appeared to suffer oxidation and deterioration upon exposure to the atmosphere. The hydrazines were identified as the hydrazones of *p*-nitrobenzaldehyde (Table V). In several cases the hydrochlorides of the hydrazines were prepared; however, difficulties were encountered in purification and their physical properties are not reported here.

From the lithium aluminum hydride reduction of *N*-nitroso-*N*-(*p*-methanesulfonylbenzyl)benzylamine, a compound thought to be 1-benzyl-1-(*p*-methanesulfonylbenzyl)hydrazine was obtained. It could not be purified by distillation. The crude product reacted with oxalic acid, forming what appeared to be an oxalate salt, but analysis of this salt did not agree with values calculated for an oxalate of 1-benzyl-1-(*p*-methanesulfonylbenzyl)-

TABLE II

SECONDARY AMINES: $RCH_2NHCH_2C_6H_5$ (IV)

R	Time Required for Reduction of Schiff Base, Hr.[a]	Yield, %	M.P. or B.P. (Mm.)	Lit. M.P. or B.P. (Mm.)
p-$CH_3OC_6H_4$[b]	2	92	193–194 (7)	206(10)[c]
p-$(CH_3)_2NC_6H_4$[d]	1	82	190–194(1–2)	
p-$CH_3SO_2C_6H_4$[e]	18	69	...	
p-$CH_3C_6H_4$[f]	1	92	147(2)	
p-ClC_6H_4	2	67	192(10)	193–196(13)[g]
p-$NO_2C_6H_4$	...	49	247–249[h]	
2-furyl	6	77	127–134(5)	115–124(4)[i]
p-OHC_6H_4	1	[j]		

[a] All reductions were carried out in absolute ethanol according to the directions in *Org. Reactions*, **IV**, p. 197 (1948), with the exception of *N*-(*p*-methanesulfonylbenzylidene)benzylamine which was reduced in absolute methanol and *N*-(*p*-hydroxybenzylidene)benzylamine which was reduced in dimethylformamide. [b] n_D^{32} 1.5728, d_4^{37} 1.078. [c] Ref. 8. [d] n_D^{12} 1.5984, d_4^{22} 1.035. [e] This material was not purified. Derivative: 1-benzyl-1-(*p*-methanesulfonylbenzyl)-3-phenyl-2-thiourea. Calcd. for $C_{22}H_{22}N_2S_2O_3$: C, 64.35; H, 5.29; N, 6.82. Found: C, 64.06; H, 5.39; N, 7.14. [f] n_D^{27} 1.5660; d_4^{27} 1.018. Derivative: 1-benzyl-1-(*p*-methylbenzyl)-3-phenyl-2-thiourea. Calcd. for $C_{22}H_{22}N_2S$: C, 76.25; H, 6.41. Found: C, 76.42; H, 6.33. [g] J. V. Braun, M. Kuhn, and J. Weismantel, *Ann.*, **449**, 249 (1926). [h] Melting point of hydrochloride, in which form the amine was isolated. [i] K. N. Campbell, J. F. Ackerman, B. K. Campbell, *J. Am. Chem. Soc.*, **71**, 2905 (1949). [j] Although the reaction mixture rapidly took up the calculated quantity of hydrogen, the product decomposed during distillation. No product could be isolated from attempts to nitrosate the crude product from the hydrogenation.

The preparation of *N*-(*p*-nitrobenzyl)benzylamine differed from the general procedure in the use of sodium borohydride and aluminum chloride[3] to reduce the carbon-nitrogen double bond of the Schiff base without affecting the nitro group. The reduction of *N*-nitroso-*N*-(*p*-nitrobenzyl)benzylamine hydrazine. Attempts to prepare a hydrazone with *p*-nitrobenzaldehyde and to prepare the 4-phenyl-3-thiosemicarbazide with phenyl isothiocyanate were unsuccessful. For these reasons the identity of the reduction product remains in doubt.

(3) H. C. Brown and B. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

(4) H. Felkin, *Compt. rend.*, **230**, 304 (1950).

TABLE III

Nitrosamines: $RCH_2NCH_2C_6H_5$ (V)
$N = O$

R[a]	Yield, %	M.P., B.P., °C., (Mm.)	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
p-$CH_3OC_6H_4$	91	53–55	$C_{15}H_{16}N_2O_2$	74.34	7.50	...	74.07	7.18	...
p-$(CH_3)_2NC_6H_4$	55	60–63	$C_{16}H_{19}N_3O$	71.33	7.12	15.60	71.13	7.24	15.73
p-$CH_3SO_2C_6H_4$	64	86–88	$C_{15}H_{16}N_2O_3S$	59.18	5.31	9.21	58.62	5.19	9.24
p-$CH_3C_6H_4$[b]	87	176–177(3)	$C_{15}H_{16}N_2O$	74.96	6.72	11.66	75.09	6.59	11.57
p-ClC_6H_4	74	190(2)	$C_{14}H_{13}N_2OCl$	64.48	5.04	...	64.19	4.70	...
α-Furyl-[c]	67	158–164(4)	$C_{12}H_{12}N_2O_2$	66.64	5.60	12.96	66.40	5.23	12.80
p-$NO_2C_6H_4$	95	78–80	$C_{14}H_{13}N_3O_3$	61.97	4.84	15.49	62.98	4.55	14.39

[a] All the nitrosamines were recrystallized from 95% ethanol with the exception of *N*-nitroso-*N*-(*p*-methoxybenzyl)benzylamine, which was recrystallized from absolute ethanol. [b] n_D^{24} 1.5783, d_4^{23} 1.145. [c] n_D^{27} 1.5582, d_4^{27} 1.158.

TABLE IV

NH_2
1,1-Dibenzylhydrazines: $RCH_2NCH_2C_6H_5$ (I)[a]

R	Yield, %	B.P. (Mm.)	n'_D	d'_4
p-$CH_3OC_6H_4$	67	185–188 (0.5–1)	1.5815 [18]	1.067 [25]
p-$(CH_3)_2NC_6H_4$	50	188–190 (1)	1.5983 [18]	1.073 [28]
p-$CH_3C_6H_4$	71	144–146 (1)	1.5737 [26]	1.064 [24.6]
p-ClC_6H_4	71	165–167 (1)	1.5855 [27]	1.132 [23]
α-Furyl	58	132–134 (3)	1.552 [30]	1.087 [31]

[a] Reduction of corresponding nitrosamine carried out by method of Schueler and Hanna [*J. Am. Chem. Soc.*, 74, 3693 (1952)]. The rate of addition of the nitrosamine solution was not permitted to exceed one drop per second to keep the reaction from taking place with explosive violence [L. F. Audrieth, *et al.*, *J. Am. Chem. Soc.*, 77, 790 (1955)].

TABLE V

Hydrazones of *p*-nitrobenzaldehyde: $R—CH_2NN{=}CHC_6H_4NO_2$
CH_2
C_6H_5

R[a]	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
p-$CH_3OC_6H_4$[b]	76–77	$C_{21}H_{22}N_3O_3$	70.37	5.65	11.19	70.25	5.86	11.59
p-$(CH_3)_2NC_6H_4$	110–111	$C_{23}H_{24}N_4O_2$	71.13	6.24	14.43	71.00	6.09	14.52
p-$CH_3C_6H_4$	123–125	$C_{22}H_{21}N_3O_2$	73.50	5.90	11.69	73.41	5.43	11.49
p-ClC_6H_4	122.5–123.5	$C_{22}H_{18}N_3O_2Cl$	66.39	4.79	...	66.45	4.65	...
α-Furyl-	65–66	$C_{19}H_{17}N_3O_3$	68.04	5.12	12.53	68.40	5.28	12.54

[a] The procedure employed was that of R. L. Shriner, R. C. Fuson and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Edition, Wiley & Sons, New York, New York, 1956, p. 219. [b] This hydrazone was recrystallized from absolute ethanol. All the others were recrystallized from 95% ethanol.

EXPERIMENTAL[5]

With the exception of the reactions described below, the hydrazines were prepared by well-known procedures.

N-(p-Nitrobenzyl)benzylamine hydrochloride. A solution of 1.2 g. (0.35 mole) of sodium borohydride and 16.9 g. (0.07 mole) of N-(*p*-nitrobenzylidene)benzylamine in 100 ml. of tetrahydrofuran was vigorously stirred as 1.6 g. (0.01 mole) of aluminum chloride in 50 ml. of tetrahydrofuran was added, at such a rate that the temperature of the reaction did not rise above 50°. After all of the aluminum chloride solution had been added, the mixture was stirred at room temperature for 30 min. and then heated on a steam bath for 1.5 hr. The reaction mixture was then cooled and poured into 70 g. of crushed ice and 12 ml. of concentrated hydrochloric acid. A light yellow precipitate was removed by filtration and recrystallized from 200 ml. of 95% ethanol. A white precipitate was obtained which weighed 9.5 g. (49%) and melted at 247–249°. This precipitate gave a positive Beilstein test for halogen and a Hinsberg test for a secondary amine.

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 60.31; H, 5.44. Found: C, 60.97; H, 5.52.

Attempt to reduce N-nitroso-N-(p-nitrobenzyl)benzylamine with sodium borohydride. The procedure was the same as that employed in the preparation of *N*-(*p*-nitrobenzyl)benzylamine hydrochloride. From 3.5 g. (0.01 mole) of *N*-nitroso-*N*-(*p*-nitrobenzyl)benzylamine, 0.4 g. (0.01 mole) of sodium borohydride, and 0.5 g. (0.004 mole) of aluminum chloride, an oil was obtained which solidified upon cooling. The solid was recrystallized from 95% ethanol to yield 2.6 g. of a light yellow solid, m.p. 76–80°. A mixed m.p. of 76–80° was obtained with a sample of *N*-nitroso-*N*-(*p*-nitrobenzyl)benzylamine (m.p. 78–80°). This represented a 74% recovery of starting material.

Attempt to reduce N-nitroso-N-(p-nitrobenzyl)benzylamine with lithium aluminum hydride. The procedure employed was that of Felkin.[4] From 7.4 g. (0.03 mole) of *N*-nitroso-*N*-(*p*-nitrobenzyl)benzylamine and 0.4 g. (0.01 mole) of lithium aluminum hydride a light orange solid, m.p. 68–76°, was obtained. After two recrystallizations of this material from 80% ethanol two products were obtained. One was a light yellow solid which melted at 80–81° and did not depress the melting point of an authentic sample of *N*-nitroso-*N*-(*p*-nitrobenzyl)benzylamine. The other product was a light orange solid which melted at approximately 135° and did not have the properties of the desired hydrazine.

(5) Melting points and boiling points are uncorrected.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Physical Properties of the Aminoazobenzene Dyes. IX. Absorption Spectra in Alcohol and Acid Solution of Disazobenzene Dyes[1]

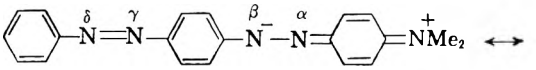
EUGENE SAWICKI[2]

Received September 25, 1957

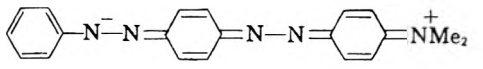
The position of proton addition and the absorption spectra in various solvents of 4-dimethylamino-*p*-disazobenzene dyes has been investigated. Spectral evidence has been presented which indicates that the first proton adds to the β-azo nitrogen and the second proton to the δ-azo nitrogen. The tautomerism of these salts has also been investigated.

In previous papers the *beta* and amino nitrogens of a large number of 4-aminoazobenzene derivatives[3-6] were shown to be of the same order of basicity. For example, the basicity of the amino nitrogen relative to the β-nitrogen is increased by the following substitutions in 4-dimethylaminoazobenzene: (*a*) replacement of one or both methyl groups by ethyl groups; (*b*) a methyl,[6] fluoro,[7] or methoxy[8] group in the 3-position; (*c*) alkyl, methoxy, chloro, or nitro groups in the 2′-position;[6] (*d*) electron donor groups in the 4′-position.[6] The basicity of the β-nitrogen relative to the amino nitrogen in dyes such as 4-dimethylaminoazobenzene is increased by (*a*) substitution in the 2-position by an alkyl[6] or fluoro[7] group; (*b*) the presence of a 2′-carboxy group;[6] (*c*) 4′-substitution by electron-attracting groups;[6] (*d*) replacement of an *N*-methyl group by a base-weakening phenyl, benzyl, or β-chloroethyl[3] group. As the amino and β-nitrogens are of the same order of basicity, the 4-aminoazobenzene dyes tend to form a mixture of monocationic tautomers in acid solution consisting of the C tautomer involving proton addition to the β-nitrogen and the A tautomer involving proton addition to the amino nitrogen. With C_ϵ equivalent to the molar extinction coefficient of the long wave length band of the C tautomer and A_ϵ equivalent to the molar extinction coefficient of the long wave length band of the A tautomer, the C_ϵ/A_ϵ ratio has been shown to give a crude indication of what one would expect for the relative tautomeric equilibria on the basis of structural modifications and *p*K's.

Knowing the effect of the position of a methyl group on the C_ϵ/A_ϵ ratio of 4-dimethylaminoazobenzene, it was believed that the position of proton addition in 4-dimethylamino-*p*-disazobenzene (I) should be capable of determination. 4-Dimethylaminoazobenzene has a C_ϵ/A_ϵ ratio of 3.6 in 50% alcoholic 1.2*N* hydrochloric acid, its 2′-methyl derivative has a C_ϵ/A_ϵ ratio of 0.29, while the 3′-, 4′-, and 2-methyl isomers have C_ϵ/A_ϵ ratios of 4.1, 2.6, and 10.0, respectively.[6] In the 4-dimethylamino-*p*-disazobenzene dyes a much more complicated situation is present. There are five nitrogens at which salt formation can take place. If we consider zwitterionic resonance structures such as Ia and Ib as contributors to the over-all structure of



Ia



Ib

these dyes, then the β- and δ-azo nitrogens have a greater electron density than the α- or γ-azo nitrogens which cannot act as a negative resonance terminal. As Ia involves one *p*-benzoquinonic ring and Ib involves two such rings and also a greater separation of charge, Ib is probably of higher energy and the β-nitrogen would consequently have a higher electron density than the δ-nitrogen. Consequently in a competition for the first proton, the amino and β-nitrogens would probably be the chief competitors. In the derivatives under study the only methyl groups that appear to definitely affect the C_ϵ/A_ϵ ratio of I, C_ϵ/A_ϵ 3.5, are those that would be expected to affect the electron density of the β-azo nitrogen. For example, 2′, 2″-dimethyl-I has a C_ϵ/A_ϵ ratio of 0.28. Just as in 2′-methyl-4-dimethylaminoazobenzene the 2′-methyl group has strongly decreased the C_ϵ/A_ϵ ratio. In 3′,4″-dimethyl-I the C_ϵ/A_ϵ ratio is practically the same as in I, Table I. These methyl groups would not be expected to have a strong electronic effect on the β-nitrogen, but would be expected to increase the

(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service. Paper VIII, E. Sawicki, *J. Org. Chem.*, 22, 1084 (1957).

(2) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) E. Sawicki and F. Ray, *J. Org. Chem.*, 19, 1686 (1954).

(4) E. Sawicki and D. Gerber, *J. Org. Chem.*, 21, 410 (1956).

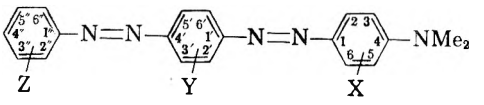
(5) E. Sawicki, *J. Org. Chem.*, 21, 605 (1956).

(6) E. Sawicki, *J. Org. Chem.*, 22, 621 (1957).

(7) G. Cilento, E. Miller, and J. Miller, *J. Am. Chem. Soc.*, 78, 1718 (1956).

(8) This is a prediction based on the results of W. Ross and G. Warwick, *J. Chem. Soc.*, 1719 (1956), who showed that in the acid spectra of some thirty 4-di(2-chloroethyl)aminoazobenzene dyes only the 3-methoxy-4′-carboxy derivative had an A band. They pointed out that the 3-methoxy derivative increased the basicity of the amino nitrogen.

TABLE I



ABSORPTION SPECTRA OF 4-DIMETHYLAMINO-*p*-DISAZOBENZENE DYES IN ALCOHOL AND ACID SOLUTION[a]

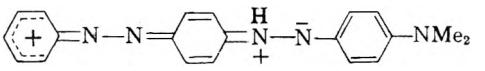
X	Y	Z	λ_{max} ($\epsilon \times 10^{-3}$)		Solvent[b]	$\frac{C_\epsilon}{A_\epsilon}$[c]
H	H	H	330 (16.0)	476 (35.8)	A	
			355 (17.1)	548 (59.6)	B	3.5
				635 (106.3)	C	
				490[d] (39.7)	D	
H	2′-CH_3	2″-CH_3	335 (14.2)	470 (34.6)	A	
			370 (35.8)	534 (9.80)	B	0.28
				630 (73.2)	E	
				540 (46.4)	D	
H	3′-CH_3	4″-CH_3	340 (14.6)	475 (38.0)	A	
			360 (17.1)	558 (58.7)	B	3.4
			428 (7.08)	647 (110.0)	C[e]	
				545 (51.4)	D	
2-CH_3	3′-CH_3	4″-CH_3	344 (14.2)	475 (37.4); 490 (36.4)	A	
			360 (12.3)	550 (69.0)	B	5.6
			425 (6.02)	645 (108.0)	C[e]	
				540 (46.4)	D	

[a] Spectral data for the 320–800 mμ region. [b] A = 95% ethanol containing 0.25% dioxane; B = 50% alcoholic 1.2*N* HCl; C = 50% alcoholic 50% sulfuric acid; D = 95% sulfuric acid; E = 50% alcoholic, 40% sulfuric acid. [c] This ratio gives a crude idea of the tautomeric equilibrium. C_ϵ is the molecular extinction coefficient at the wave length maximum of the C band (~540 mμ); A_ϵ is the molecular coefficient at the wave length maximum of the A band (~360 mμ). [d] Also a shoulder at 620 mμ, log ϵ 3.97 due to the presence of some dicationic salt. [e] Spectrum in 50% alcoholic 6*N* HCl very closely similar.

electron density of the δ-nitrogen. This would be mainly due to the 3′-methyl group. As the C_ϵ/A_ϵ ratio shows no change, this must mean that the first proton adds to the β-azo nitrogen. This is substantiated by the C_ϵ/A_ϵ ratio of 2,3′,4″-trimethyl-I, C_ϵ/A_ϵ 5.6. The 2-methyl group has increased the electron density of the β-nitrogen. The increased C_ϵ/A_ϵ ratio must mean that the first proton adds at the β-nitrogen. The definite effect of the 2- and 2′-methyl groups on the spectra and the tautomeric equilibrium of the 4-dimethylamino-*p*-disazobenzene dyes are shown in Fig. 1. The band at approximately 360 mμ is the A band of the A tautomer which is iso-pi-electronic to *p*-disazobenzene, λ_{max}^{EtOH} 359, ϵ 80600.[9]

Substitution of a phenylazo group into the 4′-position of 4-dimethylaminoazobenzene, λ_{max}^{EtOH} 408, log ϵ 4.44 shifts the values to λ_{max}^{EtOH} 476, log ϵ 4.55. In this respect the phenylazo group is approximately equivalent to a nitro group for 4′-nitro-4-dimethylaminoazobenzene has λ_{max}^{EtOH} 478, log ϵ 4.52.[6]

In 50% alcoholic 1.2*N* hydrochloric acid the long wave length band of the C tautomer of 4-dimethylamino-*p*-disazobenzene, λ_{max} 548, absorbs at a longer wave length than the long wave length band of the C tautomer of 4-dimethylaminoazobenzene, λ_{max} 516. This absorption is probably due to the contribution of extraconjugative structures such as



to the excited state of the molecule. Essentially this type of conjugation could cause a net stabilization of the excited state. This, of course, has a

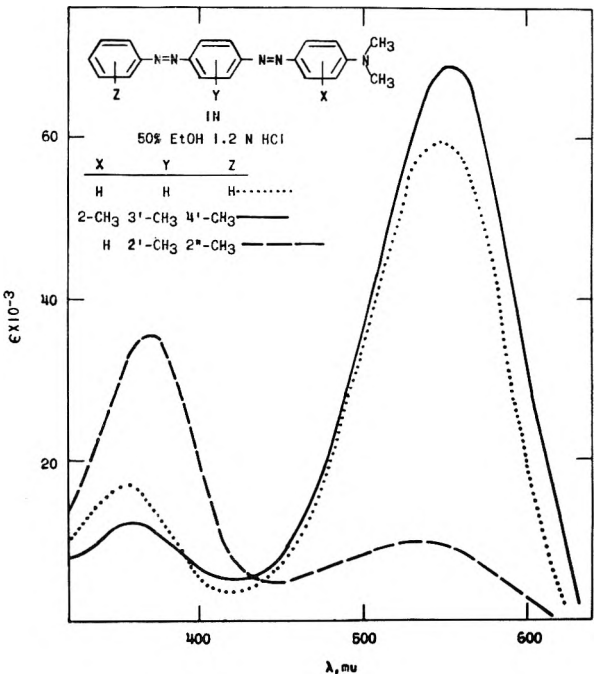


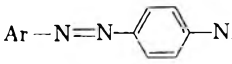
Fig. 1. Absorption spectra in 50% alcoholic 1.2*N* HCl: 4-dimethylamino-*p*-disazobenzene (.....); 2′,2″-dimethyl-4-dimethylamino-*p*-disazobenzene (———); and 2,3′,4″-trimethyl-4-dimethylaminoazobenzene (———)

(9) H. Dahn and H. Castelmur, *Helv. Chim. Acta*, **36**, 638 (1953).

bathochromic and hyperchromic effect on the long wave length band. This same type of extraconjugative effect is shown by phenyl- or benzo-substituents in the prime ring of 4-dimethylaminoazobenzene, Table II. While electron acceptor groups (e.g., the nitro group) in the 4′-position of 4-dimethylaminoazobenzene cause an increase in the C_ϵ/A_ϵ ratio,[6] the interposition of another benzene ring between the nitro group and the prime ring (as in the nitrofluorene derivative, Table II) destroys this effect. As was mentioned previously many types of 2′-substituents in the 4-dialkylaminoazobenzene dyes cause a strong decrease in the C_ϵ/A_ϵ ratio. This same type of effect is seen in the 1-naphthyl dye as compared to its 2-isomer, Table II.

TABLE II

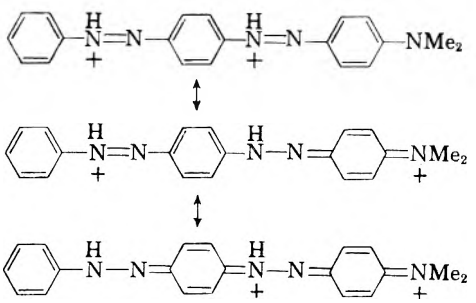
THE C_ϵ/A_ϵ RATIO OF SOME POLYNUCLEAR AZO DYES



Ar	λ_{max} ($\epsilon \times 10^{-3}$) C band	λ_{max} ($\epsilon \times 10^{-3}$) A band	Normality HCl[a]	C_ϵ/A_ϵ
p-Biphenylyl-	544 (39.5)	350 (13.4)	1.2	3.0
2-Fluorenyl-	565 (36.9)	370 (15.5)	1.2	2.4
2-(7-Nitrofluorenyl)-	545 (42.3)	368 (19.4)	1.2	2.2
2-Naphthyl-	545 (35.9)	325 (14.1)	1.2	2.6
1-Naphthyl	540 (3.20)	380 (11.9)	1.2	0.27
	540 (8.08)	380 (10.1)	6.0	0.8

[a] In 50% ethanol.

The addition of a second proton causes another strong bathochromic and hyperchromic effect to an approximate λ_{max} 640, log ϵ 5.0, Fig. 2. These data strongly indicate that the second proton has added to the δ azo nitrogen. The spectral data show that the dicationic tautomer involving salt formation at the β- and δ-nitrogens is present to a very large extent in 50% alcoholic 50% sulfuric acid, Table I, Fig. 2. The dicationic dye is apparently also formed in pure trifluoroacetic acid for solutions of all the 4-dimethylamino-*p*-disazobenzene dyes in this acid are brilliant blue. In these dicationic dyes the absorption at such a long wavelength is apparently due to the increased length of conjugation involved in the cationic resonance structures contributing to the ground and excited states of the molecule.



The third proton possibly adds to these dyes with a protropic shift as shown in Fig. 2. The presence of other tautomers is also possible. The main structure for the tricationic salt is based on the fact that *p*-disazobenzene, $\lambda_{max}^{H_2SO_4}$ 502, log ϵ 4.74,[9] is spectrally similar to 4-dimethylamino-*p*-disazobenzene, $\lambda_{max}^{H_2SO_4}$ 490, log ϵ 4.60.

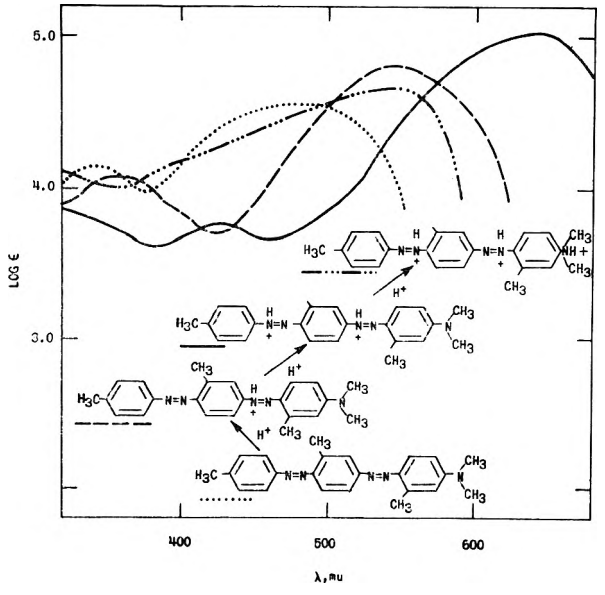


Fig. 2. Absorption spectra of 2,3′,4″-trimethyl-4-dimethylamino-*p*-disazobenzene in 95% ethanol containing 0.25% dioxane (.....); in 50% alcoholic 1.2*N* HCl (———); in 50% alcoholic 50% sulfuric acid (———); and in 95% sulfuric acid (— · · · —)

EXPERIMENTAL[10]

4-Dimethylamino-p-disazobenzene. To a stirred solution of 19.6 g. of 4-aminoazobenzene in 12 ml. of *N,N*-dimethylformamide was added a mixture of 100 g. of ice and 20 ml. of concentrated hydrochloric acid. A solution of 7.4 g. of sodium nitrite in 20 ml. of water was added slowly with stirring at 0–5°. Five grams of urea were added gradually followed by a 10-min. stirring period. Then 12.1 g. of dimethylaniline in 18 ml. of acetic acid followed by 40 g. of potassium acetate in 100 ml. of water were gradually added to the stirred solution at 0–5°. The mixture was stirred an additional hour, filtered cold, and then washed thoroughly with water. Crystallization from dimethylformamide followed by two crystallizations from Methyl Cellosolve (β-methoxyethanol) gave an approximately 60–70% yield of glistening brown-red micro crystals, m.p. 198–199°. Lit. m.p. 190°.[11]

Anal. Calcd. for $C_{20}H_{19}N_5$: N, 21.3. Found: N, 21.0.

2′,2″-Dimethyl-4-dimethylamino-p-disazobenzene. The same procedure was used for this compound. Three crystallizations from Methyl Cellosolve gave an approximately 50–60% yield of gleaming brown-red crystals, m.p. 139–140°.

Anal. Calcd. for $C_{22}H_{23}N_5$: N, 19.6. Found: N, 19.9.

3′,4″-Dimethyl-4-dimethylamino-p-disazobenzene. Several crystallizations of the crude product prepared by the standard procedure from Methyl Cellosolve gave an approximately 50–60% yield of brown-red crystals, m.p. 187–189°.

Anal. Calcd. for $C_{22}H_{23}N_5$: N, 19.6. Found: N, 19.5.

2,3′,4″-Trimethyl-4-dimethylamino-p-disazobenzene. Sev-

(10) All melting points are uncorrected. Analyses are by the Peninsular ChemResearch, Inc., Gainesville, Fla.

(11) J. Hewitt and F. Thole, *J. Chem. Soc.*, **95**, 1393 (1909).

eral crystallizations of the crude product, prepared by the standard procedure, from Methyl Cellosolve gave an approximately 50–60% yield of gleaming red plates, m.p. 177–179°.

Anal. Calcd. for $C_{23}H_{25}N_5$: N, 18.9. Found: N, 18.6.

Preparation of the remainder of the dyes. 4'-Phenyl-4-dimethylaminoazobenzene,[12] m.p. 219–220° (1. xylene, 2. kerosene, 3. Methyl Cellosolve); 2-(4'-dimethylaminophenylazo)fluorene,[13] m.p. 227° (1, 2. Methyl Cellosolve, 3. acetone); 1-(4'-dimethylaminobenzeneazo)naphthalene,[14] m.p. 134–135° (1. heptane, 2,3. Methyl Cellosolve); 2-(4'-dimethylaminobenzeneazo)naphthalene,[15] m.p. 174° (1,2. heptane); and 2-(4'-dimethylaminophenylazo)-7-nitrofluorene, m.p. 270–271° (1,2. nitrobenzene) were prepared by the procedure used for the preparation of 4-dimethylamino-p-diazobenzene.

Ultraviolet-visible absorption spectra. The absorption spectra were determined with a Beckman Model DU Quartz spectrophotometer in the range of 325–800 mμ.

GAINESVILLE, FLA.

(12) W. Brode, J. Gould, and G. Wyman, *J. Am. Chem. Soc.*, **74**, 4641 (1952).

(13) A. Korczynski, G. Karlowska, and L. Kierzik, *Bull. soc. chim. France*, [4] **41**, 65 (1927).

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[CONTRIBUTION NO. 813 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Reduction of Schiff Bases. II. Benzhydrylamines and Structurally Related Compounds[1a,b]

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A new method has been developed for the preparation of secondary amines of the *N*-aryl substituted benzhydryl type and structurally related compounds by reduction of the corresponding Schiff bases with lithium aluminum hydride. In connection with this study, a series of Schiff bases has been prepared by a modification of procedures previously described. In preliminary studies, the optimum ratio of the lithium aluminum hydride to the Schiff bases has been found to be one hundred percent excess above the theoretical amount. The chlorine atoms present in the *N*-aryl group of the Schiff bases were not removed by the hydride. Acetyl and phenylurea derivatives and hydrochloride salts of the secondary amines were prepared. The *N*-aryl substituted anthrylidenimine failed to give the corresponding anthrylamines by this method. An explanation has been offered.

The present investigation was concerned with a new method for the preparation of secondary amines of the benzhydryl type, having the general formula $Ar_2CH\text{-}NHAr'$(II). The Ar_2 represents aryl groups which may be the same or different, or the aryl groups in fluorene and xanthene. Ar' represents an aryl group.

Schiff bases, in general, form with little difficulty. However, those that were needed for the present work had to be made by an extension of the procedure of Reddelien[2,3] in which a catalyst such as fused zinc chloride or 48% hydrobromic acid was used.

$$Ar_2{=}O + H_2N{-}Ar' \xrightarrow[HBr]{ZnCl_2 \text{ or}} Ar_2C{=}N{-}Ar'$$

I

The two catalysts worked equally well but the Schiff bases prepared through the use of hydrobromic acid were easier to purify. In the experiments where 2,4-dichloroaniline was used the yield of Schiff base was lower than in other cases. 2,4,6-Trichloroaniline failed to react with the corresponding ketones probably due to excessive steric hindrance and the decreased basicity of the amine. The Schiff bases that were prepared are listed in Table I.

A survey of the literature showed that only a limited number of secondary amines of the aforementioned type (II) have been synthesized. In most instances the methods of preparation were rather inconvenient and gave poor yields or the author failed to report yields. At the time this work was started, no information had been published on the catalytic hydrogenation of these compounds. However, during the course of the investigation it was reported[4] that *N*-phenylbenzhydrylidenimine could be reduced catalytically but since no other compounds of this type were reduced it is impossible to draw any conclusions as to how general the procedure may be. Since none of the literature references gave evidence of a general preparative method for complex amines of the type under investigation, it was decided to try lithium aluminum hydride as the reducing agent which has been shown previously to reduce simpler Schiff bases.[5]

1(a) Taken in part from the Ph.D. thesis of Kwang M. Tai, Indiana University, 1953. (b) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

(2) G. Reddelien, *Ber.*, **43**, 2476 (1910).

(3) G. Reddelien, *Ber.*, **46**, 2718 (1913).

(4) I. H. Kaye, I. C. Kogon and C. L. Parris, *J. Am. Chem. Soc.*, **74**, 403 (1952).

(5) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948). E. D. Bergmann, D. Lavie, and S. Pinchas, *J. Am. Chem. Soc.*, **73**, 5662 (1951). W. Stühmer and G. Messwarb, *Arch. Pharm.*, **286**, 19 (1953). R. N. Castle, D. L. Aldous, and M. Hall, *J. Am. Pharm. Assoc.*, **42**, 435

TABLE I

SCHIFF BASES

$Ar_2C{=}N{-}Ar'$

Product	Reactants (mole) Amine	Reactants (mole) Ketone	Reaction time (hr.)	Procedure[l]	Solvent for Recryst.	Yield, %	M.P., °C. (uncorr.)	Formula	N Analyses, % Calcd.	N Analyses, % Found
1. benzhydrylidenimine										
N-Phenyl[a]	0.4	0.2	4 2/3	A	Ethanol	81	113–114			
N-4-Methoxyphenyl[a]	0.4	0.2	5 1/4	A[d]	Ethanol	78.5	75[j]	$C_{20}H_{17}NO$	4.88	5.02
N-Phenyl-*p*-methoxy[a]	0.4	0.2	6	A[d]	Methanol[e]	73	71–71.5			
	0.3	0.1	3	B	Methanol	72.4	71–71.5			
N-Phenyl-4,4′-dimethoxy[b]	0.3	0.1	2 1/2	B	Methanol	76	93.5–94	$C_{21}H_{19}NO_2$	4.41	4.37
N-4-Chlorophenyl[a]	0.3	0.2	3	A[d]	Ethanol	80	92.5–93			
N-2,4-Dichlorophenyl-	0.3	0.2	2 1/2	A[d]	Methanol	50.8	93.5–94	$C_{19}H_{13}Cl_2N$	4.30	4.45
N-2,4,6-Trichlorophenyl[c]	0.3	0.2	10	A, B						
N-1-Naphthyl[a]	0.3	0.2	8	A	Ethanol	74	136–136.5			
2. 9-fluorenylidenimine										
N-Phenyl[a]	0.3	0.2	2	B	Pet. ether[f]	75	88.5–90			
N-4-Methylphenyl[a]	0.3	0.2	3 1/2	B	Ethanol	80.5	122.5–123			
N-4-Methoxyphenyl-	0.3	0.2	4 1/2	B	Ethanol	76	135–136	$C_{20}H_{15}NO$	4.91	5.23
N-4-Chlorophenyl-	0.3	0.2	3 1/2	B	Pet. ether[g]	71	147–147.5	$C_{19}H_{12}ClN$	4.84	5.04
N-2,4-Dichlorophenyl	0.3	0.2	3 1/2	A	Ethanol	28	108–108.5	$C_{19}H_{11}Cl_2N$	4.32	4.47
	0.3	0.2	3	B	Ethanol	25	108–108.5			
N-2,4,6-Trichlorophenyl[c]	0.1	0.05	10	A, B						
3. 9-xanthydrylidenimine										
N-Phenyl[a]	0.8	0.4	12	B[h]	Pet. ether[f]	38	131–132[k]	$C_{19}H_{13}NO$	5.16	5.17
4. 9-anthrylidenimine										
N-Phenyl[a]	0.3	0.2	3 1/2	A	[i]	74.3	202–203			
N-4-Methoxyphenyl-	0.3	0.2	3	A	[i]	70	164–165	$C_{21}H_{17}NO$	4.68	4.66
N-4-Chlorophenyl-	0.3	0.2	4	A	[i]	71.5	197.5–199	$C_{20}H_{14}ClN$	4.61	4.65
N-2,4-Dichlorophenyl-	0.3	0.2	4	A	[i]	49.5	146–147	$C_{20}H_{13}Cl_2N$	4.14	4.43

[a] Previously reported. [b] Previously mentioned but neither yield nor analytical data was given, A. Schonberg and W. Urban, *J. Chem. Soc.*, 530 (1935). [c] Only starting materials were isolated. [d] Reaction carried out under CO_2 atmosphere. [e] Compound was purified by fractional distillation (b.p. 191–195° at 6 mm.) before crystallization. [f] B.p. 30–60°. [g] B.p. 90–120°. [h] The residue, after removing chloroform and unreacted aniline, was triturated with low boiling pet. ether and extracted with ether; dry hydrogen chloride was then passed into the cold ethereal solution to separate the compound as its hydrochloride salt. The Schiff base was liberated by treating the salt with 20% NaOH solution. [i] Pet. ether (b.p. 90–120°) and benzene; the reaction mixture was treated with boiling benzene, and the benzene solution filtered. Crystallization was affected upon adding pet. ether to the filtrate and cooling. [j] Reported m.p. 70°, G. Reddelien, *Ber.*, **47**, 1360 (1914). [k] Reported m.p. 134–135°, C. Graebe and P. Röder, *Ber.*, **32**, 1688 (1899); 134.5°, A. Schonberg and W. Urban, *J. Chem. Soc.*, 530 (1935). [l] Procedure A employed hydrobromic acid as catalyst whereas procedure B employed zinc chloride as catalyst.

In general, it was found that lithium aluminum hydride was a good reducing agent for Schiff bases to produce amines of the *N*-aryl substituted benzhydryl type (II) as well as their structurally related compounds.

$$Ar_2C{=}N{-}Ar' + LiAlH_4 \longrightarrow \underset{\text{II}}{Ar_2CH{-}NH{-}Ar'}$$

Table II lists the amines that were prepared by this method.

Although no systematic study was made as to the effect of varying the molar ratio of lithium aluminum hydride, some preliminary experiments on the reduction of *N*-phenyl-9-fluorenylidenimine indicated that the optimum ratio of hydride to Schiff base was 0.5:1, which amounts to an excess of 100% of the hydride. The results are shown in Table III.

No reduction of *N*-phenyl-9-xanthydrylidenimine was observed when the reduction was carried out in diethyl ether even by varying the molar ratio of the hydride to a tenfold excess. However, by using tetrahydrofuran as a solvent and increasing the reaction temperature, the Schiff base was successfully reduced to the corresponding amine. In no instance were halogen atoms removed by the lithium aluminum hydride.

Although this method seemed to be general and suitable for the preparation of *N*-aryl substituted benzhydrylamines, fluorenylamines, and xanthydrylamines, it was not successful for the synthesis of secondary amines derived from *N*-arylanthrylidenimines. Both *N*-phenyl-9-anthrylidenimine and *N*-(4-methoxyphenyl)-9-anthrylidenimine were treated with varying amounts of hydride in diethyl ether and tetrahydrofuran but all modifications failed to give reduction. The failure of these Schiff bases to react with lithium aluminum hydride might be explained by considering the tautomeric nature of the parent compound, anthrone. The keto form of

(1953). B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499 (1953). A. H. Sommers and S. E. Aaland, *J. Org. Chem.*, **21**, 484 (1956). M. Mousseron, R. Jacquier, M. Mousseron-Canet and R. Zagdoun, *Bull. soc. chim. France*, [5] **19**, 1042 (1952). J. Thesing, *Ber.*, **87**, 507 (1954).

TABLE II

N-ARYLBENZHYDRYLAMINES AND RELATED COMPOUNDS

$Ar_2CH—NHAr'$

Secondary Amines	Reaction Time[d] (min.)	Solvent for Recryst.	Yield, %	M.p., °C. (uncorr.)	Formula	*N* Analyses, % Calcd.	Found
A. benzhydrylamine							
N-Phenyl[a]	50	Ethanol[h]	77.1	57			
N-4-Methoxyphenyl[a]	50	Ethanol[h]	84.3	81			
N-Phenyl-*p*-methoxy-	70	[i]	80	140–141[p]	$C_{20}H_{20}ClNO$[p]	4.29[p]	4.60[p]
N-Phenyl-4,4′-dimethoxy-	140	[j]	86	[j]	$C_{21}H_{21}NO_2$	4.40	4.51
N-4-Chlorophenyl-	80	[k]	93.5	89.5–90	$C_{19}H_{16}ClN$	4.77	4.79
N-2,4-Dichlorophenyl	60[e]	Ether[l]	93.5	91.5–92	$C_{19}H_{15}Cl_2N$	4.28	4.40
N-1-Naphthyl[b]	7 hrs.[f]	Methanol[l]	80.8	109.5–110	$C_{23}H_{19}N$	4.53	4.91
B. 9-flurorenylamine							
N-Phenyl[a]	150	[l,m]	94.2	121			
N-4-Methylphenyl[a]	150	Ethanol[l]	86.6	123.5–124			
N-4-Methoxylphenyl-	6 hr.[f]	*n*-Butanol[l]	72	134.5–135	$C_{20}H_{17}NO$	4.87	5.11
N-4-Chlorophenyl-	7 hrs.[f]	*n*-Butanol[l]	71	115–116	$C_{19}H_{14}ClN$	4.80	4.04
N-2,4-Dichlorophenyl	80[g]	Ether[l]	89	140–140.5	$C_{19}H_{13}Cl_2N$	4.29	4.42
C. 9-xanthydrylamine							
N-Phenyl[c]	4 hr.	Pet. ether[n]	70.6	97–97.5	$C_{19}H_{15}NO$	5.12	5.35

[a] Previously reported. [b] Previously mentioned, R. Cantarel, *Compt. rend.*, 226, 931 (1948), but no melting point and analytical data were given. [c] The amine was prepared in tetrahydrofuran; no reduction of the corresponding Schiff base occurred in diethyl ether. [d] Including period of addition or extraction of the Schiff base. [e] The Schiff base was added as solid suspension in ether. [f] The Schiff base was added by extraction via Soxhlet setup. [g] The Schiff base was added as solid form. [h] Purified by fractionation under reduced pressure before crystallization. [i] A viscous colorless oil which failed to crystallize from various solvents; b.p. 187–189° (1 mm.). [j] A viscous colorless oil; b.p. 208–210° (1 mm.). [k] Recrystallized from ethanol acetone (4:1). [l] Crystallized without first purification by fractionation. [m] Recrystallized from pet. ether (b.p. 30–60°) 90–120°. [n] B.p. benzene (3:1). [p] Recorded for its hydrochloride.

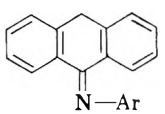
TABLE III

EFFECT OF VARYING THE RATIO OF LITHIUM ALUMINUM HYDRIDE TO THE SCHIFF BASE

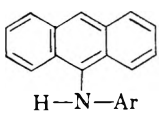
Moles Schiff Base[a]	$LiAlH_4$	Yield %
1	0.25	82.5
1	0.50	94.2
1	1.00	92.0
1	2.00	92.4

[a] N-Phenyl-9-fluorenylidenimine.

anthrone, in general, is indifferent to most reagents; whereas the enol form is highly reactive. When either form is dissolved in an organic solvent, tautomerization occurs and the material is slowly converted into an equilibrium mixture; the point of equilibrium being dependent upon the nature of the solvent and the temperature.[6] Furthermore, a basic medium and elevated temperatures favor the existence of the enolic form of anthrone. Likewise, the imino derivatives of anthrone should undergo a similar tautomeric shift under corresponding conditions.



III



IV

Since the Schiff bases were prepared in a basic medium (aniline) and the products later subjected to reduction with potentially basic lithium aluminum hydride at elevated temperatures, the equilibrium might be expected to shift completely to the amino form IV. On the other hand, the anthrone might first rearrange in the presence of the aniline to anthrol which would then react with the aniline to give form IV.

If the condensation products were in the form of structure III, reduction would certainly be expected in view of the results with the other Schiff bases. However, if they were in the form of structure IV, then reduction should not be expected since such a reduction would require an attack of a benzenoid system which is not accomplished by lithium aluminum hydride under ordinary conditions. In view of the experimental results, structure IV seems to be the favored form.

Whereas most of the secondary amines involved in this work gave satisfactory acetyl and phenylurea derivatives, some of them failed to react with acetic anhydride, acetyl chloride, and phenyl isocyanate. Some of the amines likewise failed to form hydrochlorides. The derivatives that were prepared are listed in Tables IV, V, and VI.

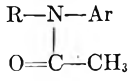
EXPERIMENTAL

Schiff bases. The Schiff bases in Table I were prepared by modification of the methods described by Reddelien[2,3] in which the aromatic amine was allowed to react with the appropriate ketone, using a moisture trap to collect water as it formed. Fused zinc chloride or 48% hydrobromic acid was used as a catalyst. Several hours of heating, instead of 20–30 minutes, were required to collect approximately the

(6) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd Ed., Reinhold Publishing Corp., New York (1956), p. 768.

TABLE IV

ACETYL DERIVATIVES OF *N*-ARYLBENZHYDRYLAMINES AND RELATED COMPOUNDS

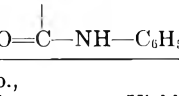


R—	Ar—	M.p., °C. (uncorr.)	Yield, %	Formula	*N* Analyses, % Calcd.	Found
Benzhydryl	Phenyl	84.5–85	98	$C_{21}H_{19}NO$	4.65	4.73
Benzhydryl	4-Methoxyphenyl	100.5–101	94	$C_{22}H_{21}NO_2$	4.22	4.35
Benzhydryl	4-Chlorophenyl	98–98.5	78	$C_{21}H_{18}ClNO$	4.17	4.17
Fluorenyl	Phenyl[a]	177–177.5	93	$C_{21}H_{17}NO$	4.68	4.65
Fluorenyl	4-Methylphenyl	160–161	95	$C_{22}H_{19}NO$	4.47	4.52
Fluorenyl	4-Methoxyphenyl	125–126	87	$C_{22}H_{19}NO_2$	4.25	4.39
Fluorenyl	4-Chlorophenyl	184–185	85	$C_{21}H_{16}ClNO$	4.19	4.35

[a] Previously reported, A. J. Hailwood and R. Robinson, *J. Chem. Soc.*, 1292 (1932).

TABLE V

PHENYLUREA DERIVATIVES OF *N*-ARYLBENZHYDRYLAMINES AND RELATED COMPOUNDS



R—	Ar—	M.p., °C. (uncorr.)	Yield, %	Formula	*N* Analyses, % Calcd.	Found
Benzhydryl	Phenyl[a]	118–118.5	75	$C_{26}H_{22}N_2O$	7.40	7.50
Benzhydryl	4-Methoxyphenyl[a]	132–133	64	$C_{27}H_{24}N_2O_2$	6.86	6.84
Fluorenyl	Phenyl	165–165.5	55	$C_{26}N_{20}N_2O$	7.44	7.28
Fluorenyl	4-Methylphenyl	174.5–176	72	$C_{27}H_{22}N_2O$	7.17	7.18
Fluorenyl	4-Methoxyphenyl	177–178.5	68	$C_{27}H_{22}N_2O_2$	6.89	6.99
Fluorenyl	4-Chlorophenyl	170–171	78	$C_{26}H_{19}ClN_2O$	6.82	7.03
Xanthydryl	Phenyl	214–215	73	$C_{26}H_{20}N_2O_2$	7.14	7.07

[a] Previously reported, P. Grammaticakis, *Compt. rend.*, **210**, 716 (1940).

TABLE VI

HYDROCHLORIDES OF *N*-ARYLBENZHYDRYLAMINES AND RELATED COMPOUNDS

R—NH—AR·HCl

R—	Ar—	M.p., °C. (uncorr.)	Formula	*N* Analysis, % Calcd.	Found
Benzhydryl	Phenyl[a]	201–203[e]	$C_{19}H_{18}ClN$	4.73	
Benzhydryl	4-Methoxyphenyl[b]	191–192[e]	$C_{20}H_{20}ClNO$	4.29	4.62
4-Methoxybenzhydryl	Phenyl	140–141[e]	$C_{20}H_{20}ClNO$	4.29	4.60
Benzhydryl	4-Chlorophenyl	176–178	$C_{19}H_{17}Cl_2N$	4.24	4.41
Fluorenyl	Phenyl	222–223.5[e]	$C_{19}H_{16}ClN$	4.77	4.77
Fluorenyl	4-Methylphenyl	217–219[e]	$C_{20}H_{18}ClN$	4.55	4.94
Fluorenyl	4-Methoxyphenyl	214.5–216.5	$C_{20}H_{18}ClNO$	4.32	4.45
Fluorenyl	4-Chlorophenyl	192–193	$C_{19}H_{15}Cl_2N$	4.27	4.38
Xanthydryl	Phenyl[c]	248–251[d]	$C_{19}H_{16}ClNO$	4.52	4.62

[a] Reported m.p. 194°, H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, **49**, 1928 (1916); and 202.5°, A. Skita, *Ber.*, **48**, 1685 (1915). [b] Reported m.p. 187°, M. Busch and A. Rinck, *Ber.*, **38**, 1761 (1905); and 194°, P. Grammaticakis, *Compt. rend.*, **210**, 716 (1940). [c] Color changed to greenish after drying. [d] Started to sinter at 148°. [e] Melted with decomposition.

theoretical amount of water. Because of the difference in time of heating, the yields of the Schiff bases obtained in this work were 10 to 20% higher than those given by Reddelien. The yields of several Schiff bases prepared by both methods are listed in Table VII.

A number of comparisons of the fused zinc chloride and 48% hydrobromic acid procedures were made and it was found that the crude yields were roughly the same. However, it was found that the hydrobromic acid method gave products that were easier to purify and thus gave slightly higher yields of pure products.

Secondary amines. Stock solutions of the lithium aluminum hydride were prepared and standardized according to the procedure of Finholt, Bond, and Schlesinger.[10]

In a typical preparation of the secondary amines, 25 ml.

(7) G. Reddelien, *Ber.*, **48**, 1462 (1915).

(8) G. Reddelien, *Ber.*, **47**, 1360 (1914).

(9) E. Bergmann, L. Engel, and H. Meyer, *Ber.*, **65**, 446 (1932).

(10) A. E. Finholt, A. C. Bond, and H. I. Schlesinger, *J. Am. Chem. Soc.*, 69, 1199 (1947).

TABLE VII
COMPARISON OF YIELDS OF SCHIFF BASES

Schiff Bases	Yield, % Method 1[a]	Yield, % Method 2[b]	References
N-Phenylbenzhydrylidenimine	81	71	(7)
N-p-Methoxyphenylbenzhydrylidenimine	78.5	56	(8)
N-*p*-Chlorophenylbenzhydrylidenimine	80	59	(9)
N-α-Naphthylbenzhydrylidenimine	74	66	(3)
N-Phenyl-9-florenylidenimine	75	56	(2)

[a] Modified method. [b] Reddelien's method, see refs. (2) and (3).

of a one-molar stock solution of lithium aluminum hydride (0.025 mole) diluted with 200 ml. of absolute ether was refluxed in a 1-liter, three-necked flask equipped with a dropping funnel, a mercury-sealed stirrer, and a reflux condenser. A solution of 13 g. (0.05 mole) of *N*-phenylbenzhydrylidenimine in 100 ml. of absolute ether was added dropwise at a rate to maintain gentle refluxing. The addition required 20 min. and the solution was refluxed for an additional 30 min. During this time, the yellow color of the solution gradually faded and finally became nearly colorless. The complex formed and the excess of hydride were decomposed by careful addition of water with cooling of the flask in an ice bath. Through the top of the condenser, enough ordinary ether was added to compensate for the amount which had been entrained by the evolved hydrogen. This was followed by the addition of 100 ml. of 20% sodium potassium tartrate and 40 ml. of 10% sodium hydroxide, which caused most of the precipitate to dissolve. The contents of the flask were then transferred to a separatory funnel and the ether layer separated. After the ether solution had been dried over sodium hydroxide pellets, the ether was evaporated, leaving an oily residue which was fractionally distilled. The material that distilled at 178–182° under 2 mm. pressure was collected as a pale yellow oil. For isolation of the product in crystalline form, the oily mass was dissolved in 125 ml. of boiling absolute ethanol and the hot solution filtered. The filtrate was allowed to cool slowly, and then chilled at 0° for 24 hr. The precipitate which crystallized was collected and washed twice with 5-ml. portions of cold ethanol. The filtrate and washings were evaporated to a volume about one half that of the original filtrate, and a second crop of crystals was obtained upon cooling. The crude product weighed 10.6 g., and melted at 54–56°. Two recrystallizations from absolute ethanol gave 10.1 g. (77.1%) of colorless crystals, melting at 57°. The melting point agrees with that previously described.[11–13]

Acetyl derivatives of N-arylbenzhydrylamines and related compounds (Table IV). One gram of the amine and a four- to fivefold excess of acetic anhydride were mixed and heated under gentle reflux for 15 to 30 min. After being cooled, the reaction mixture was poured into 30–40 moles of cold water. The aqueous mixture was then neutralized by careful addition of solid sodium carbonate. The mixture was cooled, and the insoluble acetamide was collected, washed, and dried in a vacuum desiccator. Recrystallization was effected from water-ethanol mixtures or from cyclohexane-benzene mixtures.

Phenylurea derivatives of N-arylbenzhydrylamines and related compounds (Table VI). A slight excess of phenyl isocyanate was added to a solution of 1 or 2 g. of the amine in 10–20 ml. of petroleum ether (b.p. 90–120°). If the amine was only slightly soluble, heating was necessary to bring it into solution. The mixture was boiled at a gentle reflux for about 5 min., and then allowed to cool. When the precipitate did not form even after the wall of the container had been rubbed, the heating was repeated, two times if necessary. The solid product was collected and extracted with 10–20 ml. of boiling petroleum ether (b.p. 90–120°), and the solution was filtered and cooled. If the phenylurea did not crystallize, the filtrate was concentrated. The crystals were collected, dried, and the melting point determined. If the latter was not sharp, petroleum ether (b.p. 60–120°) or 95% of ethanol was used for recrystallization.

Hydrochlorides of N-arylbenzhydrylamines and related compounds (Table VII). The hydrochlorides were prepared by dissolving one gram of the amine in 15–30 ml. of absolute ether and passing dry hydrogen chloride through this solution for 5 to 15 min. The precipitate which formed was collected and dried over phosphorus pentoxide. The amine hydrochlorides were recrystallized from an ether-ethanol mixture. All of the salts obtained were white, solid, and nonhygroscopic. The yields in all cases were over 95%.

BLOOMINGTON, IND.

(11) W. Schlenk, J. Appenrodt, H. Michael, and A. Thal, *Ber.*, **47**, 473 (1914).
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(13) P. Grammaticakis, *Comp. rend.*, **210**, 716 (1940).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

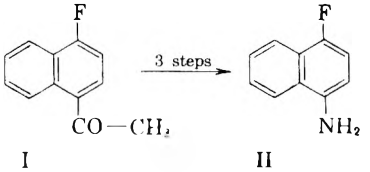
Some Nitrogen Derivatives of 1-Fluoronaphthalene

N. P. BUU-HOÏ, N. D. XUONG, AND V. Q. YEN

Received September 9, 1957

4-Fluoro-1-naphthylamine has been synthesized from 4-fluoro-1-acetonaphthone, and used for the preparation of a number of fluorinated *N*,*N'*-diarylthioureas of interest as potential antiviral agents. Various nitrogen-containing heterocyclic derivatives of 1-fluoronaphthalene have also been prepared from various 4-fluoro-1-acylnaphthalenes, for biological testing.

A number of aryl derivatives of thiourea bearing nuclear fluorine substituents, especially 4-chloro-4'-fluorothiocarbanilide, have been found to possess chemotherapeutic activity against influenza virus,[1] and these observations prompted the preparation of similar compounds derived from the 4-fluoro-1-naphthyl radical. 4-Fluoro-1-naphthylamine (II),

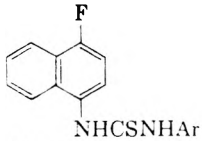


I II

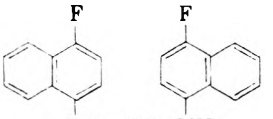
(1) N. P. Buu-Hoï, P. Gley, N. D. Xuong, and A. Bouffanais, *Compt. rend.*, **238**, 2582 (1954); N.P. Buu-Hoï, P. Gley, A. Bouffanais, N. D. Xuong, and N. H. Nam, *Experientia*, **12**, 73 (1956).

required for these syntheses, was prepared free from isomers by a Beckmann rearrangement of the oxime of 4-fluoro-1-acetonaphthone (I);[2] this, treated with phosphorus pentachloride in ether, furnished 4-fluoro-1-acetonaphthalide, which was subsequently submitted to acid hydrolysis. Amine II has previously been obtained in another way,[3] and in a less pure state.

Condensation of 4-fluoro-1-naphthylamine with aryl isothiocyanates yielded various *N*-aryl-*N'*-(4-fluoro-1-naphthyl)thioureas (III), and *N*,*N'*-bis(4-fluoro-1-naphthyl)thiourea (IV) was obtained by reaction between carbon disulfide and amine II.

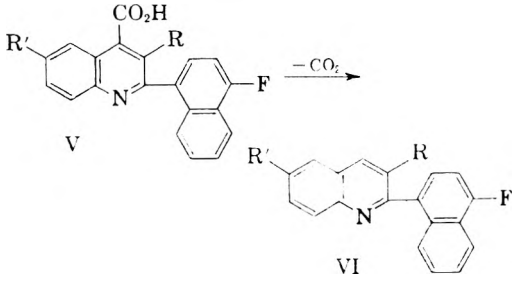


III



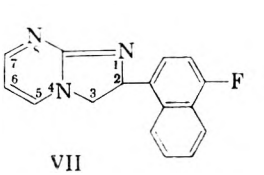
IV

For the preparation of a number of nitrogen-containing heterocyclic compounds bearing a 1-fluoronaphthyl radical, various 4-fluoro-1-acylnaphthalenes were used as intermediates. In the quinoline series, Pfitzinger reaction[4] of isatin and its 5-bromo- and 5-chloro- derivative on the one hand, and 4-fluoro-1-acetonaphthone, 4-fluoro-1-propionaphthone, and 4-fluoro-1-phenacetonaphthone on the other hand, readily afforded the corresponding 2-(4-fluoro-1-naphthyl)cinchoninic acids (V), listed in Table I; these underwent thermal de-

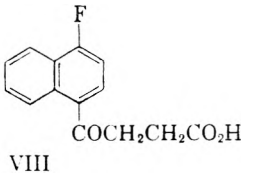


carboxylation to give the corresponding 2-(4-fluoro-1-naphthyl)quinolines (VI). Bromination of 4-fluoro-1-acetonaphthone yielded the liquid 4-fluoro-1-bromoacetonaphthone, along with the solid 4-fluoro-1-dibromoacetonaphthone.

The reaction of 4-fluoro-1-bromoacetonaphthone with 2-aminopyrimidine in ethanol resulted in 2-(4-fluoro-1-naphthyl)-8-azapyrimidazole (VII), following a reaction recently described by Buu-Hoï and Xuong,[5] and involving the tautomeric imino form of 2-aminopyrimidine. Compound VII bears



VII



VIII

a heterocyclic arrangement which resembles the purine nucleus, and is therefore of potential biological interest as a possible competitor of purines.

In the course of this work it was found that, contrary to what was expected, 4-fluoro-1-acetonaphthone and 4-fluoro-1-propionaphthone could not be reduced by the Kishner-Wolff method[6] to the corresponding fluoro hydrocarbons, and in both instances only high boiling products of unknown constitution were obtained; nor could β-(4-fluoro-1-naphthoyl)propionic acid (VIII), prepared in good yield by Friedel-Crafts succinoylation of 1-fluoronaphthalene, be satisfactorily reduced by the same method. This remarkable lability of the fluoro radical in these naphthalene derivatives is in contrast both with the stability of the chlorine group in similar reductions, and with the known possibility to reduce fluoro ketones in the benzene group.[7]

EXPERIMENTAL

4-Fluoro-1-acetonaphthone (I) and corresponding chalcones. The preparation of this ketone, b.p. 180–181°/30 mm., $n_D^{29.5}$ 1.6049, has already been reported.[2,8] The *piperonylidene derivative*, prepared by condensation of this ketone with piperonal in ethanol in the presence of aqueous sodium hydroxide, crystallized from ethanol in shiny yellowish prisms, m.p. 114°.

Anal. Calcd. for $C_{20}H_{13}FO_3$: C, 75.0; H, 4.1. Found: C, 75.1; H, 4.3.

The *2-methoxy-1-naphthylidene derivative*, similarly prepared from 2-methoxy-1-naphthaldehyde, crystallized from ethanol in pale yellow leaflets, m.p. 162°.

Anal. Calcd. for $C_{24}H_{17}FO_2$: C, 80.9; H, 4.8. Found: C, 80.6; H, 5.0.

4-Fluoro-1-propionaphthone. This ketone was prepared from 50 g. of 1-fluoronaphthalene, 35 g. of propionyl chloride, and 55 g. of aluminum chloride in 200 ml. of dry carbon disulfide, the mixture left for 24 hr., and then refluxed for 1 hr. on the water bath. After decomposition with ice and hydrochloric acid, the organic layer was washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. The yield was 56 g. of a pale yellow oil, b.p. 188°/18 mm., n_D^{32} 1.5895.

Anal. Calcd. for $C_{13}H_{11}FO$: C, 77.2; H, 5.4. Found: C, 77.3; H, 5.7.

4-Fluoro-1-phenacetonaphthone, prepared with phenacetyl chloride, crystallized from methanol in long colorless needles, m.p. 76°.

Anal. Calcd. for $C_{18}H_{13}FO$: C, 81.8; H, 4.9. Found: C, 82.0; H, 4.8.

Preparation of 4-fluoro-1-naphthylamine (II). *4-Fluoro-1-acetonaphthone oxime* (21 g.), prepared by refluxing for 12 hr. a solution of 28 g. of the ketone, 20 g. of hydroxylamine

(2) The structure of compound I had already been established by T. L. Jacobs, S. Winstein, J. W. Ralls, and J. H. Robson, *J. Org. Chem.*, 11, 27 (1946).

(3) G. Schiemann, W. Gueffroy, and W. Winkelmueller, *Ann.*, 487, 270 (1931).

(4) See N. P. Buu-Hoï, R. Royer, N. D. Xuong, and P. Jacquignon, *J. Org. Chem.*, 18, 1209 (1953).

(5) N. P. Buu-Hoï and N. D. Xuong, *Compt. rend.*, 243, 2090 (1956).

(6) Using the Huang-Minlon technique [*J. Am. Chem. Soc.*, 68, 2487 (1946)].

(7) N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *Rec. trav. chim.*, 71, 285 (1952).

(8) N. P. Buu-Hoï, N. D. Xuong, and R. Rips, *J. Org. Chem.*, 22, 193 (1957).

TABLE I

2-(4-FLUORO-1-NAPHTHYL)CINCHONINIC ACIDS (V)

Substituents	Formula	M.P., °C.	Analyses			
			Calcd.		Found	
			C	H	C	H
R = R′ = H	$C_{20}H_{12}FNO_2$	260	75.7	3.8	75.4	3.6
R = H; R′ = Cl	$C_{20}H_{11}ClFNO_2$	294	68.3	3.1	68.2	3.2
R = H; R′ = Br	$C_{20}H_{11}BrFNO_2$	>310	60.6	2.8	60.3	2.7
R = CH_3; R′ = H	$C_{21}H_{14}FNO_2$	306	76.2	4.2	75.9	4.1
R = CH_3; R′ = Cl	$C_{21}H_{13}ClFNO_2$	295	68.9	3.6	68.6	3.5
R = CH_3; R′ = Br	$C_{21}H_{13}BrFNO_2$	293	61.5	3.2	61.3	3.0

hydrochloride, and 18 g. of sodium hydroxide in aqueous ethanol, crystallized from ethanol in fine colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{12}H_{10}FNO$: N, 6.9. Found: N, 7.0.

The Beckmann rearrangement was effected by shaking a solution of 21 g. of the foregoing oxime in anhydrous ether with 30 g. of finely powdered phosphorus pentachloride. After treatment with water and evaporation of the ether, the crude *4-fluoro-1-acetonaphthalide* was directly hydrolyzed by refluxing its solution in ethanol for two hours with hydrochloric acid; after evaporation of the solvent, and basification with aqueous sodium hydroxide, the *4-fluoro-1-naphthylamine* obtained was taken up in ether and purified by vacuum-distillation. The yield was 14 g. of a product, b.p. 165°/15 mm., crystallizing from petroleum ether in colorless prisms, m.p. 57–58°.

Anal. Calcd. for $C_{10}H_8FN$: C, 74.5; H, 5.0. Found: C, 74.6; H, 5.3.

N,N′-Bis(4-fluoro-1-naphthyl)thiourea (IV). Prepared by refluxing a solution of the foregoing amine (2 moles) in ethanol with carbon disulfide (1.5 moles) in the presence of a small amount of sulfur, this compound crystallized from ethanol in shiny colorless prisms, m.p. 219°.

Anal. Calcd. for $C_{21}H_{14}F_2N_2S$: C, 69.3; H, 3.9. Found: C, 69.0; H, 3.7.

N-p-Fluorophenyl-N′-(4-fluoro-1-naphthyl)-thiourea. To a warm solution of 4-fluoro-1-naphthylamine (1 mole) in the minimum of ethanol, *p*-fluorophenyl isothiocyanate[9] (1 mole) was added with stirring, and the mixture was left to cool. The solid precipitate, obtained in almost quantitative yield, crystallized from ethanol in shiny colorless prisms, m.p. 184°.

Anal. Calcd. for $C_{17}H_{12}F_2N_2S$: C, 65.0; H, 3.8. Found: C, 64.7; H, 4.0.

N-p-Chlorophenyl-N′-(4-fluoro-1-naphthyl)-thiourea. Similarly prepared from *p*-chlorophenyl isothiocyanate, this thiourea crystallized from ethanol in colorless needles, m.p. 215°.

Anal. Calcd. for $C_{17}H_{12}ClFN_2S$: C, 61.8; H, 3.7. Found: C, 61.5; H, 3.8.

N-p-Bromophenyl-N′-(4-fluoro-1-naphthyl)thiourea. Prepared from *p*-bromophenyl isothiocyanate, this compound crystallized from ethanol in colorless needles, m.p. 219°.

Anal. Calcd. for $C_{17}H_{12}BrFN_2S$: C, 54.5; H, 3.2. Found: C, 54.4; H, 3.2.

N-p-Chlorophenyl-N′-(4-fluoro-1-naphthyl)urea. Prepared from 4-fluoro-1-naphthylamine (1 mole) and *p*-chlorophenyl isocyanate in benzene, this compound crystallized from that solvent in shiny colorless prisms, m.p. 280°.

Anal. Calcd. for $C_{17}H_{12}ClFN_2O$: C, 64.9; H, 3.8. Found: C, 64.6; H, 3.6.

Bromination of 4-fluoro-1-acetonaphthone. To a solution of 18 g. of ketone I in 30 ml. of dry chloroform, 16 g. of bromine (dissolved in 15 ml. of chloroform) was added portionwise with stirring, and the mixture was warmed at 50° for one hour on the water bath. After cooling, water was added, the chloroform layer was dried over sodium sulfate, and the solvent was distilled. The oily residue deposited 2 g. of *dibromo-4-fluoro-1-acetonaphthone*, which crystallized from ethanol in shiny colorless prisms, m.p. 83°.

Anal. Calcd. for $C_{12}H_7Br_2FO$: C, 41.6; H, 2.0. Found: C, 41.8; H, 2.2.

The residual yellow oil, consisting mainly of the crude 4-fluoro-1-bromoacetonaphthone, was directly used for the following syntheses.

2-(4-Fluoro-1-naphthyl)-8-azapyrimidazole (VII). A solution of 2 g. of 4-fluoro-1-bromoacetonaphthone and 1 g. of 2-aminopyrimidine in ethanol was refluxed for 12 hr. After evaporation of the solvent, the residue was basified with aqueous sodium carbonate, and the solid obtained was recrystallized from ethanol, giving colorless needles, m.p. 158°.

Anal. Calcd. for $C_{16}H_{10}FN_3$: C, 73.0; H, 3.8. Found: C, 72.9; H, 3.8.

β-(4-Fluoro-1-naphthoyl)propionic acid (VIII). To a solution of 200 g. of 1-fluoronaphthalene and 137 g. of succinic anhydride in 800 ml. of nitrobenzene, 200 g. of finely powdered aluminum chloride was added in portions with stirring, and the mixture was left for 24 hr. at room temperature. After decomposition with dilute hydrochloric acid, the nitrobenzene was removed by steam distillation; after cooling, the keto acid obtained was purified *via* the sodium salt, and recrystallized from benzene to yield 100 g. of fine colorless prisms, m.p. 135°.

Anal. Calcd. for $C_{14}H_{11}FO_3$: C, 68.3; H, 4.5. Found: C, 68.5; H, 4.8.

Pfitzinger reactions. These were effected by refluxing for 24 hr. a solution of isatin or one of its 5-halogenated derivatives (1 mole), the ketone (1 mole), and potassium hydroxide (3 moles) in ethanol (in sufficient quantity to make a 15% solution of potassium hydroxide). After evaporation of the ethanol, water was added, the neutral impurities removed by ether extraction, and the *cinchoninic acid* precipitated with acetic acid. Recrystallization was from ethanol or acetic acid, and the yields ranged from 60 to 80%. All the cinchoninic acids, which are listed in Table I, crystallized in yellowish prisms.

2-(4-Fluoro-1-naphthyl)quinoline (VI, R = R′ = H). Prepared by heating the corresponding cinchonic acid above its melting point, this base crystallized from ethanol in shiny colorless needles, m.p. 79°.

Anal. Calcd. for $C_{19}H_{12}FN$: N, 5.1. Found: N, 4.8.

The corresponding *picrate* crystallized from benzene in yellow prisms, m.p. 234°.

6-Chloro-2-(4-fluoro-1-napthyl)quinoline (VI, R = H, R′ = Cl). This quinoline crystallized from ethanol in fine colorless prisms, m.p. 132°.

Anal. Calcd. for $C_{19}H_{11}ClFN$: N, 4.6. Found: N, 4.5.

The compounds described in this paper are currently undergoing biological tests, and results will be published at a later date.

PARIS V[e], FRANCE

(9) N. P. Buu-Hoï, N. D. Xuong, and N. H. Nam, *J. Chem. Soc.*, 1573 (1955).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

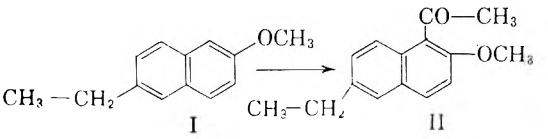
Reactivity of Some 6-Alkyl-2-naphthols and Their Ethers

N. P. BUU-HOÏ, DENISE LAVIT, AND JEANNINE COLLARD

Received September 9, 1957

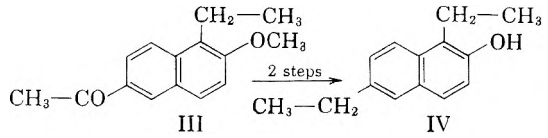
The Friedel-Crafts acetylation of 6-ethyl-2-methoxynaphthalene in nitrobenzene is shown to occur at position 1, proof being furnished by the identity of the naphthol prepared from the reaction product, with 1,6-diethyl-2-naphthol obtained from 6-acetyl-1-ethyl-2-methoxynaphthalene. Some other reactions of 6-alkyl-2-naphthols (Japp-Maitland condensation with phenylhydrazines) and their ethers (formylation) have been investigated.

It has been shown recently that the acyl group in the Friedel-Crafts acetylation of 1-alkyl-2-methoxynaphthalenes in nitrobenzene medium enters position 6.[1] It was of interest to investigate the orientation of similar acetylations in the case of 6-alkyl-2-methoxynaphthalenes. The starting material for this study was 6-ethyl-2-methoxynaphthalene (I), which reacted with acetyl chloride



I II

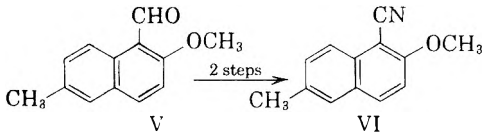
in nitrobenzene and in the presence of aluminum chloride to give a single ketone; this was 1-acetyl-6-ethyl-2-methoxynaphthalene (II), since in the course of a Wolff-Kishner reaction it underwent simultaneously reduction and demethylation, to give a small amount of 1,6-diethyl-2-naphthol (IV). The low yield in the last two operations is due to the fact that part of the ketone underwent alkaline hydrolysis to 6-ethyl-2-naphthol. The structure of naphthol IV was established by its identity with the demethylation product of 1,6-diethyl-2-methoxynaphthalene, prepared in excellent yields by Wolff-Kishner reduction of 6-acetyl-1-ethyl-2-methoxynaphthalene (III), this last ketone being obtained as a single product from the Friedel-Crafts acetylation of 1-ethyl-2-methoxynaphthalene.



III IV

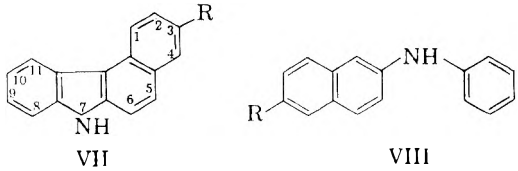
These results, together with others previously recorded,[1] establish positions 1 and 6 as the most reactive in the molecule of 2-methoxynaphthalene, while the main sites of Friedel-Crafts substitution in the molecule of 2-methylnaphthalene are positions 6 and 8;[2] it is also worth mentioning that 2-acetnaphthalide is acetylated in positions 6 and 8.[3]

The excellent yields of 2-methoxy-6-methyl-1-naphthaldehyde (V), obtained from the formylation of 2-methoxy-6-methylnaphthalene,[1] were



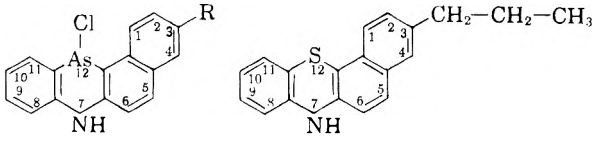
V VI

further proof of the high reactivity of position 1 in 6-alkyl-2-methoxynaphthalenes. Dehydration of the oxime of V afforded 2-methoxy-6-methyl-1-naphthonitrile (VI). Further reactions were performed with 6-alkyl-2-naphthols, to show the greater reactivity of position 1 than in the case of 2-naphthol itself. Thus, the Japp-Maitland condensation[4] of 6-alkyl-2-naphthols with phenylhydrazine gave good yields of 3-alkyl-7*H*-benzo[*c*]carbazoles (VII), in contrast with the low yields known with 2-naphthol; also, the Wieland-Rheinheimer condensation[5] of 6-alkyl-2-(phenylamino)-naphthalenes (VIII) with arsenic trichloride, to give the 3-alkyl-12-chloro-7,12-dihydrobenzo[*a*]-phenarsazines (IX), was easier than in the case of



VII VIII

2-*N*-phenylnaphthylamine. Similarly, 6-propyl-2-(phenylamino)naphthalene reacted readily with sulfur in the presence of iodine[6] to give an almost theoretical yield of 3-propyl-7*H*-benzo[*c*]pheno-



IX X

thiazine (X); this compound is of practical interest in view of its pronounced antioxidant properties and its ready solubility in fats.

(1) N. P. Buu-Hoï and D. Lavit, *J. Org. Chem.*, **22**, 912 (1957).

(2) G. A. R. Kon and W. T. Weller, *J. Chem. Soc.*, 792 (1939).

(3) N. Leonard and A. M. Hyson, *J. Am. Chem. Soc.*, **71**, 1392 (1949).

(4) F. R. Japp and W. Maitland, *J. Chem. Soc.*, **83**, 267 (1903).

(5) H. Wieland and W. Rheinheimer, *Ann.*, **423**, 1 (1921).

(6) E. Knoevenagel, *J. prakt. Chem.*, **89**, 15 (1914).

In the course of this work, it was found that 6-acetyl-1-ethyl-2-methoxynaphthalene (III) readily undergoes a Pfitzinger reaction with isatin to give 2-(1-ethyl-2-methoxy-6-naphthyl)cinchoninic acid; this gave on thermal decarboxylation, 2-(1-ethyl-2-methoxy-6-naphthyl)quinoline.

EXPERIMENTAL

1-Acetyl-6-ethyl-2-methoxynaphthalene (II). To a water-cooled, well stirred solution of 50 g. of 6-ethyl-2-methoxynaphthalene and 23.2 g. of acetyl chloride in 500 ml. of nitrobenzene, 39.5 g. of finely powdered aluminum chloride was added in small portions, and the mixture left overnight at room temperature. After decomposition with dilute hydrochloric acid, the nitrobenzene was removed by steam distillation, and the reaction product taken up in benzene. The benzene solution was then washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-distilled to yield 45 g. (73%) of a ketone, b.p. 207°/20 mm., crystallizing from petroleum ether in lustrous colorless leaflets, m.p. 70°; no isomeric ketone was found in the mother liquors.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.9; H, 7.3.

1-Ethyl-2-methoxynaphthalene. A solution of 64.7 g. of 1-acetyl-2-methoxynaphthalene, 32 g. of 95% hydrazine hydrate, and 30 g. of potassium hydroxide in 250 ml. of diethylene glycol was refluxed for 2.5 hr. with removal of water; after cooling, water was added, the impurities extracted in benzene, and the aqueous layer acidified with hydrochloric acid. The precipitate obtained was taken up in chloroform, the chloroform solution was washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-distilled to yield 32 g. (58%) of 1-ethyl-2-naphthol, m.p. 105°, b.p. 184–185°/17 mm. This naphthol was methylated with methyl sulfate (27 g.) and potassium hydroxide (11 g.), to give 29.4 g. of 1-ethyl-2-methoxynaphthalene, b.p. 160°/20 mm., which solidified to colorless needles, m.p. 47°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.8; H, 7.6. Found: C, 84.0; H, 7.5.

The preparation of 1-ethyl-2-naphthol was found much more convenient by this method than by those reported in the literature,[7] as 1-acetyl-2-methoxynaphthalene could be readily obtained by Friedel-Crafts acetylation of neroline, along with some of the 6-acetyl isomer; during the Kishner-Wolff reaction, this last ketone is reduced with no significant demethylation, and the 6-ethyl-2-methoxynaphthalene thus formed is easily eliminated by the benzene extraction.

6-Acetyl-1-ethyl-2-methoxynaphthalene (III). A solution of 27 g. of 1-ethyl-2-methoxynaphthalene and 12.5 g. of acetyl chloride in 100 ml. of nitrobenzene was treated with 21.3 g. of aluminum chloride in the usual way to yield 25 g. (75%) of a ketone, b.p. 215–216°/15 mm., crystallizing from ethanol in long colorless needles, m.p. 88°; here again, no isomer was found in the mother liquors.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.8; H, 7.1.

2-(1-Ethyl-2-methoxy-6-naphthyl)cinchoninic acid. A solution of 2 g. of the foregoing ketone, 1.4 g. of isatin, and 1.5 g. of potassium hydroxide in 20 ml. of ethanol was gently refluxed for 24 hr., the ethanol was distilled off in a vacuum, and the residue treated with water; after ether-extraction of the neutral impurities, the aqueous layer was acidified with acetic acid, and the precipitate was recrystallized from ethanol, giving 2.5 g. (80%) of fine yellowish needles, m.p. 248°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.3; H, 5.4. Found: C, 77.0; H, 5.3.

(7) K. Fries and H. Engel, *Ann.*, **439**, 232 (1924).

2-(1-Ethyl-2-methoxy-6-naphthyl)quinoline, prepared by heating the foregoing cinchoninic acid above its melting point, and purified by vacuum-distillation, crystallized from ethanol in shiny yellowish leaflets, m.p. 148°.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1. Found: C, 84.2; H, 6.2.

The picrate of this base crystallized from benzene in fine orange-yellow prisms, m.p. 235°.

1,6-Diethyl-2-naphthol (IV). 1,6-Diethyl-2-methoxynaphthalene was prepared by reduction of 20 g. of ketone III with 19 g. of 95% hydrazine hydrate and 16 g. of potassium hydroxide in 120 ml. of diethyl glycol. The yield was 14.5 g. (77%) of a pale yellow oil, b.p. 183°/18 mm., n_D^{25} 1.6100.

Anal. Calcd. for $C_{16}H_{18}O$: C, 88.2; H, 4.0. Found: C, 88.0; H, 4.2.

A mixture of 13 g. of this ether and 39 g. of redistilled pyridine hydrochloride was refluxed for 1 hr.; on cooling, water was added, and the demethylation product was taken up in chloroform. The chloroform solution was washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, the solvent removed, and the residue was vacuum-fractionated to yield 9.5 g. of 1,6-diethyl-2-naphthol, b.p. 189–191°/20 mm., crystallizing from petroleum ether in shiny colorless needles, m.p. 75°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: C, 83.7; H, 8.4.

The same product was obtained, in poorer yield (10%) in the reduction of 1-acetyl-6-ethyl-2-methoxynaphthalene (accompanied by demethylation) together with some 6-ethyl-2-naphthol (m.p. 98°).

2-Methoxy-6-methyl-1-naphthaldehyde (V). Fifty grams of the methyl ether of 6-methyl-2-naphthol,[8] 50.5 g. of *N*-methylformanilide, and 60 g. of phosphorus oxychloride was refluxed for 5 hr. on a water bath; after cooling, a concentrated aqueous solution of sodium acetate was added, and the mixture refluxed for 30 min. more. The reaction product was taken up in benzene, washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. The yield was 50 g. (86%) of an aldehyde, b.p. 228–229°/30 mm., crystallizing from petroleum ether in shiny colorless leaflets, m.p. 72°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0. Found: C, 77.9; H, 6.0.

The corresponding semicarbazone crystallized from ethanol in shiny colorless needles, m.p. 244°. The *oxime* crystallized from ethanol in shiny colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{13}H_{13}NO_2$: N, 6.5. Found: N, 6.4.

2-Methoxy-6-methyl-1-naphthonitrile (VI). Dehydration of 2.6 g. of the foregoing oxime was effected by shaking its ether solution with 3 g. of finely powdered phosphorus pentachloride; the ether layer was decanted, washed with aqueous sodium carbonate, then with water, and dried over sodium sulfate. The residue from evaporation of the solvent was recrystallized from cyclohexane, giving 1.9 g. (80%) of silky colorless needles, m.p. 100°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.2; H, 5.6. Found: C, 79.0; H, 5.5.

3-Propyl-7H-benzo[c]carbazole (VII; R = *n*-C_3H_7). A mixture of 4 g. of 6-propyl-2-naphthol, 4 g. of phenylhydrazine, and 4 g. of phenylhydrazine hydrochloride was cautiously refluxed for 1 hr.; after cooling, dilute aqueous sodium hydroxide was added, and the reaction product taken up in toluene. The toluene layer was washed with water and dried over sodium sulfate, the solvent was removed, and the residue vacuum-fractionated. The portion boiling at 280–305°/17 mm. (4 g., 72%) was recrystallized from cyclohexane, giving lustrous colorless leaflets, m.p. 127°. This substance crystallized with solvent, which was eliminated only at 115°.

(8) K. Dziewonski, J. Schoenowna, and E. Waldmann, *Ber.*, **58**, 1211 (1925).

Anal. Calcd. for $C_{19}H_{17}N$: C, 88.0; H, 6.6. Found: C, 88.2; H, 6.9.

This carbazole gave with tetrachlorophthalic anhydride an orange addition-product, crystallizing from acetic acid in fine orange needles; with picric acid, a picrate was formed, which crystallized from ethanol in fine brown red needles, m.p. 162°.

3-Butyl-7H-benzo[c]carbazole (VII; R = *n*-C_4H_9). Similarly prepared from 4 g. of 6-butyl-2-naphthol, this carbazole (3.5 g., 64%) crystallized from cyclohexane in lustrous colorless leaflets, m.p. 127°; the crystals were solvated, and the solvent was given off above 115°.

Anal. Calcd. for $C_{20}H_{19}N$: C, 87.9; H, 7.0. Found: C, 88.1; H, 7.0.

The corresponding picrate crystallized from ethanol in brown red needles, m.p. 168–169°; the addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in shiny orange prisms, m.p. 165–166°.

3-Propyl-12-chloro-7,12-dihydrobenzo[a]phenarsazine (IX; R = *n*-C_3H_7). 6-Propyl-2-(phenylamino)naphthalene (VIII; R = *n*-C_3H_7), previously described as a viscous oil,[9] was now obtained as a solid, m.p. 75°. A solution of 2.6 g. of this diarylamine in 5 ml. of *o*-dichlorobenzene was gently heated with 1.1 g. of arsenic trichloride until a vigorous reaction set up, then refluxed for 3 min.; cyclohexane was then added, and the solid obtained in 85% yield was filtered off and recrystallized from toluene, giving shiny deep yellow leaflets, m.p. 217–218°.

Anal. Calcd. for $C_{19}H_{17}AsClN$: C, 61.7; H, 3.8. Found: C, 61.4; H, 3.6.

3-Methyl-10-phenyl-12-chloro-7,12-dihydrobenzo[a]phenarsazine. 6-Methyl-2-(p-xenylamino)naphthalene was prepared by heating for 24 hr. a mixture of 3 g. of 6-methyl-2-naphthol, 4 g. of *p*-aminobiphenyl, and 0.1 g. of iodine;[10] the reaction product was taken up in benzene, the benzene solution washed with aqueous sodium hydroxide, then with water, dried over sodium sulfate, the solvent removed, and the residue recrystallized from ethanol, giving shiny colorless needles, m.p. 170°. The yield was 1.6 g. (27.5%).

Anal. Calcd. for $C_{23}H_{19}N$: C, 89.3; H, 6.2. Found: C, 89.2; H, 6.2.

Condensation of this amine (3.1 g.) with arsenic trichloride (1.1 g.) in *o*-dichlorobenzene was almost instantaneous, and gave a 90% yield of the phenarsazine, which crystallized from *o*-dichlorobenzene in shiny deep yellow prisms, melting with decomposition at 268°, and giving a deep blue coloration in sulfuric acid.

Anal. Calcd. for $C_{23}H_{17}AsClN$: C, 66.1; H, 3.4. Found: C, 65.8; H, 3.1.

3-Propyl-7H-benzo[c]phenothiazine (X). A mixture of 2.6 g. of 6-propyl-2-(phenylamino)naphthalene and 0.64 g. of sulfur was heated with 0.02 g. of iodine until a vigorous reaction set up, then kept at 150–160° for 2 min.; the reaction product gave on recrystallization from cyclohexane, 2.1 g. (72%) of pale yellow needles, m.p. 143–144°, giving a deep blue coloration in sulfuric acid.

Anal. Calcd. for $C_{19}H_{17}NS$: C, 78.3; H, 5.9. Found: C, 78.2; H, 6.2.

6-Butyl-2-(phenylamino)naphthalene (VIII; R = *n*-C_4H_9). This amine, prepared in the usual way from 3 g. of 6-butyl-2-naphthol, 2 g. of aniline, and 0.05 g. of iodine, boiled at 277–279°/20 mm., and crystallized from petroleum ether in shiny needles, m.p. 60°. Yield: 2 g. (48%).

Anal. Calcd. for $C_{20}H_{21}N$: C, 87.2; H, 7.7. Found: C, 87.1; H, 8.0.

PARIS Ve, FRANCE

(9) N. P. Buu-Hoï, R. Royer, B. Eckert, and P. Jacquignon, *J. Chem. Soc.*, 4867 (1952).

(10) See N. P. Buu-Hoï, *J. Chem. Soc.*, 4346 (1952).

[CONTRIBUTION FROM THE MELLON INSTITUTE]

Preparation of Vinylphenols and Isopropenylphenols

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Directions for the preparation of five alkenylphenols are reported.

Five alkenylphenols were prepared for evaluation as monomers—*o*-vinylphenol, *m*-vinylphenol, *p*-vinylphenol, *m*-isopropenylphenol, and *p*-isopropenylphenol. Of these alkenylphenols, *o*-vinylphenol and *p*-vinylphenol are the most accessible. Five preparative methods were employed: (*a*) decarboxylation of *o*-coumaric acid for *o*-vinylphenol; (*b*) dehydrogenation of *m*- and *p*-ethylphenols for *m*- and *p*-vinylphenols, dehydrogenation of *m*- and *p*-isopropylphenols for *m*- and *p*-isopropenylphenols; (*c*) hydrogenation of *p*-acetoxyacetophenone followed by dehydration-hydrolysis for *p*-vinylphenol; (*d*) cracking of 2,2-bis(*p*-hydroxyphenyl)propane and 2,2-bis(*p*-acetoxyphenyl) propane for *p*-isopropenylphenol; (*e*) depolymerization of poly-*p*-isopropenylphenol for *p*-isopropenylphenol.

o-Vinylphenol has usually been prepared by the decarboxylation of *o*-coumaric acid.[1–7] It has also been prepared from salicylaldehyde *via* the Grignard reaction[8] and by the pyrolysis of 2,4-dimethyl-1,3-benzodioxane.[9] Our starting material was *o*-coumaric acid. We confirmed the findings of

(1) K. Fries and G. Fickewirth, *Ber.*, **41**, 367 (1908).

(2) K. Auwers, *Ann.*, **413**, 253 (1917).

(3) H. Kunz-Krause, *Arch. Pharm.*, **236**, 542 (1898); *Chem. Zentr.*, II, 973 (1898).

(4) H. Kunz-Krause and P. Manicke, *Arch. Pharm.*, **267**, 555 (1929).

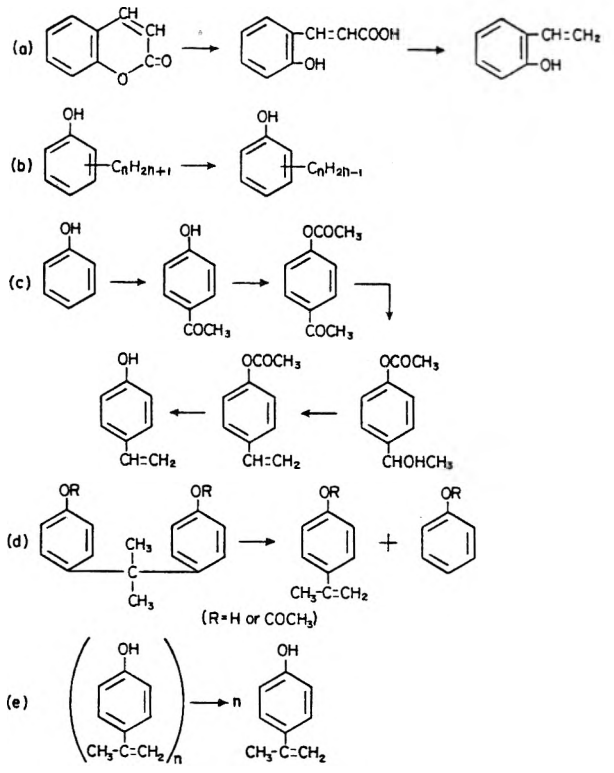
(5) C. S. Marvel and N. S. Rao, *J. Poly. Sci.*, **4**, 703 (1949).

(6) A. R. Bader, *J. Am. Chem. Soc.*, **77**, 4155 (1955).

(7) W. J. Dale and H. E. Hennis, Atlantic City A.C.S. Meeting, 1956.

(8) P. Hoering and F. Baum, Ger. patent 208,886 (1907).

(9) E. Adler, H. Euler, and G. Gie, *Arkiv. Kemi, Mineral., Geol.*, 16A, No. 12, 1 (1943).



Bader[6] and Williams, Borden, and Laakso[10] that *o*-vinylphenol is not obtainable by following the directions of Smith and Niederl[11] (reaction of phenol with ethylene oxide or ethylene chlorohydrin) nor those of Niederl, Smith, and McGreal[12] (reaction of vinyl acetate with phenol). Other fruitless attempts included the alkenylation of phenol with vinyl chloride and the rearrangement of vinyl phenyl ether.

The yield of *o*-vinylphenol by the thermal decarboxylation of *o*-coumaric acid was 61%. Numerous attempts to improve the yield by catalysis failed. For example: (*a*) mixtures of *o*-coumaric acid in pyridine and quinoline were passed over copperized pumice at 200 to 300° at 15 mm. and 740 mm.; (*b*) quinoline solutions of *o*-coumaric acid containing soluble metal naphthenates (copper, cobalt, and manganese) were passed through a tube at 238°; (*c*) quinaldine and 2,4,6-collidine solutions of *o*-coumaric acid were distilled at atmospheric pressure in the presence of copper powder.

o-Vinylphenol is relatively stable on storage. Its purity fell from 100 to 76% in 257 hr. under laboratory conditions of temperature and illumination, and from 100 to 89% in 2015 hr. at −5° in the dark.

m-Vinylphenol has been prepared from *m*-aminostyrene *via* diazotization by Komppa,[13] Dahlig,[14] and Matsui;[15] by cracking several *m*-alkyl-substituted phenols according to the patent literature;[16] and recently by Dale and Hennis[7] from *m*-hydroxybenzaldehyde *via* the Grignard reaction.

We prepared *m*-vinylphenol by the dehydrogenation of *m*-ethylphenol. With chromia-alumina catalyst the maximum yields of *m*-vinylphenol were 42% per pass and 68% ultimate, obtained at 600°. With 1707 dehydrogenation catalyst[17] the maximum yields were 11% per pass and 48% ultimate, obtained at 525°. The dehydrogenation yield is satisfactory but it is difficult to separate *m*-vinylphenol from the catalyzate by distillation because of loss due to polymerization. Acetylation of the dehydrogenation catalyzate prior to distillation did not eliminate this difficulty.

p-Vinylphenol has been obtained by Schmid and Karrer[18] in small amount from poppy straw and in trace yield by the decarboxylation of *p*-hydroxycinnamic acid. Recently it was made by Dale and Hennis[7] *via* the decarboxylation of the benzoate of *p*-hydroxycinnamic acid. Schmid and Karrer showed the alleged preparation of *p*-vinylphenol *via* diazotization by Miller and Kinkelin[19] to be inoperative.

We prepared *p*-vinylphenol from phenol in 53% yield by a five-step process: (1) acetylation of phenol to *p*-hydroxyacetophenone, (*2*) acetylation of the latter to *p*-acetoxyacetophenone, (*3*) hydrogenation of the ketone to *p*-acetoxyphenylmethylcarbinol, (*4*) dehydration of the carbinol to *p*-acetoxystyrene, (*5*) saponification of *p*-acetoxystyrene to *p*-vinylphenol.

p-Acetoxystyrene, the immediate precursor of *p*-vinylphenol, has good storage stability. Storage for 4 months under laboratory conditions lowered its freezing point from 7.19 to 6.99° which corresponds to a fall in purity from 97.8 to 97.2 mole %. The conversion of *p*-acetoxystyrene to *p*-vinylphenol is quantitative and the conditions of hydrolysis are so gentle that the sensitive *p*-vinylphenol requires no purification.

We also prepared *p*-vinylphenol by the dehydrogenation of *p*-ethylphenol over chromia-alumina catalyst at 600°. Only one experiment was made; the yield of *p*-vinylphenol was 15%.

m-Isopropenylphenol has been prepared by Auwers[2] from ethyl *m*-hydroxybenzoate *via* the Grignard reaction. We prepared it by the dehydrogenation of *m*-isopropylphenol. With 1707 catalyst

(10) J. L. R. Williams, D. G. Borden, and T. M. Laakso, *J. Org. Chem.*, **21**, 1461 (1956).

(11) R. A. Smith and J. B. Niederl, *J. Am. Chem. Soc.*, **53**, 806 (1931).

(12) J. B. Niederl, R. A. Smith, and M. E. McGreal, *J. Am. Chem. Soc.*, **53**, 3390 (1931).

(13) G. Komppa, *Ber.*, **26**, Ref., 677 (1893).

(14) W. Dahlig, *Prace Placówek Nauk-Badawczych. Ministerstwa Przemysłu Chem.*, **1**, 29 (1952).

(15) E. Matsui, *J. Soc. Chem. Ind. Japan*, **46**, Suppl. binding, 125 (1943).

(16) J. E. S. Whitney and E. M. Evans, Brit. patent 669,074 (1952).

(17) K. Kearby, U. S. patent 2,395,875 (1946).

(18) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **28**, 722 (1945).

(19) W. Miller and F. Kinkelin, *Ber.*, **22**, 1705 (1889).

TABLE I

DEHYDROGENATION OF ALKYLPHENOLS
(12-HR. RUNS)

Alkylphenol	*m*-Ethylphenol		*p*-Ethylphenol	*m*-Isopropylphenol	*p*-Isopropylphenol	
Conditions						
Catalyst[a]	1707	Cr_2O_3-Al_2O_3	Cr_2O_3-Al_2O_3	1707	1707	Cr_2O_3-Al_2O_3
Water rate, ml./hr.	52	48	48	52	52	48
Alkylphenol rate, ml./hr.	36	32	32	40	40	36
Temperature, °C.	525	600	600	525	525	600
Products, wt. % of charge						
Light ends[b]	1	2	—	1	3	7
Recovered alkylphenol	77	39	—	75	62	25
Alkenylphenol (purity, %)[c]	11 (95)	43 (95)	15 (95)	17 (95)	28 (90)	52 (80)
Residue[d]	11	16	—	7	7	16
Alkenylphenol yield, wt. %						
Per pass	11	42	15	16	25	43
Ultimate	48	68	—	69	64	56

[a] 100 ml. of $1/8 \times 1/8$-inch pellets. [b] Includes gaseous products and material distilling below starting alkylphenol. [c] Purity determined by analytical hydrogenation. [d] Includes high boiling liquid products and carbonaceous deposit on catalyst.

the maximum yields were 17% per pass and 69% ultimate, obtained at 525°. Auwers' product was a liquid; we were able to obtain crystalline *m*-isopropenylphenol.

p-Isopropenylphenol has not previously been reported in the scientific literature. We prepared it by the dehydrogenation of *p*-isopropylphenol. With chromia-alumina catalyst the maximum yields were 43% per pass and 56% ultimate, obtained at 600°. With 1707 catalyst the maximum yields were 25% per pass and 64% ultimate, obtained at 525°. We also prepared *p*-isopropenylphenol by both thermal and catalytic cracking of 2,2-bis(*p*-hydroxyphenyl)propane[20] and its diacetate.

p-Isopropenylphenol polymerizes slowly on storage. At −5° in the dark its purity fell from 100 to 87% in 3000 hr., whereas under laboratory conditions of temperature and illumination it fell from 100 to 25% in 3000 hr. *p*-Isopropenylphenol polymer can be depolymerized thermally.

EXPERIMENTAL

All melting points and freezing points are corrected; the latter were determined by extrapolation of freezing curves, temperature being measured by a certified platinum resistance thermometer and G-2 Mueller bridge. Purities were estimated from the shapes of the freezing curves. Boiling points are uncorrected.

Catalysts. The chromia-alumina (15% Cr_2O_3-85% Al_2O_3), activated alumina, nickel-kieselguhr (65% Ni-35% SiO_2), and copper chromite catalysts were purchased from the Harshaw Chemical Co. "Solid phosphoric acid" was the Universal Oil Products catalyst No. 2. Super Filtrol was obtained from the Filtrol Corp., and the 1707 catalyst[17] (72.4% MgO—18.4% Fe_2O_3—4.6% CuO—4.6% K_2O) from the Standard Oil Development Co. of New Jersey.

Alkylphenols. m-Ethylphenol (b.p. 112–114°/20 mm., m.p. −3.4°) and *p*-ethylphenol (b.p. 112–114°/20 mm., m.p. 47.0°) were purchased from the Reilly Tar and Chemical Co. *m*-Isopropylphenol (b.p. 121–122°/20 mm., m.p. 25.6°) and *p*-isopropylphenol (b.p. 121–122°/20 mm., m.p. 62.6°) were obtained from Koppers Co., Inc.

Dehydrogenation apparatus and procedure. The apparatus and procedure employed have been described.[21] The separate alkylphenols were dehydrogenated (Table I) at atmospheric pressure in the presence of about 10 moles of diluent steam per mole of alkylphenol, water and alkylphenol being delivered separately by micro bellows pumps to the preheater section of the vertical reactor whence the gasified mixture passed down through the catalyst bed. The catalyzates were collected in an ice-cooled receiver. The *m*-ethyl-, *m*-isopropyl-, and *p*-isopropylphenol catalyzates were distilled at 20 mm. through a 27-plate column at 5/1 reflux ratio. Fractions were collected as follows: *m*-ethylphenol, b.p. 100–116°; *m*-vinylphenol, b.p. 116–123°; *m*-isopropylphenol, b.p. 118–125°; *m*-isopropenylphenol, b.p. 125–160°; *p*-isopropylphenol, b.p. 118–125°; *p*-isopropenylphenol, b.p. 125–160°. The *p*-ethylphenol catalyzate was not distilled; *p*-vinylphenol was isolated from it by crystallization. The other alkenylphenols were purified by redistillation and/or crystallization.

Analysis and proof of structure of alkenylphenols. Approximate purities (±3%) were determined by analytical hydrogenation of 1.5-g. samples of alkenylphenols in 100 ml. of methanol in the presence of 0.08 g. of Adams' platinum catalyst at room temperature and pressure. Proof of structure of the alkenylphenols was accomplished by mixture melting point comparisons of hydrogenated derivatives with authentic specimens.

o-Coumaric acid. To a solution of 143 g. (6.2 g.-atoms) of sodium in 2180 ml. of ethanol was added 450 g. (3.1 moles) of coumarin and the solution was refluxed for 3 hr. The solution was diluted with 2 l. of water and distilled to remove 2 l. of distillate. The residue was diluted with 2 l. of water and 800 ml. of distillate was removed. The residual liquid was stirred at 85° with 25 g. of activated carbon for 0.5 hr. and filtered. To the cooled filtrate (40°) was added 1 l. of benzene and the stirred mixture was acidified with 620 ml. (7.3 moles) of concentrated hydrochloric acid, stirring being continued for 0.5 hr. The mixture was filtered and the filter cake was washed with two 500-ml. portions of water followed by two 150-ml. portions of benzene. The weight of the air-dried *o*-coumaric acid was 425 g. [84% yield, 93–95% pure by electrometric titration, m.p. 205–206° (dec.);

(20) Schering-Kahlbaum, Fr. patent 657,122 (1928); U. S. Patent 1,798,813 (1931).

(21) J. E. Nickels, G. A. Webb, W. J. Heintzelman, and B. B. Corson, *Ind. Eng. Chem.*, 41, 563 (1949).

lit. m.p. 190°,[22a] 207–208°[22b]]. This preparative method is a modification of that of Reychler.[23]

A sample of *o*-coumaric acid, air-dried after 3 crystallizations from water, analyzed 99.4% pure by electrometric titration. Air-dried *o*-coumaric acid, therefore, does not contain water of crystallization, contrary to the report of Kuntz-Krause and Manicke.[4]

o-Vinylphenol by thermal decarboxylation of o-coumaric acid. *o*-Coumaric acid prepared by the preceding directions gave a low yield of *o*-vinylphenol, presumably because of its fluffiness and the resultant low heat transfer rate. The yield was improved by using a dense variety of acid obtained by slow evaporation of an acetone solution or by reprecipitation from its sodium salt with concentrated hydrochloric acid.

Dense *o*-coumaric acid (100 g., 0.61 mole) in a 500-ml. flask connected *via* an air condenser to a 500-ml. ice-cooled receiver containing 250 g. of 25% aqueous sodium hydroxide (1.6 moles) was heated in an oil bath to 260°/15 mm. until distillate no longer came over (1 hr.). In the decarboxylation flask there remained 14 g. of polymeric residue and 10 g. of *o*-coumaric acid sublimate. The pyrolyzate, diluted with 750 ml. of cold water, was extracted with ether to remove 3 g. of viscous oil. The stirred alkaline solution was acidified at 0–5° with gaseous carbon dioxide to *p*H 8 and extracted with ether. The extract was concentrated under reduced pressure and the residue evacuated at 35°/2 mm. for 1 hr. to yield 46.5 g. of *o*-vinylphenol (61% per pass, 68% ultimate).

o-Vinylphenol by catalytic decarboxylation of o-coumaric acid. (*a*) Copperized pumice containing 6% of copper was prepared as follows: 4–8 mesh pumice was soaked in hot saturated copper sulfate solution and the impregnated pumice was drained, dried at 110°, and reduced in a stream of hydrogen for 6 hr. at 300°. A quinoline (200 g.) solution of o-coumaric acid (50 g.) was passed (150 ml./hr.) down through a 50-ml. bed of copperized pumice under nitrogen at 250°. The catalyzate, diluted with an equal volume of ether, was acidified with cold 6*N* hydrochloric acid. The ether layer was extracted with cold 5% aqueous sodium hydroxide and the extract acidified with carbon dioxide to yield 16 g. (44%) of *o*-vinylphenol. When Pyrex beads were substituted for copperized pumice the yield of *o*-vinylphenol was the same.

(*b*) A solution containing 50 g. of *o*-coumaric acid, 200 g. of quinoline, and 5 g. of copper naphthenate was passed (160 ml./hr.) down a glass spiral path (125-cm. long) at 238° under nitrogen. The yield of *o*-vinylphenol was 18.5 g. (51%). Experiments in which copper naphthenate was replaced by cobalt and manganese naphthenates gave similar yields of *o*-vinylphenol.

(*c*) A mixture of 78 g. of *o*-coumaric acid, 102 g. of quinaldine, and 14 g. of copper powder was heated to 250°; the yield of *o*-vinylphenol was 20 g. (36%). When 2,4,6-collidine was substituted for quinaldine the yield of *o*-vinylphenol was 27 g. (47%).

Recovery of o-vinylphenol by selective springing. A 100-g. composite of crudes containing about 30% of *o*-vinylphenol was extracted with 10% aqueous sodium hydroxide and the extract was washed with ether. The stirred alkaline solution was acidified with carbon dioxide at 0–5° and extracted with ether. Concentration of the ether extract yielded 20 g. of *o*-vinylphenol (yellow oil which solidified, m.p. 23–24°). Reaction of this solid with monochloroacetic acid yielded *o*-vinylphenoxyacetic acid; melting point and mixture melting point with an authentic specimen 136.5–137.5° (lit. m.p. 137°[1]).

Purification of o-vinylphenol by equilibrium melting. A 510-g. sample of *o*-vinylphenol (m.p. about 24°) was frozen, then allowed to melt and drain at 28° to the extent of 50%. The residual solid was held at 28°/1 mm. for 4 hr., then flash-distilled through a continuous unit at 165°/15 mm. The constants of the distillate were: f.p. 26.0° (lit. m.p. 29°[1,2]), n_D^{20} 1.5850 (lit. n_D^{20} 1.584[2], $n_D^{27.5}$ 1.5783[5]), d_4^{20} 1.0607 (lit. d_4^{20} 1.060,[2] $d_4^{25.5}$ 1.0293[5]).

o-Vinylphenyl N-phenylcarbamate. White needles from carbon tetrachloride, m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{13}NO_2$: N, 5.85. Found: N, 5.91.

The identity of this urethane was established by hydrogenation to *o*-ethylphenyl *N*-phenylcarbamate; melting point and mixture melting point with an authentic specimen 144–145° (lit. m.p. 141°[24]).

o-Vinylphenyl N-(α-naphthyl)carbamate. White fluffy powder from carbon tetrachloride, m.p. 146–147°.

Anal. Calcd. for $C_{19}H_{15}NO_2$: N, 4.84. Found: N, 4.80.

m-Vinylphenol by dehydrogenation of m-ethylphenol. Redistillation of the crude *m*-vinylphenol fraction gave a heart cut boiling at 120°/20 mm. (lit. b.p. 114–116°/16–17 mm.[13]); n_D^{25} 1.5770, d_4^{25} 1.0459, m.p. 0.5 to 1.0°. Hydrogenation of *m*-vinylphenol yielded *m*-ethylphenol which was identified by converting it to *m*-ethylphenyl *N*-phenylcarbamate; melting point and mixture melting point with an authentic specimen 140.0–141.5° (lit. m.p. 138.8°[25]).

m-Vinylphenyl benzoate (white leaflets from ethanol, m.p. 63–64°, lit. m.p. 62.5–63.5°[13]) was identified by hydrogenation to *m*-ethylphenyl benzoate; melting point and mixture melting point with an authentic specimen 50–52° (lit. m.p. 52°,[25,26] 50°[27]).

m-Vinylphenyl p-nitrobenzoate. Ivory needles from methanol, m.p. 84–85°.

Anal. Calcd. for $C_{15}H_{11}NO_4$: N, 5.20. Found: N, 5.23.

Separation of m-vinyl- and m-ethylphenols as acetates Dehydrogenation catalyzate (395 g., 3.3 moles) containing 45% of *m*-vinylphenol was mixed with 800 g. of 25% aqueous sodium hydroxide (5.0 moles) and 7.5 kg. of cracked ice, and to the mixture was quickly added 420 g. (4.1 moles) of acetic anhydride. The mixture was stirred for 5 min. and extracted with ether; the extract was washed with cold 10% sodium hydroxide followed by water. The dried extract was concentrated at 50 mm. to yield 491 g. (96%) of mixed acetates. Distillation at 20 mm. through a 27-plate column at 5/1 reflux ratio gave: (*a*) 16 g., b.p. 94–111°, phenyl acetate; (*b*) 204 g., b.p. 111–117°, *m*-ethylphenyl acetate; (*c*) 42 g., b.p. 117–121°, 12% *m*-vinylphenyl acetate–88% *m*-ethylphenyl acetate; (*d*) 74 g., b.p. 121–130°, 87% *m*-vinylphenyl acetate; (*e*) 106 g., brown residue. Redistillation of the *m*-ethylphenyl acetate fraction (*b*) gave 184 g. of distillate with the following constants: b.p. 117°/20 mm. (lit. b.p. 222–223°[26]), n_D^{25} 1.4981, d_4^{25} 1.0232, f.p. −38.69°, purity 97.0 ± 1.0 mole %.

The 74 g. (0.45 mole) of 87% *m*-vinylphenyl acetate (fraction *d*) was stirred with 180 ml. of 25% aqueous sodium hydroxide (1.2 moles) until the mixture was homogeneous (15 min.). The solution was washed with ether, acidified at 0–5° with carbon dioxide and extracted with ether. The extract was washed with water, dried, and concentrated to give 53 g. (0.44 mole) of 87% *m*-vinylphenol.

p-Vinylphenol from phenol via 5-step synthesis. p-Hydroxyacetophenone. Boron trifluoride was passed into a 0–5° stirred mixture of 470 g. (5.0 moles) of phenol and 600 g. (10 moles) of acetic acid until the gas was no longer absorbed (12 hr.); 1020 g. (15 moles) of boron trifluoride was absorbed. The solution was stirred for 5 hr. at 80°, allowed to stand for 16 hr. at 30°, then poured into a mixture of cracked ice and water. After stirring for 1 hr. at 0–5° the mixture was filtered and the red solid was dissolved in 2 l. of aqueous

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caustic containing 280 g. (7.0 moles) of sodium hydroxide. The solution was stirred at 30° with 10 g. of activated carbon for 0.5 hr. and filtered. The filtrate was cooled to −5°, acidified with concentrated hydrochloric acid and filtered. The light tan solid was air-dried; 640 g., 85% yield,[28] m.p. 105–108°, lit. m.p. 107°,[29a,b] 109°,[29c] 110°.[29d]

p-Acetoxyacetophenone. To a stirred solution of 98 g. (0.72 mole) of *p*-hydroxyacetophenone in 780 ml. of 7.5% aqueous sodium hydroxide (1.45 moles) was added 110 g. (1.08 moles) of freshly distilled acetic anhydride during 5 min. at 5–10°. The mixture was stirred for 1 hr. at 5–10° and filtered. The solid was crystallized from 55–45 water-ethanol to yield 119 g. (93%) of *p*-acetoxyacetophenone, m.p. 52–53°. This product is satisfactory for the next step. A portion of it was recrystallized from methanol to give material with f.p. 52.05°; purity 97.3 ± 0.9 mole % (lit. m.p. 54°[30]).

p-Acetoxyphenylmethylcarbinol. *p*-Acetoxyacetophenone (300 g., 1.7 moles) diluted with 700 ml. of methanol was hydrogenated at 30°/110 p.s.i. in the presence of 10 g. of 10% palladiumized carbon (9 hr., hydrogen consumption 1.6 moles). The catalyzate was filtered and the filtrate concentrated under reduced pressure to yield 295 g. (95%) of *p*-acetoxyphenylmethylcarbinol.

Anal. Calcd. for $C_{10}H_{12}O_3$: hydroxyl, 9.44; sapon. equiv., 180. Found: hydroxyl, 9.00; sapon. equiv., 173.

p-Acetoxyphenylmethylcarbinol can be distilled through a 10-cm. Vigreux column at 1 mm. without decomposition (b.p. 115–125°). However, extensive dehydration-polymerization took place in an attempt to distill it through a 27-plate column at 10 mm.

In two experiments the previous use of the autoclave in copper chromite–catalyzed hydrogenations seemed to poison palladium for the hydrogenation of *p*-acetoxyacetophenone. This trouble was remedied by filtering off the poisoned palladium catalyst and replacing it with fresh catalyst. With nickel-kieselguhr as hydrogenation catalyst it was difficult to prevent over-hydrogenation to *p*-acetoxyethylbenzene. With Raney nickel it was possible to halt the reaction at the carbinol stage, but the ester group was cleaved to give *p*-hydroxyphenylmethylcarbinol.

p-Acetoxystyrene. Three dehydration methods were tried for the conversion of *p*-acetoxyphenylmethylcarbinol to *p*-acetoxystyrene.

(*a*) *Liquid phase dehydration in the presence of potassium acid sulfate.* A mixture of 280 g. (1.56 moles) of *p*-acetoxyphenylmethylcarbinol, 3 g. of fused potassium acid sulfate, and 3 g. of *t*-butylcatechol (TBC) was heated at 190–200°/20 mm. for 1.8 hr. and the distillate (b.p. 105–121°) collected in an ice-cooled receiver containing 1 g. of TBC. A 51-g. residue (18% of the charge) remained in the flask. The distillate was dissolved in ether (water yield 22 ml., 79%) and the solution washed with 5% sodium carbonate followed by saturated calcium chloride solution and dried over anhydrous calcium chloride. The ether was evaporated and the residue distilled through a 10-cm. Vigreux column to yield 179 g. (71%) of *p*-acetoxystyrene; b.p. 73–75°/0.6 mm. (lit. b.p. 100–105°/4 mm.[31] and 83–86°/1 mm.[32]), f.p. 6.94°, purity 97.5 ± 0.5 mole %.

(*b*) *Vapor phase dehydration over potassium acid sulfate-impregnated pumice.* A solution of 150 g. (0.88 mole) of *p*-acetoxyphenylmethylcarbinol, 1.5 g. of TBC, and 385 g. of toluene was passed at a rate of 60 ml./hr. at 225°/20 mm. through a 100-ml. bed of 4–8 mesh pumice impregnated with 3% of potassium acid sulfate. The catalyzate passed into a flask at 150° whence it was continuously flash-distilled into an ice-cooled receiver containing 1 g. of TBC (water yield 8.4 ml., 56%). The distillate was redistilled to yield 58 g. (43%) of *p*-acetoxystyrene (f.p. 7.19°, purity 97.7 ± 0.8 mole %) plus 34.6 g. of residue.

(*c*) *Vapor phase dehydration of p-acetoxyphenylmethylcarbinol over activated alumina.* A 700-g. mixture of *p*-acetoxyphenylmethylcarbinol, acetic acid, and acetic anhydride in a mole ratio of 1:3.3:1 was passed at a rate of 170 ml./hr. through a 100-ml. bed of activated alumina at 350°/25 mm. and the catalyzate collected in an ice-cooled receiver containing 7 g. of TBC. The purpose of the acetic acid–acetic anhydride was to repress cleavage of the acetoxy group. Acetic acid and acetic anhydride were distilled from the catalyzate at 85°/30 mm. and the concentrate was distilled through a 10-cm. Vigreux column. The yields of *p*-acetoxystyrene were 56% per pass and 78% ultimate. The product was 80 ± 5 mole % pure; its infrared spectrum indicated the main impurity to be *p*-vinylphenol. A 100-g. batch of product was cooled at −5° for 15 hr. with seeding. The mother liquor was drained from the solid. The solid was melted and the process repeated four times to yield 27 g. (27%) of *p*-acetoxystyrene; n_D^{25} 1.5360, d_4^{25} 1.056,[33] f.p. 7.64°, purity 98.9 ± 0.4 mole %.

p-Acetoxystyrene is dimorphic, the freezing points of the α- and β-modifications being 8.2 ± 0.1° and 7.4 ± 0.2°, respectively. Several samples of *p*-acetoxystyrene froze initially in the β-form which quickly changed to the α-form upon addition of α-seed.

p-Vinylphenol. A mixture of 16.2 g. (0.10 mole) of *p*-acetoxystyrene, 13.8 g. (0.25 mole) of potassium hydroxide, and 140 ml. of water was stirred at 0–5° until homogeneous (1 hr.). Gaseous carbon dioxide was passed into the stirred cold solution to *p*H 8 to produce 12 g. (100% yield) of *p*-vinylphenol, m.p. 68–69° (lit. m.p. 73.5°[18]). *p*-Vinylphenol was identified by hydrogenating it to *p*-ethylphenol and converting the latter to *p*-ethylphenyl *N*-phenylcarbamate; melting point and mixture melting point with an authentic specimen 119–120° (lit. m.p. 120°[25]).

p-Vinylphenyl benzoate. Crystallized from methanol, white needles, m.p. 75.5–76.5°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39; double bond, 1.00. Found: C, 80.45; H, 5.50; double bond, 0.98.

p-Vinylphenyl benzoate was hydrogenated to *p*-ethylphenyl benzoate; melting point and mixture melting point with authentic *p*-ethylphenyl benzoate 58–59° (lit. m.p. 59–60°[25]).

p-Vinylphenyl p-nitrobenzoate. Yellow needles from methanol, m.p. 109.5–110.5°.

Anal. Calcd. for $C_{15}H_{11}NO_4$: N, 5.20. Found: N, 4.99.

p-Vinylphenyl 3,5-dinitrobenzoate. White needles from methanol, m.p. 132.5–133.0°.

Anal. Calcd. for $C_{15}H_{10}N_2O_6$: N, 8.92. Found: N, 9.18.

p-Vinylphenol by dehydrogenation of p-ethylphenol. The chromia-alumina catalyst was badly carbonized; oxidation of the used catalyst showed the presence of 19 g. of carbon. Half of the catalyzate was heated under a 27-plate column at 20 mm. There resulted 5 g. of distillate (b.p. 70–100°) and a viscous residue, neither of which was investigated. The other half of the catalyzate was extracted with a 50–50 mixture of ether–petroleum ether. The extract was cooled at −5° for 18 hr. and filtered. The solid was recrystallized from *n*-hexane to yield 29.5 g. of *p*-vinylphenol, m.p. 68–69°; its mixture melting point with authentic *p*-vinylphenol was not depressed. The solubility of *p*-vinylphenol in 10 ml. of

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n-hexane is 0.04 g. at 13°, 0.11 g. at 25°, 0.31 g. at 31°, and 0.49 g. at 39°.

m-Isopropenylphenol by dehydrogenation of m-isopropylphenol. The *m*-isopropenylphenol fraction was crystallized from Skellysolve B to yield white crystals (m.p. 39.5–40.5°) which liquefied on standing at room temperature for 8 days; the resulting liquid was insoluble in Skellysolve B. The crystalline *m*-isopropenylphenol was converted to *m*-isopropenylphenoxyacetic acid (white needles from water, m.p. 98.5–99.5°, lit. m.p. 98° [2]).

m-Isopropylphenoxyacetic acid. White flakes from *n*-hexane, m.p. 65.5–66.0°; its mixture melting point with hydrogenated *m*-isopropenylphenoxyacetic acid was not depressed.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.27; H, 7.35.

m-Isopropylphenyl N-phenylcarbamate. White needles from Skellysolve B, m.p. 116.5–117.5°, prepared from *m*-isopropylphenol plus phenyl isocyanate.

Anal. Calcd. for $C_{16}H_{17}NO_2$: N, 5.49. Found: N, 5.58.

Its mixture melting point with product obtained by the reaction of hydrogenated *m*-isopropenylphenol with phenyl isocyanate was not depressed.

m-Isopropenylphenyl p-nitrobenzoate. Ivory needles from ethanol, m.p. 90.5–91.5°.

Anal. Calcd. for $C_{16}H_{13}NO_4$: N, 4.95. Found: N, 4.96.

p-Isopropenylphenol by dehydrogenation of p-isopropylphenol. Redistillation of the crude *p*-isopropenylphenol fraction gave a heart cut boiling at 136–137°/20 mm. The latter was crystallized from cyclohexane to yield white crystals, m.p. 83–84°.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51; double bond, 1.00. Found: C, 80.26; H, 7.60; double bond, 1.00.

The hydrogenation of *p*-isopropenylphenol produced *p*-isopropylphenol; melting point and mixture melting point with an authentic specimen 62–64° (lit. m.p. 61°,[34a] 60.5–61.5°).[34b]

2,2-bis(p-Hydroxyphenyl)propane. A mixture of 2205 g. (23.4 moles) of phenol, 458 g. (7.9 moles) of acetone and 366 ml. of concentrated hydrochloric acid was allowed to stand for 6 days at room temperature, then filtered. The water-washed solid was air-dried for 7 days to yield 1400 g. (55%) of a solid (m.p. 103–121°) containing approximately equimolal amounts of bisphenol and phenol. Crystallization from benzene or 50% aqueous acetic acid yielded bisphenol, m.p. 157–159° (lit. m.p. 151–152°,[35] 155°[36]); m.p. of dibenzoate 161–162° (lit. m.p. 153.5°,[35] 161°[36]). Phenol can also be removed from the complex by steam distillation or vacuum distillation. For example, 473 g. of air-dried complex was heated under a 23-plate column until the vapor temperature was 100°; 146 g. of distillate (phenol) was obtained and a flask residue of 326 g. (bisphenol, m.p. 157–159° after crystallization from benzene). This corresponds to a phenol/bisphenol mole ratio of 1.08/1.00.

p-Isopropenylphenol by cracking of 2,2-bis(p-hydroxyphenyl)propane. Molten bisphenol (90 g.) was passed through a 20-ml. bed of "solid phosphoric acid" at 250° during 28 min. The catalyzate was dissolved in benzene and the solution was washed with aqueous sodium bicarbonate, dried azeotropically and concentrated. The concentrate was distilled at 20 mm. to yield 41 g. of phenol, 29 g. of *p*-isopropenylphenol (48%, b.p. 125–145°) plus 14 g. of residue.

2,2-Bis(p-acetoxyphenyl)propane. A mixture of 114 g. (0.5 mole) of 2,2-bis(*p*-hydroxyphenyl)propane, 204 g. (2.0 moles) of acetic anhydride, and 50 g. of anhydrous sodium acetate was refluxed for 2 hr. The cooled reaction mixture was stirred with 400 ml. of water and filtered. The product was crystallized from methanol to yield 147 g. (94%) of 2,2-bis(*p*-acetoxyphenyl)propane, heavy white crystals, m.p. 79.5–81.5° (lit. m.p. 78°[37]).

p-Isopropenylphenol by cracking of 2,2-bis(p-acetoxyphenyl)-propane. (*a*) 2,2-Bis(*p*-acetoxyphenyl)propane (100 g.) was heated to 370° to yield 85 g. of distillate which was stirred for 2 hr. at 25° with dilute sodium hydroxide. The mixture was extracted with ether and the extract concentrated to give 18.5 g. of recovered 2,2-bis(*p*-acetoxyphenyl)propane, m.p. and mixture m.p. 80–82°. The aqueous layer was acidified to *p*H 8 at 0–5° with carbon dioxide and extracted with ether. The extract was concentrated and the residue distilled through a 27-plate column to yield 18 g. of *p*-isopropenylphenol (37%), b.p. 125–145°, m.p. 83–84°.

(*b*) A mixture of 100 g. of 2,2-bis(*p*-acetoxyphenyl)propane and 4.5 g. of Super Filtrol was heated to 370° to give 72 g. of distillate which was worked up as in method (*a*). The yield of *p*-isopropenylphenol was 15 g.

p-Isopropenylphenol by depolymerization of poly-p-isopropenylphenol. Sixty grams of 90% *p*-isopropenylphenol changed to a yellow, taffy-like material during a 6-month storage in the laboratory. This material was heated under a 27-plate column at 20 mm. to give: (*a*) 10 g., b.p. 105–125°, not identified; (*b*) 45 g., b.p. 125–145°, m.p. 83–84°, *p*-isopropenylphenol; (*c*) 5 g. of residue.

The *p*-isopropenylphenol obtained from depolymerization and cracking was identified by mixture melting point with an authentic specimen.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF IOWA STATE COLLEGE]

Reactions of Lithium with Some Aromatic Hydrocarbons in Tetrahydrofuran

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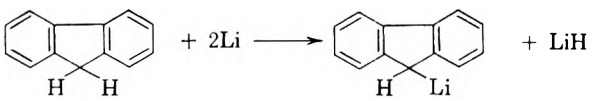
Certain aromatic hydrocarbons have been found to react with lithium metal in tetrahydrofuran to give compounds having a carbon—lithium bond. 9,9-Diphenylfluorene has been cleaved by lithium in tetrahydrofuran to give 9-phenylfluorenyllithium and phenyllithium.

Aromatic hydrocarbons like fluorene and 9-phenylfluorene[1] have been metalated in high yields by a variety of organolithium compounds. On the other hand, cyclopentadienyllithium has been successfully prepared from the reaction of cyclopentadiene with lithium in liquid ammonia.[2] It has also been obtained by the metalation of cyclopentadiene by phenyllithium[3] and *n*-butyllithium.[4]

We are now reporting convenient methods for synthesizing some organolithium compounds by the direct reaction of aromatic hydrocarbons with lithium metal in tetrahydrofuran (THF). To our knowledge this is the first reported example wherein an aromatic hydrocarbon reacts with lithium metal in an ethereal solvent. Fluorene and 9-phenylfluorene,



when treated with lithium in THF, yielded 72 and 38% of 9-fluorenecarboxylic acid and 9-phenylfluorenecarboxylic acid, respectively, subsequent to carbonation. Likewise, cyclopentadiene reacted with lithium in a similar fashion to give a 45% yield of diphenylfulvene after treatment of the reaction mixture with benzophenone. Thus, this appears to be a well-suited method for preparing certain organolithium compounds, which are free of halide salts, in an organic solvent.

The open-chained model of 9-phenylfluorene, triphenylmethane, did not react with lithium in THF.

9-Phenylfluorenyllithium was also prepared by another method. 9,9-Diphenylfluorene underwent almost a quantitative cleavage in 15 hr. by lithium in THF to give 9-phenylfluorene subsequent to hydrolysis of the reaction mixture. This reaction is not novel since Koelsch[5] found that stirring 9-benzyl-9-phenylfluorene with sodium amalgam in diethyl ether for 5 days afforded, after hydrolysis, 40% of 9-phenylfluorene; but it does emphasize that THF has a pronounced effect on facilitating the cleavage.

In connection with the synthesis of 9,9-diphenylfluorene, we have found that the intermediate carbinol, 2-biphenylyldiphenyl carbinol, can be obtained in a higher yield from the reaction of 2-biphenylyllithium with benzophenone than by a previously reported[6] procedure in which 2-phenylbenzophenone was treated with phenylmagnesium bromide. The former method also involves fewer steps.

EXPERIMENTAL[7]

Reaction of lithium with fluorene. A solution of 5 g. (0.03 mole) of fluorene in 35 ml. of tetrahydrofuran (THF) was added, during 1.5 hr., to a stirred suspension of 1.23 g. (0.178 g. atom) of finely cut lithium wire contained in 10 ml. of THF. The color of the mixture which was periodically cooled by a water bath during the addition changed from green to orange. When the addition was complete, the mixture was stirred at room temperature for 50 min. and was poured through a glass wool plug onto a slurry of Dry Ice and diethyl ether. Following hydrolysis with water, the aqueous layer was separated, boiled to expel THF and diethyl ether, filtered, and acidified with hydrochloric acid to give a solid which was crystallized from acetic acid to yield 4.46 g. (71%) of needles, m.p. 230–232°, which showed no depression in melting point when admixed with an authentic sample of 9-fluorenecarboxylic acid.

Reaction of lithium with 9-phenylfluorene. A mixture of 4.0 g. (0.0165 mole) of 9-phenylfluorene, 1.7 g. (0.245 g. atom) of lithium, and 45 ml. of tetrahydrofuran was stirred at room temperature for 4 hr. before carbonating and working the reaction mixture up as described in the preceding experiment. The yield of acid, m.p. 180–182°, was 1.81 g. (38%). The melting point was undepressed when the compound was admixed with an authentic sample of 9-phenylfluorenecarboxylic acid.

Reaction of lithium with triphenylmethane (attempted). A mixture of 5.0 g. (0.02 mole) of triphenylmethane, 0.8 g. (0.115 g. atom) of lithium wire, and 40 ml. of tetrahydrofuran was stirred at room temperature for 5 days. Work-up of the organic layer gave 4.71 g. (94%) of triphenylmethane, m.p. 90–92°, identified by mixed melting point.

Reaction of lithium with cyclopentadiene. A solution of 4.03 g. (0.061 mole) of cyclopentadiene in 30 ml. of tetrahydrofuran (THF) was added to a rapidly stirred suspension

(1) Metalation of these compounds as well as other types has been reviewed recently; H. Gilman and J. A. Morton, Jr., *Org. Reactions*, VIII, 258 (1954).

(2) E. O. Fischer, W. Hafner, and H. O. Stahl, *Z. anorg. allgem. Chem.*, 282, 59 (1955).

(3) W. E. Doering and C. H. Depuy, *J. Am. Chem. Soc.*, 75, 5955 (1953).

(4) L. Summers, R. H. Uloth, and A. Holmes, *J. Am. Chem. Soc.*, 77, 3604 (1955).

(5) C. F. Koelsch, *J. Am. Chem. Soc.*, 56, 1605 (1934).

(6) R. G. Clarkson and M. Gomberg, *J. Am. Chem. Soc.*, 52, 2881 (1930).

(7) All melting points are uncorrected. Reactions involving organolithium compounds were carried out under an atmosphere of dry, oxygen-free nitrogen in sodium-dried solvents.

of 2.0 g. (0.288 g. atom) of lithium in 40 ml. of THF. Initially about 5 ml. of the cyclopentadiene solution was added. After 20 min. bubbles began to evolve around the pieces of lithium. The remaining cyclopentadiene solution was added, during 45 min. while cooling at 0°. The mixture was stirred at room temperature for 30 min. before filtering it into a stirred solution of 10.9 g. (0.06 mole) of benzophenone in 35 ml. of THF. The orange mixture was stirred at room temperature for 21 hr. and was poured into a mixture of ice and water. The organic layer was separated, dried, and most of the solvent was evaporated under a stream of dry air. The red residue was refluxed in petroleum ether (b.p. 28–38°) and filtered to leave a brown, gummy material. The petroleum ether was slowly evaporated under reduced pressure to leave orange crystals which were washed with 95% ethanol, filtered, and dried to give 4.88 g. (35%) of diphenylfulvene, m.p. 75–77°, identified by mixed melting point.

In another run using 8.05 g. (0.122 mole) of cyclopentadiene and 2.85 g. (0.41 g. atom) of lithium, a 45% yield of diphenylfulvene was obtained.

2-Biphenylyldiphenylcarbinol. An ethereal solution containing 0.344 mole of 2-biphenylyllithium[8] was added to a solution of 62.6 g. (0.344 mole) of benzophenone. The mixture was hydrolyzed with water and the organic layer was worked up in the usual fashion. Evaporation of the solvent under a stream of dry air left a solid which was crystallized from ethanol to give 97 g. (84%) of product, m.p. 86–88°.

2-Biphenylyldiphenylcarbinol, m.p. 87–88°, has previously been prepared in 63% yield from phenylmagnesium bromide and 2-phenylbenzophenone.[6] Refluxing the carbinol in acetic acid gave 9,9-diphenylfluorene.

Reaction of lithium with 9,9-diphenylfluorene. A mixture of 6.0 g. (0.019 mole) of 9,9-diphenylfluorene, 2.0 g. (0.29 g. atom) of lithium wire, and 50 ml. of tetrahydrofuran was stirred at room temperature for 15 hr. The organic layer was separated and dried over sodium sulfate after hydrolyzing with water. Distillation of the solvent left a material which was crystallized from a minimum of ethanol to give 3.88 g. (85%) of colorless needles, m.p. 143–144°, which showed no depression in melting point when admixed with an authentic sample of 9-phenylfluorene.

When the reaction time was limited to 1.75 hr., only a 25% yield of 9-phenylfluorene was obtained.

Acknowledgment. This research was supported in whole by the United States Air Force under contract AF 33(616)-3510 monitored by Materials Laboratory, Directive of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio.

(8) H. Gilman and K. Oita, *J. Org. Chem.*, **20**, 862 (1955).

AMES, IOWA

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Addition of Ethyl Mercaptan to Acetylenic Compounds[1]

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The free-radical addition of two equivalents of ethyl mercaptan to several acetylenic compounds has been studied. These comprised propargyl alcohol, propargyl acetate, 2-butyn-1,4-diol diacetate, 1-hexyne, 2-methyl-3-butyn-2-ol, propiolic acid, dimethyl acetylenedicarboxylate, and phenylacetylene. Vicininal *bis*-ethylmercapto derivatives were obtained in all but two instances. Phenylacetylene afforded phenylacetaldehyde diethyl mercaptal while from dimethyl acetylenedicarboxylate only a monoadduct was realized.

These bisethylmercapto derivatives were not active when tested *in vivo* against *M-tuberculosis* infection in mice.

Although the literature abounds with reports of studies of the addition of thiols to ethylenic substances, relatively little attention has been given to such additions involving acetylenic compounds.[2,3]

(1) The work reported here was done as part of a general research program in organic chemistry at Cornell University, sponsored by the B. F. Goodrich Co.

(2) (a) S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.*, **77**, 1179 (1900); (b) C. Finzi, *Gazz. chim. ital.*, **60**, 798 (1930); (c) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 945 (1946); (d) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3109 (1949); (e) H. Behringer, *Ann.*, **564**, 219 (1949); (f) B. R. Baker and M. V. Querry, *J. Org. Chem.*, **15**, 417 (1950); (g) B. Weibull, *Arkiv Kemi*, **3**, 225 (1951); (h) C. S. Marvel and H. Wexler, *J. Am. Chem. Soc.*, **75**, 6318 (1953); (i) H. Fiesselmann and P. Schipprak, *Ber.*, **89**, 1897 (1956).

(3) (a) W. H. Carothers, *J. Am. Chem. Soc.*, **55**, 2008 (1933); (b) E. P. Kohler and H. Potter, *J. Am. Chem. Soc.*, **57**, 1316 (1935); (c) S. D. Jones and E. E. Reid, *J. Am. Chem. Soc.*, **60**, 2452 (1938); (d) W. Reppe and F. Nicolai, Ger. Patent **617,543**; *Chem. Abstr.*, **30**, 733 (1936); (e) W. Reppe and F. Nicolai, Ger. Patent **625,660**; *Chem. Abstr.*, **30**, 5595 (1936); (f) W. Reppe and F. Nicolai, U. S. Patent **2,156,005**; *Chem. Abstr.*, **33**, 5874 (1939); (g) W. Reppe and A. Freytag, Ger. Patent **704,235**; *Chem. Abstr.* **36**, 1958 (1942); (h) N. V. deBataafsche Petroleum Maatschappij, Brit. Patent **532,676**; *Chem. Abstr.*, **36**, 1045 (1942); (i) M. H. M. Arnold, U. S. Patent **2,336,916**; (j) W. E. Vaughn and F. F. Rust, Brit. Patent **581,775**; *Chem. Abstr.*, **41**, 2999 (1947); (k) H. Bader, L. C. Cross, I. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 619 (1949); (l) A. Kh. Khomenko, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk*, 280 (1951); *Chem. Abstr.*, **46**, 884 (1952); (m) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952); (n) W. Franke, K. Weissbach, W. Dietrich, and H. Weber, Ger. Patent **859,307**; *Chem. Abstr.*, **47**, 11220 (1953); (o) E. N. Prilezhaeva and M. F. Shostakovskii, *Akad. Nauk S.S.S.R., Inst. Org. Khim., Sintezy Org. Soedinenii, Sbornik.*, **2**, 54 (1952); *Chem. Abstr.*, **48**, 731 (1954); (p) T Mo, Japan Patent **7667** (1951); *Chem. Abstr.*, **48**, 731 (1954); (q) S. J. Cristol, A. Begoon, W. P. Norr, and P. S. Ramey, *J. Am. Chem. Soc.*, **76**, 4558 (1954); (r) H. Bader, *J. Chem. Soc.*, 116 (1956); (s) M. F. Shostakovskii, E. N. Prilezhaeva, and N. I. Uvarova, *Izvest. Akad. Nauk S.S.S. Otdel. Khim. Nauk*, 906 (1955); *Chem. Abstr.*, **50**, 9278 (1956); (t) K. Yamagishi, Tanaka, and T. Hoshino, *Bull. Chem. Soc. Japan*, **29**, 447 (1956); (u) W. Reppe, *et al.*, *Ann.*, **601**, 111 (1956); (v) W. E. Truce and J. A. Sims, *J. Am. Chem. Soc.*, **78**, 2756 (1956); (w) W. E. Truce, M. M. Boudakian, R. F. Heine, and R. J. McManimie, *J. Am Chem. Soc.*, **78**, 2743 (1956); (x) W. E. Truce and R. F. Heine, *J. Am. Chem. Soc.*, **79**, 1770 (1957).

Further, these additions to acetylenes have, for the most part, involved thiolacetic acid. It was of interest therefore, to study the free-radical addition of ethyl mercaptan to a representative number of acetylenic compounds. Since during the course of this study, it was announced that certain ethylmercapto compounds possessed antitubercular activity,[4] it seemed desirable also to have the ethylmercapto derivatives tested for physiological activity.

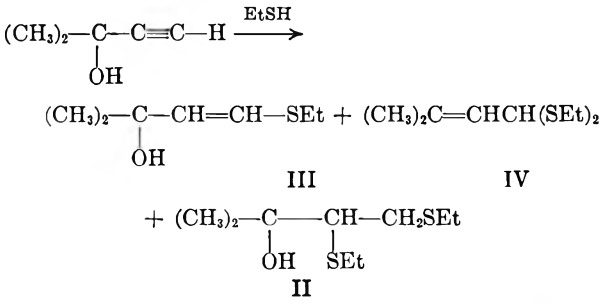
In this study all additions were carried out by irradiating with ultraviolet light for two to four weeks[5] a mixture of one molecular equivalent of the acetylene and two equivalents of ethyl mercaptan containing a catalytic amount of benzoyl peroxide. Products were isolated by direct distillation of the reaction mixtures. Structure of two of the adducts was established by conventional chemical and physical methods. In the remaining cases assignment of structure was made on the basis of analogy and qualitative tests.

The addition of ethyl mercaptan to propargyl alcohol afforded 2,3-bis(ethylmercapto)-1-propanol (I) in 95% yield.[6] This I was identical with I prepared by ethylation of 2,3-dimercapto-1-propanol (BAL). This BAL was prepared by hydrolysis of the mixture of acetates which resulted from the addition of thiolacetic acid to propargyl alcohol. The BAL obtained showed b.p. 86–90° (1 mm.), n_D^{22} 1.5690 and gave a benzylidene derivative which had m.p. 75–77°.

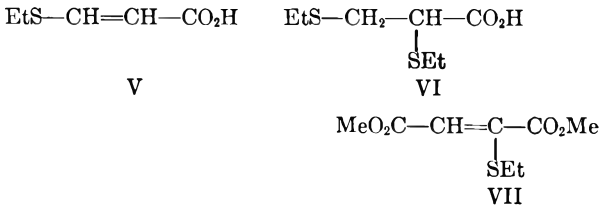
Free-radical addition of ethyl mercaptan to propargyl acetate, 2-butyn-1,4-diol diacetate, and 1-hexyne proceeded smoothly and essentially quantitatively. By analogy to propargyl alcohol the products obtained were 2,3-bis(ethylmercapto)-1-propyl acetate, 2,3-bis(ethylmercapto)-1,4-butanediol diacetate, and 1,2-bis(ethylmercapto)hexane, respectively. All three products were inert toward Brady's reagent.[10] Attempts to oxidize these bissulfides to sulfones gave water soluble products only.

Similarly, ethanedithiol and 2-butyn-1,4-diol diacetate afforded 1,2-bis(acetoxymethyl)1,4-dithiane (43%) and viscous, insoluble polymeric products which were not investigated.

The addition of ethyl mercaptan to 2-methyl-3-butyn-2-ol gave two colorless liquid organic products and water. The higher boiling product failed to respond to Brady's reagent and hence is considered to be 3,4-bis(ethylmercapto-)2-methyl-2-butanol (II). The lower boiling product developed a pinkish color rapidly on standing. It reacted immediately with Brady's reagent to give a red crystalline solid of m.p. 182–183° which proved to be identical with the 2,4-dinitrophenylhydrazone of β-methylcrotonaldehyde. The lower-boiling product thus appeared to be III and/or IV.



From the addition of ethyl mercaptan to propiolic acid two products were realized: β-ethylmercaptoacrylic acid (V), m.p. 74–75°, and α,β-bis(ethylmercapto)propionic acid (VI), b.p. 128–131° (0.5 mm.). The product V gave the 2,4-dinitrophenylhydrazone of acetaldehyde when treated with Brady's reagent. Its infrared spectrum showed strong absorption at 6.36μ and its ultraviolet spectrum showed λ_{max} 276 mμ, ε 6,000. The elemental analysis of VI was not satisfactory. This was probably due to the fact that it was very hygroscopic. VI gave no reaction with Brady's reagent, showed no maximum in the ultraviolet, and its infrared spectrum was void of absorption maxima in the region 6.0–6.7μ.



The monoadduct VII was the only product isolated from the addition of ethyl mercaptan to dimethyl acetylenedicarboxylate. Small amounts of higher boiling substances were obtained, but in quantity too small to characterize. VII displayed a strong maximum at 6.30μ in its infrared spectrum and possessed an ultraviolet maximum at λ_{max} 283 mμ, ε, 13,720. VII gave a 2,4-dinitrophenylhydrazone derivative, m.p. 173–180°. This derivative was not examined further.

The addition of ethyl mercaptan to phenylacet-

(4) H. D. Brown, *et al.*, *J. Am. Chem. Soc.*, **76**, 3860 (1954); S. Kushner, *et al.*, *J. Am. Chem. Soc.*, **77**, 1152 (1955).

(5) The volume of the reactants generally became constant after 3 to 6 days which suggested that reaction was complete. As a matter of convenience and in order to insure complete addition, the reactants were irradiated for the periods specified.

(6) Yamagishi[3f] reported that irradiation of a mixture of propargyl alcohol and methyl mercaptan gave 2,3-bis-(methylmercapto)-1-propanol. However, this structural assignment to the product was based on its similarity to a compound prepared by Barbieri[7] which recently has been best described as 1,3-bis(methylmercapto)-2-propanol.[8,9]

(7) A. De Barbieri and S. Tricerri, *Boll. soc. ital. biol. sper.*, **25**, 522 (1949); *Chem. Abstr.*, **44**, 8862 (1950).

(8) F. D. Doyle and J. H. C. Naylor, *Chemistry & Industry*, 714 (1955).

(9) N. S. Johary and L. N. Owen, *J. Chem. Soc.*, 1302 (1955).

(10) O. L. Brady, *J. Chem. Soc.*, 756 (1931).

ylene proved to be different from the other additions studied since phenylacetaldehyde diethyl mercaptal (VIII) was obtained. VIII was identified by its conversion to the 2,4-dinitrophenylhydrazone of phenylacetaldehyde, by oxidation to a sulfone derivative and finally by comparison with an authentic sample of VIII prepared directly from phenylacetaldehyde and ethyl mercaptan. The formation of a stable benzyl free radical intermediate, as pictured below, apparently controls the path of addition in this instance.[11]

$$C_6H_5{-}C{\equiv}C{-}H \longrightarrow C_6H_5{-}CH{=}CH{-}SEt \longrightarrow C_6H_5{-}\dot{C}H{-}CH(SEt)_2$$

$$\longrightarrow C_6H_5{-}CH_2{-}CH(SEt)_2$$

VIII

Several of these compounds were tested *in vivo* against experimental *M-tuberculosis* (My 5) infection in mice. None of the compounds prolonged significantly the survival time of the treated mice.[12]

EXPERIMENTAL[13]

2,3-Dimercapto-1-propanol (BAL). A solution of 20 g. (0.357 mole) of propargyl alcohol, 60 g. (0.789 mole) of thiolacetic acid, and 0.1 g. of benzoyl peroxide was irradiated in a sealed Pyrex tube for one month. The reaction mixture was dissolved in ether and washed with aqueous sodium carbonate solution. Distillation afforded 30.5 g. of an orange liquid; b.p. 102–117° (0.6 mm), n_D^{25} 1.5147–1.5161, λ_{max} 230–233 mμ, ϵ, 6,100 [reported for the diacetate of BAL;[14] b.p. 60° (0.1 mm.), n_D^{20} 1.5198, λ_{max} 230 mμ, ϵ, 7,800]. The infrared spectrum of this product showed weak hydroxyl and mercaptan absorption which suggested that it comprised a mixture of diacetates and possibly triacetate.

Hydrolysis of 25 g. of the above acetate mixture with 2.5 ml. of concentrated hydrochloric acid in 150 ml. of methanol gave 9.2 g. of colorless BAL; b.p. 86–90° (1.0 mm., nitrogen atmosphere), n_D^{22} 1.5690. Lit. b.p. 71–75° (1 mm.), n_D^{15} 1.5733;[13] b.p. 60° (0.1 mm.), n_D^{23} 1.5735.[15]

Heating a mixture of 0.5 g. of BAL, 0.45 g. of benzaldehyde, and 2 drops of concentrated hydrochloric acid in benzene gave 0.45 g. (53%) of a white crystalline benzylidene derivative, m.p. 75–77° from hexane (lit. m.p. 79°[15]).

2,3-Bis(ethylmercapto)-1-propanol. (I). (*A*) A solution of 20 g. (0.357 mole) of propargyl alcohol, 53 g. (0.855 mole) of ethyl mercaptan, and 0.1 g. of benzoyl peroxide was irradiated in a Pyrex bomb for two weeks. Distillation afforded 61.6 g. (95%) of a colorless liquid; b.p. 118–120° (3.4 mm.), n_D^{26} 1.5248, d_4^{25} 1.0658.

Anal. Calcd. for $C_7H_{16}OS_2$: C, 46.62; H, 8.94; S, 35.57. Found: C, 46.44; H, 8.89; S, 35.30.

The *α-naphthylurethan* derivative of this alcohol melted at 49.5–51° from benzene-hexane. This melting point was not depressed on admixture with the α-naphthylurethan derivative of authentic 2,3-bis(ethylmercapto)-1-propanol.

Anal. Calcd. for $C_{18}H_{23}O_2NS_2$: C, 61.85; H, 6.63. Found: C, 61.83, 61.90; H, 6.50, 6.62.

(*B*)[16] Ethyl iodide (25 g., 0.22 mole) was added to a well stirred solution of 8.5 g. (0.082 mole) of BAL and 6.0 g. (0.22 mole) of sodium hydroxide in 50 ml. of water. The stirred mixture was heated for one hour and extracted with ether. Distillation of the washed and dried ether extract gave 8.7 g. of colorless liquid I; b.p. 100–103.5° (1 mm.), n_D^{22} 1.5263. The α-naphthylurethan derivative of this I had m.p. 49–51° from ethanol.

Addition of ethyl mercaptan to other acetylenic compounds. The procedure used was similar to that described above for the addition of ethyl mercaptan to propargyl alcohol. (1) *To propargyl acetate.* From 15 g. (0.153 mole) of propargyl acetate, b.p. 121–122.8°, n_D^{20} 1.4169, there was obtained 31.7 g. (93%) of a colorless 2,3-bis(ethylmercapto)-1-propyl acetate; b.p. 100–102° (0.8 mm.), n_D^{25} 1.4978, d_4^{25} 1.0639.

Anal. Calcd. for $C_9H_{18}O_2S_2$: S, 28.84. Found: S, 28.95.

(2) *To 2-butyn-1,4-diol diacetate.* From 42 g. (0.247 mole) of 2-butyn-1,4-diol diacetate there was obtained 67.6 g. (93%) of 2,3-bis(ethylmercapto)-1,4-butanediol diacetate; b.p. 145–146° (1.4 mm.), n_D^{20} 1.4932, d_4^{20} 1.1100.

Anal. Calcd. for $C_{12}H_{22}O_4S_2$: C, 48.96; H, 7.53; S, 21.79. Found: C, 48.57, 48.61; H, 7.50, 7.30; S, 21.90, 21.75.

(3) *To 1-hexyne.* 1-Hexyne (20 g., 0.244 mole) afforded 47.0 g. (94%) of 1,2-bis(ethylmercapto)hexane; b.p. 72–75.5° (0.2 mm.), n_D^{25} 1.4934, d_4^{25} 0.9339.

Anal. Calcd. for $C_{10}H_{22}S_2$: C, 58.18; H, 10.75. Found: C, 57.97, 58.12; H, 10.84, 10.68.

(4) *To 2-methyl-3-butyn-2-ol.* Irradiation of a solution of 32 g. (0.516 mole) of ethyl mercaptan, 20 g. (0.238 mole) of 2-methyl-3-butyn-2-ol, and 0.15 g. of benzoyl peroxide gave 1.3 g. of an aqueous layer. Distillation of the organic layer gave two fractions: (*a*) 21.10 g. of a colorless liquid which rapidly turned pink on standing, b.p. 66–87° (0.3 mm.), n_D^{25} 1.5146–1.5115; and (*b*) 17.8 g. of colorless II, b.p. 87–89° (0.3 mm.), n_D^{25} 1.5080, d_4^{25} 1.0196. Fraction (*b*), the alcohol II, was analyzed.

Anal. Calcd. for $C_9H_{20}OS_2$: C, 51.87; H, 9.57. Found: C, 51.57; H, 9.92.

Fraction (*a*) gave an immediate precipitate with Brady's reagent. Recrystallized from ethanol–ethyl acetate the resulting red solid showed m.p. 182–183° (reported[17] for the 2,4-dinitrophenylhydrazone derivative of β-methylcrotonaldehyde, m.p. 182–183°). A precipitate was not obtained from fraction (*b*) after 24 hr. of heating with Brady's reagent.

(5) *To propiolic acid.* Irradiation of 10 g. (0.143 mole) of propiolic acid with ethyl mercaptan gave the following two fractions on distillation: (*a*) 5.7 g., b.p. 107–125° (0.5 mm.), n_D^{25} 1.5208 and (*b*) 12.04 g., b.p. 128–131° (0.5 mm.), n_D^{25} 1.5222–1.5229.

A pentane solution of fraction (*a*) deposited solid V which after several recrystallizations from pentane had m.p. 74–75°.

Anal. Calcd. for $C_5H_8O_2S$: C, 45.43; H, 6.10. Found: C, 45.92; H, 6.10.

On warming V overnight with Brady's reagent a yellow solid of m.p. 140.5–144° was obtained. Recrystallization from ethanol raised the m.p. to 145–147°. No depression in melting point was observed on admixture of this derivative with an authentic sample of the 2,4-dinitrophenylhydrazone derivative of acetaldehyde.

Anal. Calcd. for $C_8H_8N_4O_4$: C, 42.86; H, 3.60. Found: C, 42.84, 43.11; H, 3.60, 3.71.

Careful distillation of fraction (*b*) gave a sample of VI uncontaminated with V as shown by the absence of an ultraviolet maximum and the absence of a peak at 6.36μ in its infrared spectrum. VI showed b.p. 133–134° (0.65 mm.), n_D^{25} 1.5217, d_4^{25} 1.1356. No reaction was noted when VI was treated with Brady's reagent.

(6) *To dimethyl acetylenedicarboxylate.* From 20 g. (0.14 mole) of dimethyl acetylenedicarboxylate there was obtained 26.4 g. of a yellow liquid, b.p. 96–120° (1.0–2.0 mm.), n_D^{20} 1.5097–1.5038. A similar result was observed when dimethyl acetylenedicarboxylate was heated at 140° with

(11) F. G. Bordwell, R. D. Chapman, and W. H. McKellin, *J. Am. Chem. Soc.*, 76 3637 (1954).

(12) The tests were made at the laboratories of the Wm. S. Merrell Co.

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

(14) H. R. Ing, *J. Chem. Soc.*, 1393 (1948).

(15) L. A. Stocken, *J. Chem. Soc.*, 592 (1947).

(16) For related alkylations of BAL see refs. 8 and 9.

(17) M. Julia, *Ann. chim.* (*Paris*), 5, 618 (1950)

ethyl mercaptan and benzoyl peroxide. A redistilled sample of this adduct (VII) showed b.p. 107–109° (1.0 mm.) n_D^{25} 1.5132, d_4^{25} 1.1747, λ_{max} 283 mμ, ε 13,720, and a strong infrared band at 6.30μ.

Anal. Calcd. for $C_{18}H_{12}O_4S$: C, 47.04; H, 5.92; S, 15.70. Found: C, 46.67; H, 6.08; S, 16.12.

On standing with Brady's reagent VII gave a crystalline derivative which had m.p. 173–180°.

(7) *To phenylacetylene.* From 20 g. (0.484 mole) of phenylacetylene there was obtained 39.3 g. (93%) of colorless VIII; b.p. 114–116° (0.75 mm.), n_D^{25} 1.5604, d_4^{25} 1.0419. The ultraviolet spectrum showed only shoulders at λ 260, 268, and 269.5 mμ, ε, 380, 238, and 230, respectively. The infrared spectrum of this VIII was identical with that of an authentic sample of phenylacetaldehyde diethyl mercaptal;[18] b.p. 124–126° (1.0 mm.), n_D^{25} 1.5601.

Anal. Calcd. for $C_{12}H_{18}S_2$: S, 28.33. Found: S, 28.09.

Heating the above adduct VIII for an hour with Brady's reagent afforded a yellow solid, m.p. 117–119°, which did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of phenylacetaldehyde.

Oxidation of 1 g. of the adduct VIII with 2 ml. of 30% hydrogen peroxide in 7 ml. of glacial acetic acid gave 1.1 g. of a crystalline sulfone which melted at 133–134° after recrystallization from benzene. Lit. m.p. 133–135°.[19]

Anal. Calcd. for $C_{12}H_{18}O_4S$: C, 49.63; H. 6.24. Found: C, 50.02; H, 5.94.

Addition of ethanedithiol to 2-butyn-1,4-diol diacetate.[20] An exothermic reaction occurred on adding 0.25 g. of benzoyl peroxide to a solution of 50 g. (0.294 mole) of 2-butyn-1,4-diol diacetate and 28 g. (0.298 mole) of ethanedithiol. The reactants were then irradiated for 4 days. Distillation gave 21.2 g. of unreacted diacetate, b.p. 91–94° (1.2 mm.), and 20.0 g. of 1,2-bis(acetoxymethyl)-1,4-dithiane, b.p. 156–161° (1.0 mm.). The still residue was an extremely viscous oil and proved to be insoluble in benzene and in ethanol.

A redistilled portion of the dithiane showed b.p. 156° (1.0 mm.), n_D^{20} 1.5252.

Anal. Calcd. for $C_{10}H_{16}O_4S_2$: C, 45.34; H, 6.10; S, 24.26. Found: C, 45.15; H, 6.00; S, 23.97.

ITHACA, N. Y.

(18) M. L. Wolfrom and J. V. Karabinos, *J. Am. Chem. Soc.*, 66, 909 (1944).

(19) M. W. Cronyn, *J. Am. Chem. Soc.*, 74, 1225 (1952).

(20) A quartz flask was used in this experiment.

[CONTRIBUTION NO. 229 FROM THE GOODYEAR TIRE AND RUBBER RESEARCH LABORATORY]

Syntheses and Ultraviolet Absorption Spectra of Certain Sulfur-Containing Derivatives of Naphthalene

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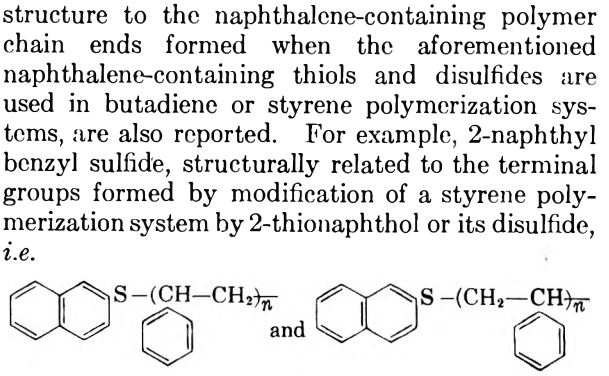
Certain mercaptans, sulfides and disulfides of naphthalene, such as the 1- and 2-thionaphthols, their respective disulfides and mixed phenyl sulfides, as well as 2-naphthyl benzyl sulfide, 1-naphthyl allyl sulfide, the 1- and 2-naphthyl methanethiols, 2-naphthylmethyl benzyl sulfide, and 1-(α-naphthyl)-2-methylpropanethiol-2 were either synthesized or purified, and their ultraviolet absorption spectra recorded and correlated. Syntheses for 2-naphthylmethyl β-hydroxyethyl sulfide, and 1,5-bis(β-naphthylmethylthio)pentane are also described.

The ultraviolet absorption spectra of various sulfur-containing naphthalene derivatives were required for a study of the number and type of sulfur linkages to be obtained from polybutadiene and polystyrene polymers prepared in polymerization systems containing either a naphthalene-substituted mercaptan or a dinaphthyl disulfide as a polymerization modifier. The use of such modifiers in these polymerization systems would provide these polymers with naphthalene-chromophore-tagged chain ends, making possile: (*1*) corroboration of the theory of the mode of interaction of polymerization systems with mercaptans and disulfides, and (*2*) a correlation of polymer molecular weight with macrostructure for polymers so prepared. Earlier work on this subject, dealing with the determination of the number of naphthalene-containing chain ends incorporated into bulk polymerized polystyrenes, has involved systems containing either 1-naphthyl methanethiol or di-2-naphthyl disulfide.[1] The syntheses, methods of purification, and ultraviolet absorption spectra of the aforementioned mercaptan and disulfide as well as a similar characterization of such other naphthalene-containing mercaptans and disulfides as 2-thionaphthol, 2-naphthyl methanethiol, di-1-naphthyl disulfide, and 1-(α-naphthyl) 2-methyl-propanethiol-2 are described in this paper.

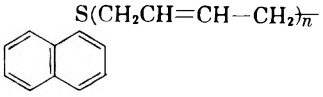
In addition, the methods of preparation and ultraviolet absorption spectra of certain model sulfides of naphthalene, which are closely related in structure to the naphthalene-containing polymer chain ends formed when the aforementioned naphthalene-containing thiols and disulfides are used in butadiene or styrene polymerization systems, are also reported. For example, 2-naphthyl benzyl sulfide, structurally related to the terminal groups formed by modification of a styrene polymerization system by 2-thionaphthol or its disulfide, *i.e.*



1-naphthyl allyl sulfide, related to a possible terminal group formed by modification of butadiene

(1) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, 17, 221 (1955).

polymerization by 1-thionaphthol or its disulfide, *i.e.*



(neglecting possible terminal groups formed as a result of 1,2 polymerization), as well as 1-naphthylmethyl benzyl sulfide, related similarly to the terminal groups formed by modification of styrene polymerization by 1-naphthyl-methanethiol, and the 1- and 2-naphthyl phenyl sulfides are so characterized herein.

The syntheses of 2-naphthylmethyl β-hydroxyethyl sulfide and 1,5-bis-(β-naphthylmethylthio)-*n*-pentane are also described.

Ultraviolet Absorption Spectra. It will be observed that two families of ultraviolet absorption curves are represented in Figs. 1 and 2. The curves shown in Fig. 1, which represent a family of sulfur derivatives of naphthalene in which the sulfur atom is separated from the naphthalene chromophore by at least one carbon atom, resemble the ultraviolet absorption spectra of the alkylnaphthalenes to which they are related. The curve for 2-naphthylmethane thiol (VII) bears a strong resemblance to that of 2-methylnaphthalene (XVII),[2a] the presence of the thiol group in the former compound contributing a slight bathochromic effect and general enhancement of molar extinction with respect to the spectrum of the hydrocarbon. In the same manner, the small family of closely related curves represented by 1-naphthyl methanethiol (VI), and its carbon- and sulfur-substituted derivatives, 1-(α-naphthyl)-2-methyl-propanethiol-2 (XI), and 1-naphthylmethyl benzyl sulfide (VIII), bear the same relationship to the curve of 1-methylnaphthalene (XVI).[2b] On the other hand, Fig. 2 represents a family of ultraviolet absorption curves containing sulfur derivatives of naphthalene in which the sulfur atom is adjacent to the naphthalene chromophore (thus containing either 1- or 2-naphthylthio- units).

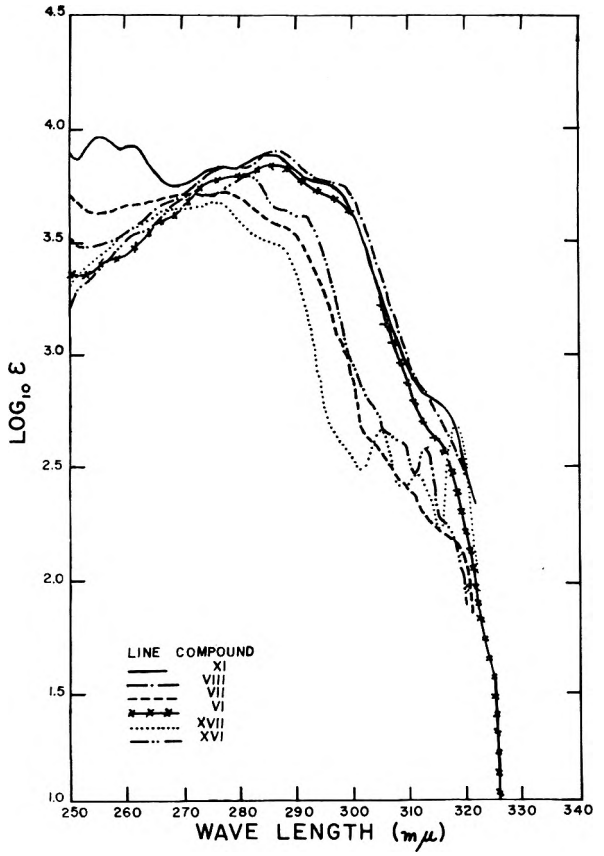


Fig. 1. Ultraviolet absorption spectra of alkylnaphthalene derivatives with sulfur-containing functions substituted on the side chain. The curves of the following compounds were obtained from chloroform solutions: 1-(α-naphthyl)-2-methyl-propanethiol-2 (XI); 1-naphthylmethyl benzyl sulfide (VIII); 2-naphthyl-methanethiol (VII); 1-naphthyl-methanethiol (VI). The curves for 1-methylnaphthalene (XVI), and 2-methylnaphthalene (XVII), which were obtained from 95% aqueous ethanol, were reproduced from the Friedel and Orchin compendium[2a,b]

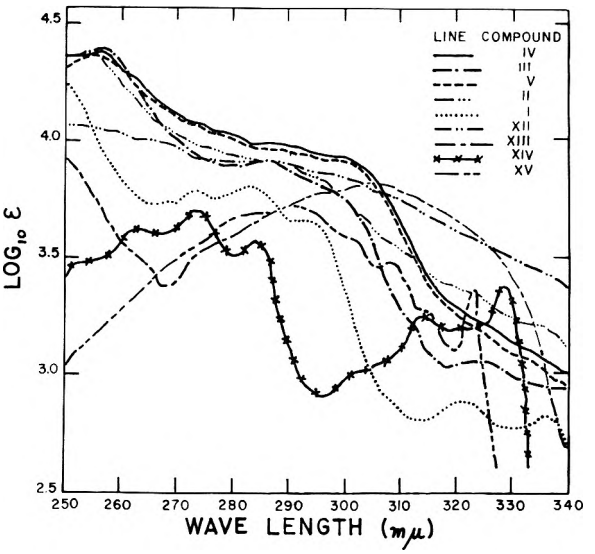


Fig. 2. Ultraviolet absorption spectra of naphthylthio-containing compounds. The curves of the following compounds were obtained from chloroform solutions: 1-naphthyl phenyl sulfide (IV); benzyl 2-naphthyl sulfide (III); 2-naphthyl phenyl sulfide (V); di-2-naphthyl disulfide (II), 2-thionaphthol (I); di-1-naphthyl disulfide (XII); 1-naphthyl allyl sulfide (XIII). The curves for 1-naphthol (XV), and 2-naphthol (XIV) which were reproduced from the compendium by Friedel and Orchin,[2c,d] were obtained from cyclohexane solutions. The ordinate for the curves of di-1- and di-2-naphthyl disulfide is $\log_{10}(\epsilon/2)$ whereas those of all other curves is $\log_{10}\epsilon$, where ϵ is the molar extinction coefficient

It will be observed that the simplest member of this series, 2-thionaphthol (I), has a spectrum resembling that of 2-naphthol (XIV),[2c] but with the peaks typical of the naphthalene chromophore

(2) The following ultraviolet absorption spectra are reprinted with permission from Friedel and Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951: a. Spectrum No. 197; b. Spectrum No. 196; c. Spectrum No. 237; d. Spectrum No. 236; e. Spectrum No. 268.

shifted even more bathochromically by the thiol auxochrome than the naphthalene chromophore is by a 2-hydroxy function (with a thiol peak value of λ_{max} 283 mμ, log ϵ 3.81, as compared with λ_{max} 273 mμ, log ϵ = 3.70 for that of 2-naphthol). It will be observed that the curve of 2-thionaphthol (I), unlike that of the corresponding naphthol XIV, rises in absorbance with decreasing wave length between 265 mμ and 250 mμ. In this respect the spectrogram of 2-thionaphthol resembles that of other members of the family of curves containing naphthylthio groups. The other compounds represented in Fig. 2 either have a similar rise in absorbance in this region, i.e. di-1 and di-2-naphthyl disulfides and 1-naphthyl allyl sulfide, or have peaks at log ϵ 4.37–4.40 in the region of 255–257 mμ, i.e. 1- and 2-naphthyl phenyl sulfides (IV and V), and 2-naphthyl benzyl sulfide (III). The latter series of peaks may be representative of a sulfur-benzene conjugative band which may be related to the peak found by Koch[3] in cyclohexyl phenyl sulfide at λ_{max} 257.5 mμ, log ϵ = 3.7. (Note that 2-naphthyl benzyl sulfide has an insulating methylene group between the benzene ring and the sulfur atom.)

Although Koch found a similar band at λ_{max} 250 mμ, log ϵ 4.07 in diphenyl sulfide, he did not attribute it to the same sulfur-benzene conjugative band found in this region in cyclohexyl phenyl sulfide but rather to a quasi-conjugation between aromatic rings and the 3*p* orbital of the sulfur atom. Koch did find a peak at λ_{max} 274 mμ, log ϵ 3.76 in diphenyl sulfide which, partly on the basis of the correspondence of its peak value with that of the 257.5 mμ band of the cyclohexyl phenyl sulfide, he attributed to this sulfur-benzene conjugative band.

It will be observed that in the whole family of naphthyl thio-containing compounds, there may be found either a series of inflections followed by a shoulder, or a series of distinct peaks in the region from 270 mμ to 310 mμ. These are undoubtedly related to the series of peaks found in naphthalene between 260–290 mμ. The general shape of the curves for 1-naphthyl and 2-naphthyl phenyl sulfides (IV and V), 2-naphthyl benzyl sulfide (III), and di-2-naphthyl disulfide (II) is very similar to that illustrated by Koch for diphenyl disulfide which has a peak at λ_{max} 238, log ϵ 4.2 and inflections near 270 mμ and 300 mμ. The fact that the molar extinction value of the corresponding thiol (as indicated in Fig. 2 where the absorbancy for the disulfide, whose ordinate is plotted as log (ϵ/2) is a little greater than that of the thiol, whose ordinate is plotted as (log ϵ) does tend to affirm: 1. the idea of a contribution to the resonance of the diaryl disulfide molecule through the two sulfur atoms (as proposed by Koch for the diphenyl disulfide system as caused by alternately charged resonating phenylthio chromophores) and 2. the general additive nature of the ultraviolet absorption of the two naphthylthio chromophore units in the disulfide molecule.

The presence of a peak in 2-naphthyl benzyl sulfide (III) at λ_{max} 286 mμ, log ϵ 3.92, bears a similar relationship to the one present in 2-naphthol (XIV) at λ_{max} 273 mμ, log ϵ 3.70, as the peak in 1-naphthyl allyl sulfide (XIII) at λ_{max} 303–304 mμ, log ϵ 3.82, bears to the one in 1-naphthol (XIV)[2d] at λ_{max} 290 mμ, log ϵ 3.71.

Syntheses. The known mixed aryl sulfides,[4,5] 1- and 2-naphthyl phenyl sulfides (IV and V) were both obtained, surprisingly enough, from the reaction mixture of the sodium salt of 2-thionaphthol (a technical grade product) with iodobenzene in presence of copper powder, along with diphenyl disulfide and mixed di-naphthyl disulfides. Since the presence of 1-thionaphthol could not be detected in the 2-thionaphthol reagent used, it appears that presence of 1-naphthyl phenyl sulfide in the reaction product was the result of a rearrangement.[6]

The 1- and 2-naphthyl methanethiols (VI and VII) were obtained in standard fashion by treatment of 1-chloromethylnaphthalene and 2-bromomethylnaphthalene with thiourea followed by subsequent basic hydrolysis of the thiouronium salts. Compound VI, which has been prepared previously,[7] is an oil, whereas the analogous new 2-naphthyl compound, VII, is a crystalline solid.

The new compounds 1-naphthyl allyl sulfide (XIII), 1-naphthylmethyl benzyl sulfide (VII), and 2-naphthylmethyl β-hydroxethyl sulfide (IX) were prepared by treatment of the alkali metal salts of the respective thionaphthol and naphthylmethanethiols with suitable alkyl, aralkyl or hydroxyalkyl halides in a manner similar to that used for the preparation of 2-naphthyl benzyl sulfide (III), a known compound,[8a,b] from 2-thionaphthol.

The bismonosulfide, 1,5-bis(β-naphthylmethylthio)-*n*-pentane (X), was synthesized by treatment

(3) H. P. Koch, *J. Chem. Soc.*, 387, 394 (1949).

(4) E. Bourgeois, *Ber.*, **28**, 2327 (1895).

(5) F. Krafft and E. Bourgeois, *Ber.*, **23**, 3045 (1890).

(6) It is possible that both β-naphthyl and β-naphthylmercaptyl radicals, as well as phenyl and phenylmercaptyl radicals were formed in the reaction mixture by thermal cleavage at 220°. Under such circumstances α-naphthyl phenyl sulfide could be formed by recombination of either a β-naphthyl or β-naphthylmercaptyl radical which had rearranged to the α-form, with the appropriate benzenoid radical. This explanation would account for the presence of diphenyl disulfide as well as a mixture of di-naphthyl sulfides in the reaction product. It is to be noted that lead aryl mercaptides are known to decompose when heated to form lead sulfide and di-aryl sulfides.

(7) This mercaptan has been prepared previously by W. Windus and H. G. Turley, *J. Am. Leather Chem. Assn.*, **33**, 246 (1938), *cf. Chem. Abstr.*, **32**, 8821 (1938), as an oil, b.p. 165–175°/16 mm., by treating the corresponding carbinol with potassium hydrosulfide.

(8) a. H. Rheinboldt, F. Berti, M. Perrier, W. Pregnolatto, G. Cilento, and G. Nazario, *Univ. São Paulo, Fac. filosof., ciênc. e letras, Quim. No. 3 Bol. No. 129*, **8** (1951); *cf. Chem. Abstr.*, **46**, 7554 (1952); b. D. S. Tarbell and D. P. Harnish, *J. Am. Chem. Soc.*, **74**, 1862 (1952).

of disodium pentamethylene dimercaptide with 2-bromomethyl-naphthalene.

The tertiary mercaptan 1-(α-naphthyl) 2-methyl-propanethiol-2 (XI) was prepared by hydrosulfurating 1-methallyl-naphthalene.

EXPERIMENTAL[9]

Absorption Spectra. The ultraviolet absorption spectra of di-1-naphthyl disulfide, 1-naphthyl allyl sulfide, and 1-(α-naphthyl)-2-methyl-propanethiol-2 were determined with a Cary Recording Spectrophotometer, Model 11. All other ultraviolet absorption spectra shown, other than those reproduced from Friedel and Orchin's compendium,[2] were determined with a Model DU Beckman quartz spectrophotometer. The solvent used for all samples and blanks was chloroform (Baker and Adamson tech. grade).

2-Thionaphthol (I). Du Pont's commercial product, pre-extracted with hot methanol, was treated with aqueous potassium hydroxide. By adding mineral acid to the alkaline extract, the thiol was reprecipitated. The collected, washed, dried precipitate was recrystallized twice from absolute ethanol to m.p. 81.8–82.4° (reported m.p. 81°[10]). The ultraviolet absorption spectrum obtained from this sample was very similar to that published for this compound by Friedel and Orchin.[2e]

Di-2-naphthyl disulfide (II). A solution of 64.0 g. of I (E. I. du Pont commercial grade β-thionaphthol) in 260 ml. of hot ethanol was filtered through a medium porosity sintered glass funnel and the residue discarded. To the filtrate, in a 3 neck 3 l. flask equipped with heating mantle, mechanical stirrer, and reflux condenser, was added 50.4 g. of iodine, in a slurry in 800 ml. methanol with stirring. The mixture was refluxed for 1 hr., and the disulfide precipitate was washed with 3 portions of 95% aqueous alcohol, then with water, and oven dried. The crude white disulfide product, weighing 51.5 g. (80.5%) having m.p. 140.5–141.5°, was recrystallized twice from benzene and once from chloroform to form yellow-white flakes of m.p. 141.8–142.6° (reported m.p. is 139°[11]).

2-Naphthyl benzyl sulfide (III). Although this compound was prepared twice in recent years[8a,b] by treatment of an alkaline solution of I with benzyl chloride, details of these preparations were not given. Therefore, our preparation of III is described as follows: To a refluxing solution of potassium 2-naphthyl mercaptide (0.086 mole) in aqueous ethanol (prepared from 13.9 g. I, 5.8 g. potassium hydroxide pellets, 400 ml. abs. ethanol, and 20 ml. water), was added, dropwise, a solution of 12.7 g. benzyl chloride (0.10 mole) in 50 ml. ethanol. After 2 hr. at reflux, the system was cooled and diluted with several volumes of water, thus precipitating the crude sulfide product. Unreacted thiol was removed from the product by extracting with hot 10% aqueous potassium hydroxide. The residual sulfide, an oil which solidified upon cooling to 0°, was washed with water and recrystallized from abs. ethanol, forming 10.6 g. of fine white crystals, m.p. 87.4–89.9 (49%), which melted at 89.8–90.5° when recrystallized again from this solvent. Analytical data for this compound are to be found in Table I.

Compounds 1-naphthylmethyl benzyl sulfide (VI), 2-naphthylmethyl β-hydroxyethyl sulfide (IX), 1,5-bis-(β-naphthylmethylthio)-n-pentane (X), and 1-naphthyl allyl sulfide (XIII) were prepared by the same general procedure as that used to prepare III. Pertinent data relating to these preparations may be found in Table I.

1- and 2-Naphthyl phenyl sulfides (IV and V). To 25.0 g. (0.137 mole) of sodium 2-naphthyl mercaptide (prepared by concentrating an alkaline extract obtained from Du Pont commercial grade β-thionaphthol) was added 8.4 g. of iodobenzene, and 1.0 g. of copper powder. After refluxing the system at 188° for 3 hr., the mixture was cooled, diluted with benzene, and filtered. After distilling benzene and iodobenzene from the filtrate *in vacuo*, the residual 24.7 g. of semisolid sulfides was fractionally distilled. The following fractions were obtained:

1. 0.5 g. orange oil, b.p. 125–137°/0.25 mm. (diphenyl disulfide).
2. 12.4 g. yellow oil, b.p. 144–156°/0.25 mm., m.p. 47.5–50°.
3. 5.0 g. yellow oil, b.p. 154–165°/0.25 mm., m.p. 38–41°.
4. 3.6 g. amber oil, b.p. 170–223°/0.25 mm. (dinaphthyl sulfides).
5. 2.0 g. black, greasy, solid residue.

By recrystallizing fraction 2 twice from absolute ethanol, 5.7 g. of 2-naphthyl phenyl sulfide (V), m.p. 50.7–51.7°, (17.6%) was obtained. The product melted at 51.2–52.2° (reported m.p. 51.8°[4]) after a third recrystallization. Recrystallization of fraction 3 from 93% aqueous ethanol yielded 3.3 g. of 1-naphthyl phenyl sulfide (IV), m.p. 39.0–40.5° (11.7%). The product melted at 40.0–41.0° (reported m.p. 41.8°[5]) after another recrystallization.

Analysis of crude β-thionaphthol. By extracting 10.0 g. of crude β-thionaphthol with several 100 ml.-portions of chloroform, and removing solvent from the extract, 7.4 g. of thiol, m.p. 73–77° (compared with m.p. 81.8–82.4° for pure II) was obtained. The chloroform insoluble residue was primarily a metallic powder which could be decomposed with mineral acid.

By treating 4.00 g. (0.0250 mole) of the extracted thiol in alcohol solution containing an equivalent of aqueous sodium hydroxide with an alcohol solution of 5.06 g. (0.0250 mole) of 2,4-dinitrochlorobenzene by the method of Bost *et al.*,[12] 6.57 g. (80%) of crude dinitrophenyl sulfide, m.p. 120–130°, was isolated. Careful repeated fractional recrystallization of the product from hot 2:1 ethanol/benzene solution yielded 5.21 g. of the 2,4-dinitrophenyl sulfide of β-thionaphthol (XIV), a golden yellow solid, m.p. 149–150°, (reported m.p. of 145°[12b]), 0.33 g. of di-β-naphthyl disulfide, m.p. 141.5–142.5° (which did not depress the m.p. of authentic II, but did depress the m.p. of XIV) and about one gram of a solid of m.p. 103–135°, believed to be a mixture of II and XIV. No trace of the α-2,4-dinitrophenyl sulfide (known to melt at 176°[12b]) could be found.

1-Naphthyl-methanethiol (VI). This compound was prepared by converting 1-chloromethyl-naphthalene (obtained by chloromethylating naphthalene[13]) to the corresponding thiol by the method of Urquhart *et al.*[14]

To 19.4 g. (0.110 mole) of 1-chloromethylnaphthalene, b.p. 122–124°/1.8 mm., was added 8.4 g. (0.11 mole) of thiourea, and 60 ml. of 98% aqueous ethanol. After refluxing the mixture for 7 hr., it was treated with a solution of 6.8 g. of sodium hydroxide, and refluxed for another 2 hr. Most ethanol was removed by distilling *in vacuo*. The residue was acidified with mineral acid, treated with brine solution, and extracted with benzene. The benzene extract was washed, dried, and the benzene removed by distillation *in vacuo*. The residual 17.5 g. of yellow oil (consisting of desired mercaptan of 91.2% purity on basis of an amperometric titra-

(9) All melting points are corrected. Element analyses were done by Messrs. William C. Hukari and Wellman W. Dietz of this laboratory.

(10) F. Krafft and R. Schönherr, *Ber.*, **22**, 824 (1889).

(11) P. T. Cleve., *Ber.*, **21**, 1100 (1888).

(12) a. R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932); b. R. W. Bost, J. O. Turner, and M. W. Conn, *J. Am. Chem. Soc.*, **55**, 4956 (1933).

(13) A. Cambron, *Can. J. Research*, **17B**, 10 (1939); *cf. Org. Reactions*, **I**, 70 (1942).

(14) G. G. Urquhart, J. W. Gates, Jr., and R. Connor, *Org. Syntheses*, **21**, 36 (1941).

TABLE I

PREPARATION OF MIXED NAPHTHALENE-CONTAINING SULFIDES

Sulfide	Formula	M.P.,[a] °C.	Recryst. Solvent	Crude Yield,[b] %	Reactants		Analysis of Sulfides					
							Carbon, %		Hydrogen, %		Sulfur, %	
					Thiol	Halide	Calcd.	Found	Calcd.	Found	Calcd.	Found
2-Naphthyl benzyl (III)	$C_{17}H_{14}S$	89.8–90.5[c]	Abs. EtOH	49	2-Naphthalene	Benzyl chloride	81.58	81.25 81.10	5.64	5.78 5.73	12.81	12.67 12.71
1-Naphthyl phenyl (IV)[d]	$C_{16}H_{12}S$	39.0–40.5	95% EtOH	12	2-Naphthalene	Iodobenzene	81.34	80.88 80.70	5.12	5.08 4.98	13.56	13.98 14.00
2-Naphthyl phenyl (V)[d]	$C_{16}H_{12}S$	50.7–51.7	Abs. EtOH	18	2-Naphthalene	Iodobenzene	81.34	81.35 81.55	5.12	5.07 5.02	13.56	13.85 13.81
1-Naphthylmethyl benzyl (VIII)	$C_{18}H_{16}S$	57.0–57.3	95% EtOH	85	1-Naphthyl-methane	Benzyl chloride	81.77	81.55 81.50	6.10	5.73 5.68	12.12	12.08 12.14
2-Naphthylmethyl β-hydroxyethyl (IX)	$C_{13}H_{14}OS$	52.0–53.5[e]	65% EtOH	100	2-Naphthyl-methane	Ethylene chloro-hydrin	72.76	71.65 71.40	6.18	6.38 6.42	14.04	14.45 14.59
Bis(β-naphthylmethyl) pentamethylene (X)	$C_{27}H_{28}S_2$	97.6–98.6	$CHCl_3/n$-C_6H_{14}	34	Pentamethyl-ene di-[g]	2-Bromomethyl-naphthalene	77.84	77.50 77.35	6.77	6.87 6.68	15.39	15.13 15.20
1-Naphthyl allyl (XIII)	$C_{13}H_{12}S$	·	—	78	1-Naphthalene	Allyl bromide	77.93	78.08 77.90	6.04	5.79 5.88	16.01	15.60

[a] Corrected melting points of analytical samples. [b] Yields are based upon products of less than 4° melting range, or in case of XIII, on oil of 95% purity. [c] Reported melting points for III are 90.7°[8a] and 88.5–89.0.[8b] [d] Compound was separated from reaction product containing its positional isomer (see experimental section). Reported m.p. of IV is 41.8°;[5] that of V is 51.8°.[4] [e] Compound depressed melting point of pure 2-naphthylmethane thiol (VII) of m.p. 47.2–47.7° to 40–50°. [f] Compound was a yellow, fluorescent oil with garlic like odor, with b.p. 153.3–155.3/4.2 mm., n_D^{20} 1.6162. [g] See reference 17 for source.

tion with silver nitrate solution[15]) was distilled. In this way, 15.1 g. of colorless oil, b.p. 142.0–143.0°/0.5.0 mm., n_D^{20} 1.6628 (78.6%) was obtained.[7]

Anal. Calcd. for $C_{11}H_{10}S$: C, 75.79; H, 5.78; S, 18.39. Found: C, 75.25, 75.40; H, 5.78, 5.68; S, 17.75, 18.00.

2-Naphthylmethanethiol (VII). Essentially the same procedure was employed for synthesis of VII as that for synthesis of VI. The 2-bromomethyl-naphthalene used in this preparation was synthesized from 2-methylnaphthalene (Matheson, Coleman & Bell pract. grade) by the procedure of Buu-Hoï.[16] A yield of 26.6 g. of crude mercaptan (VII) (79.9%) was obtained in crops of 18.0 g., m.p. 46–49°, and 8.6 g., m.p. 41–43°, by treating 42.2 g. (0.191 mole) of 2-bromomethyl-naphthalene with thiourea and base in the prescribed manner. By reprecipitating the first crop of mercaptan from aqueous-alcoholic alkaline solution with mineral acid, and recrystallizing the precipitate so obtained from absolute ethanol, 9.5 g. of pure thiol, m.p. 47.2–47.7° was obtained.

Anal. Calcd. for $C_{11}H_{10}S$: C, 75.79; H, 5.78; S, 18.39. Found: C, 75.95, 76.20; H, 6.10, 5.93; S, 18.33, 18.08.

1-(α-Naphthyl)-2-methylpropanethiol-2 (XI). This mercaptan was prepared by hydrosulfurating crude 1-methallylnaphthalene. The hydrocarbon was prepared, essentially, by the method used by Bordwell *et al.*[18] to prepare methallylbenzene.

Crude 1-methallylnaphthalene. A Grignard reagent, obtained by interaction of 104 g. of 1-bromonaphthalene (0.500 mole of Eastman Kodak white label product) with 12.2 g. magnesium turnings (Merck Grignard grade) in 500 ml. abs. ether (predried over sodium) under nitrogen atmosphere, was treated, first, with a solution of 50 ml. anhyd. ether and 200 ml. anhyd. benzene (C.P.), then, with an 0.500 mole quantity of β-methallyl chloride (Matheson, Coleman & Bell pract. grade), added, dropwise, over a 0.5 hr. period to the Grignard system on a warm water bath. The system was refluxed for 2 hr., hydrolyzed with 330 ml. of 10% sulfuric acid, and the layers separated. By removing ether, β-methallyl chloride and benzene from the washed, dried, ether layer, 89.4 g. of amber colored oil was obtained. After removal of a 14 g. forecut of naphthalene and 1-bromonaphthalene between b.p. 78–123°/7.5 mm., a 57.9 g. fraction of crude 1-methallylnaphthalene, b.p. 128–132°/6.9 mm., was obtained (63.6%[19]). The product was known to contain some 1-bromonaphthalene (which boils at 122–125°/5 mm.) but was used without further purification.

Hydrosulfuration. The crude 1-methallylnaphthalene was placed in the glass liner for a 1 liter stainless steel autoclave and cooled to −78°. To the hydrocarbon was added 10 ml. of a 48% solution of boron trifluoride in ether and 90 g. of liquid hydrogen sulfide. The glass liner (wiped free of frost) was inserted into the 1-l. steel autoclave, which had been precooled to −78°, and the autoclave sealed. The autoclave was allowed to warm to room temperature, and to stand at this temperature for 88 hrs. The vessel was opened under a hood, the product poured into water, and extracted with ether. By removing ether from the washed, dried ether extract, 60.5 g. of brown oil was obtained. The product, which contained 83.2% of desired mercaptan (on basis of amperometric titration with silver nitrate[15]), could not be purified further by formation of the lead mercaptide (a taffy-like yellow semi-solid) and liberation of the mercaptan with mineral acid. By distilling 27.4 g. of crude mercaptan under nitrogen atmosphere, the following fractions were obtained: 1. 8.6 g. of yellow oil, b.p. 152–155°/5.0 mm. (containing mercaptan of 94.5% purity). 2. 10.2 g. of pale yellow fluorescent oil, b.p. 155.7–160.0°/5.0 mm., n_D^{20} 1.6162 (containing mercaptan of 97.1% purity).

Thus, the over-all yield of fairly pure thiol (XI) in two steps from 1-bromonaphthalene is 34.8%.

Fraction 2 was used for determination of ultraviolet absorption spectrum and for element analysis.

Anal. Calcd. for $C_{14}H_{16}S$: C, 77.71; H, 7.45; S, 14.82. Found: C, 77.45, 77.30; H, 7.76, 7.65; S, 14.84, 14.79.

Di-1-naphthyl disulfide (XII). This compound was prepared in two ways. *A. By Leuckart method.* By treating diazotized 1-naphthylamine with potassium ethyl xanthate, and hydrolyzing the resultant xanthate ester with base (following the Tarbell and Fukushima adaptation of the Leuckart method for preparation of *m*-thiocresol[20]) a 19 g. (48%) quantity of crude brown colored mercaptan oil was obtained. Upon distilling this oil, a total of 5.5 g. of mercaptan, b.p. 131°/4.5 mm., and disulfide, b.p. 165°/3 mm. was obtained. By treating the combined distillate with as much iodine/aqueous potassium dioxide solution as could be decolorized by the oil, extracting the oxidation product with benzene, isolating the product, triturating with hexane, and collecting the crystals, 2.3 g. (5.7%) of yellow-white needles, m.p. 87.1–88.4°, was obtained. By recrystallizing the product from 15 pts. hot *n*-hexane, 1.48 g. of pale yellow needles, m.p. 89.4–89.9°, were obtained. (Compare with needles, m.p. 91°, from pet. ether reported by Leuckart,[21] and with leaflets, m.p. 85°, from ethanol reported by Schertel[22]). This sample was used for ultraviolet absorption spectrum determination.

B. By Grignard method. By converting a 2.00 mole quantity of 1-bromonaphthalene to the Grignard reagent by treatment with a 50% excess of magnesium turnings, in ether solvent, under nitrogen atmosphere, allowing the Grignard to react with two gram atom equivalents of sulfur, hydrolyzing the complex, and isolating the mercaptan in the usual manner,[23] 312 g. of oil, containing a 68:29 ratio of mercaptan to disulfide[24] (or a 95.6% yield of naphthylthio units) was obtained. By treating an aliquot portion of the oil mixture with sufficient iodine/potassium iodide solution to oxidize all mercaptan to disulfide, and recrystallizing the

(15) I. M. Kolthoff and W. E. Harris, *Ind. Eng. Chem., Anal. Ed.*, **18**, 161 (1946).

(16) Ng. Ph. Buu-Hoï, *Ann.*, **556**, 8 (1944).

(17) This compound was supplied to us by Mr. Max. H. Keck of this laboratory, who prepared it from the dibromide by the thiourea method (see ref. 14) in a manner, similar to that of one of the two methods by which W. P. Hall and E. E. Reid, *J. Am. Chem. Soc.*, **65**, 1466 (1943), prepared this compound. One of the boiling points recorded for this compound by H. and R. is 90.1°/10 mm. These workers also prepared this dithiol by treatment of the dibromide with sodium hydrosulfide.

(18) F. G. Bordwell, C. M. Suter, and A. J. Webber, *J. Am. Chem. Soc.*, **67**, 830 (1945).

(19) H. F. Hipsher and P. H. Wise, *Nat'l Advisory Comm. for Aeronaut. Tech. Note No. 2430*, 19 (1951), *cf. Chem. Abstr.*, **46**, 8074 (1952), report preparation of a crude uncharacterized form of this hydrocarbon, in 85% yield, by their own modification of the same general method. They fractionated an undisclosed quantity of crude isomeric 1-(α-naphthyl), 2-methylpropene-1 from this product.

(20) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, **Coll. Vol. III**, 809 (1955).

(21) Leuckart, *J. prakt. Chem.*, [2] **41**, 217 (1890).

(22) A. Schertel, *Ann.*, **132**, 94 (1864).

(23) A method used to prepare a similar mixture by Taboury, *Compt. rend.*, **138**, 982 (1904), who gave no details of the mixture ratio or yield.

(24) As determined by a method developed by Dr. Glen E. Meyer of this laboratory, as reported by G. E. Meyer, R. J. Coleman, and R. M. Pierson, "Behavior of Some Bis-Type Modifiers in Emulsion Butadiene Polymerization," private communication to Office of Synthetic Rubber, FFC 1954, based upon the fact that di-aryl disulfides are cleaved quantitatively by treatment with sodium sulfite, generally to one mole of sodium mercaptide and one mole of Bunte salt, and in special cases to two moles of sodium mercaptide. The mercaptide content is then determined by potentiometric titration with standardized silver nitrate solution.

crude solid disulfide from a 95% aqueous ethanol/*n*-hexane mixture, disulfide was obtained in two crops of 117 g. of yellow-orange crystals, m.p. 87.3–88.3°, (36.8%) and 17.5 g. of very fine pale yellow crystals, m.p. 81–83° (5.3%). The melting point of the higher melting crop was increased to m.p. 89.7–90.6° by recrystallization from 95% aqueous acetic acid. Titrimetric analysis of this product by the sodium sulfite silver nitrate method,[24] indicated a purity of 99% of XII.

1-Naphthyl allyl sulfide (XIII). By treating 60.8 g. of 1-thionaphthol (0.380 mole) with equivalent quantities of alcoholic potassium hydroxide and allyl bromide (Halogen Chem. Co.) in much the same manner as that used to prepare III, the crude mixed sulfide was isolated as a golden oil. By distilling this oil, two fractions of desired sulfide were obtained: 1. 26.8 g., b.p. 153.3–155.3°/4.2 mm., and 2. 22.3 g., b.p. 154.3–157.4°/4.2 mm., both distillates being fluorescent yellow oils (78%) with distinct garlic-like odors. Fraction 1 was used as a sample for both ultraviolet absorption spectrum determination and element analysis.

Acknowledgment. We are grateful to Mr. Robert W. Schrock and to Dr. Glen E. Meyer for their efforts in determining mercaptan and disulfide content of various compounds, to Messrs. Richard J. Coleman, Albert J. Costanza, and to Dr. Edward F. Devlin, for determining the ultraviolet absorption spectra of various compounds, and to Dr. Teh Fu Yen for preparing some di-1-naphthyl disulfide. We are indebted to Dr. H. J. Osterhof for permission to publish this work.

AKRON, OHIO

(CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY)

Studies on the Chemistry of Heterocyclics. XXXII.* Preparation and Absorption Spectra of Triarylmethane Dyes Containing a Thiophene or a Thianaphthene Ring

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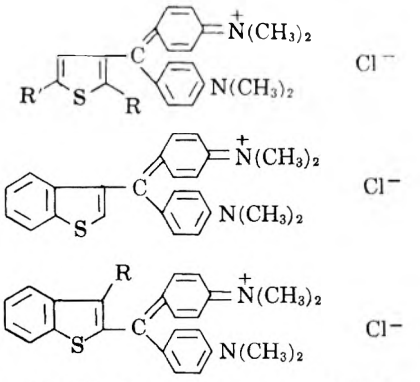
The preparation of some new thiophene and thianaphthene dyes and their derivatives has been presented and discussed. The absorption spectra of 3-Thianaphthene Malachite Green, 2-Thianaphthene Malachite Green and its derivatives, 3-Thiophene Malachite Green and its derivatives have been determined and compared with the absorption spectra of Malachite Green. An interpretation of the bathochromic effects of the thiophene and thianaphthene rings in triarylmethane dyes has been offered.

It was demonstrated earlier[3] that replacement of one of the phenyl rings in Malachite Green by a thiophene ring produces a bathochromic shift of the secondary absorption band. In a continuation of the study of the effect on the absorption spectrum of Malachite Green, of replacing one of the phenyl rings by a heterocyclic ring, a number of dyes containing either a thiophene ring or a thianaphthene ring were prepared and their absorption spectra measured. Furthermore, dyes containing various substituents on the heterocyclic moiety were also prepared to investigate the effects of these substituents.

The dyestuffs studied were those shown in the accompanying formulas.



Where R = H, CH_3, Br or Cl and R′ = H, CH_3.

The general method of preparation consisted of the condensation of the appropriate aldehyde or the substituted aldehyde with two molecules of dimethylaniline using anhydrous zinc chloride as the condensing agent. The oxidation of the leuco compounds so obtained to the dyes was achieved using manganese dioxide and sulfuric acid. The dyes were isolated as their zinc chloride complex salts. The dye bases were prepared by basification of the dye solutions with aqueous sodium hydroxide solution. During the course of purification of the dye bases, a considerable polymerization was encountered. This observation was first made in the case of the dye base of 2-Thiophene Malachite Green.[3] It could be avoided to a certain extent by isolating the dye bases immediately upon formation.

* For communication XXXI of this series see *J. Org. Chem.*, **21**, 419 (1956).

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(3) C. D. Mason and F. F. Nord, *J. Org. Chem.*, **16**, 722 (1951).

The identities of the dyes were established by their methods of preparation, analyses of the leuco bases and the dye bases and by their characteristic absorption spectra.

Of the aldehydes and the substituted aldehydes required for the preparation of these dyes, 3-bromo-, 3-chloro-, and 3-methyl-2-thianaphthenecarboxaldehyde have not been reported previously. These were prepared from the respective 3-substituted thianaphthene derivatives which are known, metalating them using *n*-butyllithium and treating the aryllithium compounds with *N*-methylformanilide. Hydrolysis of the complexes so formed gave the desired aldehydes.

Absorption spectra. The absorption spectra of triarylmethane dyes are of a particular type between 800 and 200 mμ. Three principal bands are observed, which have been referred to as the x, y, and the x′ bands.[4] The x and the y bands are in the visible region and in dilute solutions practically symmetrical. The x band is the main band and has the highest extinction.

According to the prevailing theory,[4] the main absorption band of Malachite Green is characterized by an oscillation of the electron cloud across the molecule between the two auxochromes. The y band corresponds to an oscillation through the phenyl group along an axis perpendicular to the main axis, while the x′ band has been associated with a secondary oscillation of a higher amplitude. In a dye such as Malachite Green, the y band is of a shorter wave length, since the resonance in the y direction involves a carbonium ion, which has a lower stability than an ammonium nitrogen atom. Any alteration in the structure of Malachite Green which affects the phenyl group such as replacement with a thienyl or a thianaphthenyl group, will be most pronounced in the shift of the y band. Results of these replacements can be seen in Figs. 1 and 2.

The x′ band is observed in the ultraviolet region of the spectrum. According to Lewis and Bigeleisen,[5] the main band of a molecule of a frequency V corresponds to the difference in energies between the ground state and the first excited state. When a molecule receives a higher excitation to the second excited state, resulting in an electronic oscillation of a higher amplitude in the direction of polarizability, a second band of frequency V′ is found, which is related to the x′ band. Since the differences in the energy levels are equal, the ratio V′/V should be exactly 2; however, the probability of such a jump is zero. In a molecule, in which the electronic oscillations are not entirely harmonic, as in the case of dye molecules, the energy levels of the successive excited states will lie closer together. In this case the ratio V′/V will be less than 2 and the ratio $\epsilon_{x'}/\epsilon_x$ greater than zero. However the ratio V′/V may be greater than 2, depending on the amplitude of the electronic displacements rela-

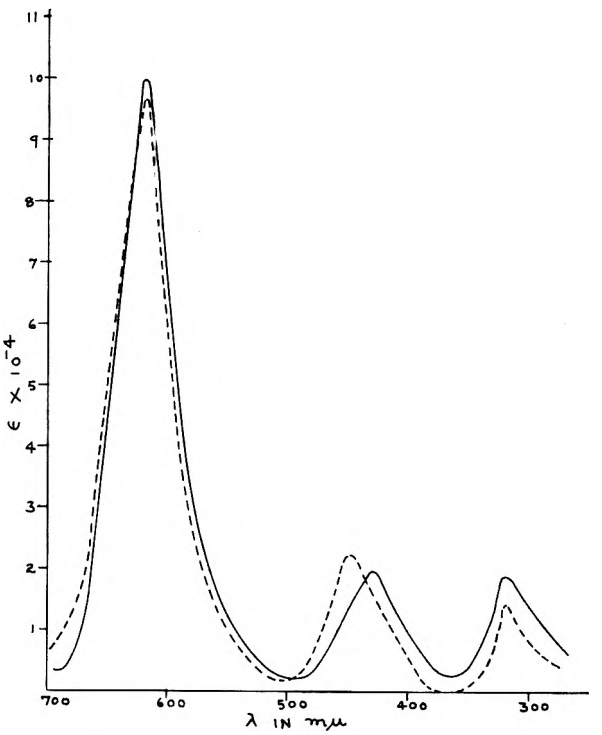


Fig. 1. Absorption spectra of Malachite Green and 3-Thiophene Malachite Green. Malachite Green, ———; 3-Thiophene Malachite Green, – – –

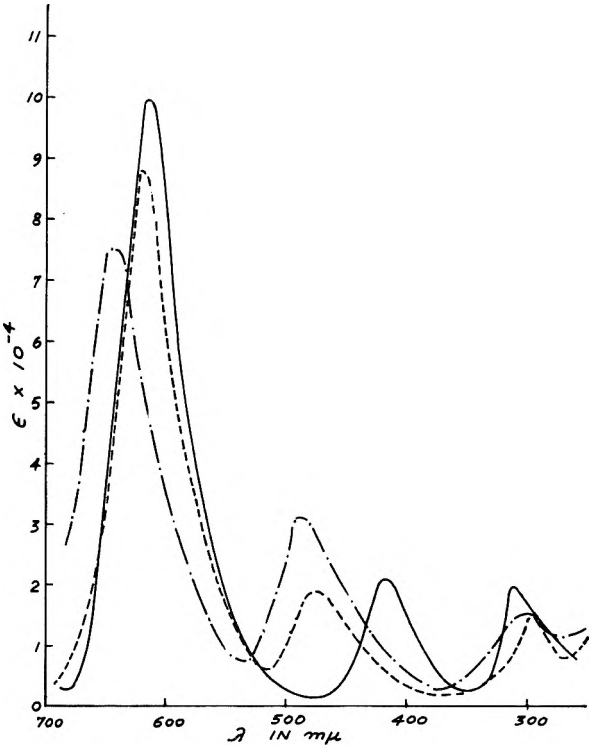


Fig. 2. Absorption spectra of Malachite Green and 2- and 3-Thianaphthene Malachite Greens. Malachite Green, ———; 3-Thianaphthene Malachite Green, – – – –; 2-Thianaphthene Malachite Green, –.–.–.

(4) G. N. Lewis and M. Calvin, *Chem. Revs.*, 25, 273 (1939).

(5) G. N. Lewis and J. Bigeleisen, *J. Am. Chem. Soc.*, 65, 2107 (1943).

TABLE I

ABSORPTION MAXIMA AND MOLECULAR EXTINCTION COEFFICENTS OF 3-THIOPHENE MALACHITE GREEN AND SUBSTITUTED DYES

Dye	λ_x, mμ	$\epsilon_x \times 10^{-4}$	λ_y, mμ	$\epsilon_y \times 10^{-4}$	$\lambda_{x'}$, mμ	$\epsilon_{y} \times 10^{-4}$	$\nu_{x'}/\nu_x$	$\epsilon_{x'}/\epsilon_x$
Malachite Green	620	9.91	428	1.88	320	1.76		
3-Thiophene Malachite Green	617	9.71	444	2.31	316	1.51	1.95	0.158
2,5-Dimethyl-3-Thiophene Malachite Green	619	10.4	464	1.92	321	1.28	1.93	0.123
2-Bromo-3-Thiophene Malachite Green	640	9.0	441	1.28	318	1.42	2.02	0.175
2-Chloro-3-Thiophene Malachite Green	642	10.70	441	1.63	318	1.88	2.01	0.158

TABLE II

ABSORPTION MAXIMA AND MOLECULAR EXTINCTION COEFFICIENTS OF THIANAPHTHENE MALACHITE GREEN DYES COMPARED WITH THOSE OF MALACHITE GREEN

Dye	λ_x, mμ	$\epsilon_x \times 10^{-4}$	λ_y, mμ	$\epsilon_y \times 10^{-4}$	$\lambda_{x'}$, mμ	$\epsilon_{x'} \times 10^{-4}$	$\nu_{x'}/\nu_x$	$\epsilon_{x'}/\epsilon_x$
Malachite Green	620	9.90	428	1.88	316	1.91		
3-Thianaphthene Malachite Green	627	8.87	476	1.86	304	1.53	2.06	0.171
2-Thianaphthene Malachite Green	645	7.56	492	3.10	311	1.50	2.07	0.198
3-Methyl-2-Thianaphthene Malachite Green	645	9.03	495	2.19	309	1.68	2.07	0.185
3-Bromo-2-Thianaphthene Malachite Green	661	8.10	480	1.54	309	1.65	2.13	0.203
3-Chloro-2-Thianaphthene Malachite Green	667	7.80	485	1.70	310	1.61	2.15	0.206

tive to the dimensions of the molecule.[5] Since the amplitude of the electron displacement depends on the polarizability of the molecule, it will be greater for those dyes with larger maximum wave lengths of absorption. Hence, in a series of similar compounds, as the value of λ_{max} of the x band increases, the ratio of the frequencies of the x′ and the x band, V′/V, will increase even to the extent of exceeding 2, and simultaneously the ratio $\epsilon_{x'}/\epsilon_x$ will decrease. When the thianaphthene dyes are placed in the order of increasing λ_x a gradation of the ratio of frequencies is evident, as can be seen in Table II. However, such a gradation is not seen in the case of the thiophene dyes (Table I).

Both the hetorocyclic rings produce a bathochromic shift of the y band of Malachite Green, as can be seen from the data listed in Tables I and II. It will also be recognized that there is a bathochromic shift of 64 mμ of the y band when the phenyl ring in Malachite Green is replaced by a 2-thianaphthenyl ring. This is much larger in comparison with a similar shift of 41 mμ observed in the case of 2-Thiophene Malachite Green.[3] This comparatively larger shift may be due to the higher electron releasing power of the thianaphthene ring as compared to that of the thiophene ring. It is therefore capable of donating more electrons to the central carbon atom, thereby increasing the basicity of the nitrogen atom and consequently lowering the absorption frequency.

It has been reported previously[6] that when one of the phenyl rings of Malachite Green is replaced by an α-naphthyl or a β-naphthyl group, prominent secondary bands are observed. Although no shift of the secondary band was mentioned in either case, it was noted that the second band is twice as high in the β- as in the α-compound. This has been attributed[6] partly to the greater extension in the y direction of the former molecule and partly to its nearer approach to coplanarity. However, in the present case, where one of the phenyl groups is replaced by a 2- or 3-thianaphthenyl ring, it is found that the second band is twice as high in the former compound as in the latter. Since the extension of the molecule in the y direction is the same in both the thianaphthene substituted dyes, it appears that the higher extinction in the case of the former dye is due to its nearer approach to coplanarity. However, it might also be due to a greater extent of conjugation from the 2- than from the 3-thianaphthenyl group.

It will be noticed from the data listed in Table II that there is practically no effect of the methyl substituent on the absorption spectrum of 2-Thianaphthene Malachite Green, while there is a bathochromic shift of the y band of 3-Thiophene Malachite Green (Table I). According to Lewis[6a]

(6) G. N. Lewis and J. Bigeleisen, *J. Am. Chem. Soc.*, **65**, 2102 (1943).

(6a) G. N. Lewis, *J. Am. Chem. Soc.*, **67**, 770 (1945).

an ortho substituent on the phenyl ring in Malachite Green should have a bathochromic effect on the main band due to a steric effect, which forces the phenyl group out of the nearly coplanar configuration, thus diminishing its share in the general resonance. Since, however, such a shift is not noticed, it appears that the introduction of either heterocyclic ring has increased the atomic distance sufficiently so that no steric hindrance is encountered. This finding is similar to previous observations regarding the effect on the absorption spectra of 2-Thiophene Malachite Green by the methyl substituent in the ortho position of the thienyl ring.[3]

The absorption spectra of the halogenated dyes reveal that there is a bathochromic shift of the x band. The deepening of the color produced by these electronegative atoms is apparently due to their ability to remove electrons from the heterocyclic ring, thus increasing the positive charge that is present.

EXPERIMENTAL

Preparation of the starting substances. Thianaphthene-2-carboxaldehyde was prepared from thianaphthene.[7] Thianaphthene-3-carboxaldehyde was prepared from thianaphthene by applying the Sommelet reaction.[8] 3-Methylthianaphthene was prepared by cyclization of phenyl acetonyl sulfide.[9] 3-Bromothianaphthene was prepared by bromination of thianaphthene.[10] 3-Thenaldehyde was prepared according to Campaigne,[11] 2,5-dimethyl-3-thiophene carboxaldehyde according to Blanchette,[12] and 2-halo-3-thiophenecarboxaldehydes according to Campaigne and Le Suer.[13]

Preparation of 3-methylthianaphthene-2-carboxaldehyde. 3-Methylthianaphthene (29.6 g., 0.2 mole) in 60 ml. of anhydrous ether was metalated by addition to an ethereal solution of *n*-butyllithium prepared from *n*-butyl bromide (41.2 g., 0.3 mole) in 50 ml. ether and lithium metal (5.04 g., 0.72 g.-atom) in 100 ml. ether. To the organometallic compound was added slowly with stirring a solution of *N*-methylformanilide (27.0 g., 0.2 mole) in 45 ml. of ether. After completion of the addition, the mixture was heated to reflux for one hour and then hydrolyzed by pouring it into a mixture of 2*N* hydrochloric acid and crushed ice. The ether layer was separated and the aqueous layer extracted three times with ether. The residue after the removal of the solvent was dissolved in the minimum amount of ethanol, and 150 ml. of an aqueous saturated solution of sodium bisulfite was added. The mixture was shaken for 0.5 hr., and the bisulfite addition compound which separated was filtered, washed with ether, and decomposed with a hot, saturated aqueous solution of sodium carbonate, yielding a colorless product (18.1 g.). On two further crystallizations from acetone it gave colorless needles, m.p. 88–88.5°.

Anal. Calcd. for $C_{10}H_8OS$: C, 68.19; H, 4.55; S, 18.19%. Found: C, 68.28; H, 4.54; S, 18.50.

The *phenylhydrazone* crystallized from alcohol in yellow needles, m.p. 178–179°.

Anal. Calcd. for $C_{16}H_{14}N_2S$: N, 10.53. Found: N, 10.90.

By applying a similar procedure, 3-bromothianaphthene (42.6 g., 0.2 mole) gave colorless needles of 3-bromothianaphthene-2-carboxaldehyde, m.p. 123–124°.

Anal. Calcd. for C_9H_5SBrO: C, 44.81; H, 2.08; S, 13.28%. Yield 5.1 g. Found: C, 45.28; H, 1.98; S, 13.50.

The *phenylhydrazone* crystallized from alcohol in pale yellow needles, m.p. 158–159°.

Anal. Calcd. for $C_{15}H_{11}BrN_2S$: C, 54.39; H, 3.57; Br, 24.18; S, 9.67%. Found: C, 54.53; H, 3.57; Br, 24.20; S, 9.61.

3-Chlorothianaphthene-2-carboxaldehyde, prepared similarly from 3-chlorothianaphthene crystallized in colorless needles from ethanol, m.p. 106–107°.

Anal. Calcd. for C_9H_5ClOS: C, 54.95; H, 2.52; Cl, 18.06%. Found: C, 55.00; H, 2.23; Cl, 18.48.

The *phenylhydrazone* crystallized from ethanol in orange flakes, m.p. 172–173°.

Anal. Calcd. for $C_{15}H_{11}ClN_2S$: N, 9.08%. Found: N, 9.50.

Preparation of intermediates. The preparation of all the leuco bases, their oxidation and the isolation of derivatives was carried out utilizing the procedure of this laboratory.[3] The yields, melting points, and analyses of the various intermediates are listed in Tables III, IV, V, and VI. As an example, preparation of 2-Thianaphthene Malachite Green is presented.

Preparation of p-p'-tetramethyldiaminodiphenyl(2-thianaphthenyl)methane (I). 2-Thianaphthenecarboxaldehyde (12.75 g., 0.079 mole) was mixed with dimethylaniline (19.5 g., 0.16 mole) in a 100-ml. three-necked flask. The mixture was heated on a steam bath and anhydrous zinc chloride (16.1 g., 0.118 mole) was gradually added under stirring. The thick mass was heated under stirring for 6 hr. After the excess of dimethylaniline and the unreacted aldehyde had been steam distilled, the residue was cooled and washed with water. The colorless product (25.8 g.), obtained on four crystallizations from benzene and petroleum ether (b.p. 60–75°), gave colorless needles, m.p. 142–143°.

Oxidation of (I). The leuco base (I) (7.8 g., 0.0202 mole) was dissolved in 2*N* sulfuric acid (30 ml.) and water (500 ml.). To the clear solution pulverized manganese dioxide (2.3 g., 0.0272 mole) was gradually added, with stirring. After the addition was completed, the mixture was stirred vigorously for 2 hr. It was then filtered and the residue extracted with 100 ml. of boiling water. The washings were added to the dye solution, which was finally made to 800 ml.

Zinc chloride complex of 2-Thianaphthene Malachite Green. To 400 ml. of the dye solution was added 1.36 g. (0.01 mole) of anhydrous zinc chloride dissolved in minimum amount of water followed by 600 ml. of saturated brine solution. The copper colored crystals were filtered and washed carefully with ice cold water.

Preparation of p-p'-tetramethyldiaminodiphenyl(2-thianaphthenyl)methanol. Aqueous sodium hydroxide (10 ml. of 10% solution) was added to 300 ml. of the dye solution with vigorous stirring. The carbinol, which precipitated, was filtered and washed with water. It was then dried *in vacuo* in a desiccator. The dry product was extracted in a Soxhlet extractor with petroleum ether (b.p. 60–75°) for 6 hr. The pink colored crystals obtained gave colorless needles on repeated crystallizations from petroleum ether (b.p. 60–75°).

Absorption spectra. These measurements were taken with a Beckman DU Quartz Spectrophotometer over a range from 260–700 mμ. Readings were taken at every 10 mμ intervals in the visible region and at every 5 mμ intervals in the ultraviolet. Near the points of maxima readings were

(7) D. A. Shirley and M. J. Danzig, *J. Am. Chem. Soc.*, **74**, 2935 (1952).

(8) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).

(9) E. G. G. Werner, *Rec. Trav. Chim.*, **68**, 509 (1949).

(10) J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.*, **72**, 571 (1950).

(11) E. Campaigne, R. C. Bourgeois, and W. C. McCarthy, *Org. Synthesis*, **33**, 93 (1953).

(12) G. Blanchette, dissertation, Fordham University (1951).

(13) E. Campaigne and W. M. Le Suer, *J. Am. Chem. Soc.*, **71**, 333 (1949).

TABLE III

LEUCO BASES AND ZINC CHLORIDE COMPLEXES OF THIOPHENE MALACHITE GREEN

Tetramethyldiaminodiphenyl-	Leuco Bases: Yield, %	M.P.,[a] °C.	Analyses: Calcd. C	H	N	S	Hal.	Found C	H	N	S	Hal.	Zinc Chloride complexes[b] Analyses: Calcd. N	Found N
(3-Thienyl)-methane	59.3	111–112	75.00	7.14	8.35			74.97	7.17	8.65			5.84	5.60
(2,5-Dimethyl-3-thienyl)-methane	49.0	139–140	75.76	7.76		8.80		75.05	7.91		8.92		5.77	5.75
(2-Bromo-3-thienyl)-methane	65.3	115–117	60.07	5.59			19.24	60.14	5.54			19.30	5.02	5.59
(2-Chloro-3-thienyl)-methane	57.0	122–123	67.98	6.26			9.56	68.00	6.14			9.89	5.45	5.50

[a] All melting points are uncorrected. [b] For $C_{21}H_{22}ClN_2R°S\cdot 2ZnCl_2\cdot 3H_2O$ where R° is a substituent on the thiophene ring.

TABLE IV

BASES OF THIOPHENE MALACHITE GREEN DYES

Tetramethyldiaminodiphenyl-	M.p.,[a] °C.	Analyses: Calcd. C	H	N	S	Hal.	Found C	H	N	S	Hal.
(3-Thienyl)methanol	183–184	71.60	6.82	7.96			71.57	6.37	7.93		
(2,5-Dimethyl-3-thienyl)-methanol	152–153	72.58	7.43		8.43		73.16	7.71		8.35	
(2-Bromo-3-thienyl)-methanol-	143–144	58.47	5.38			18.52	58.54	5.48			19.42
(2-Chloro-3-thienyl)-methanol-	140–142	65.17	6.00			9.16	65.12	6.58			9.80

[a] All melting points are uncorrected.

TABLE V

LEUCO BASES AND ZINC CHLORIDE COMPLEXES OF THIANAPHTHENE MALACHITE GREEN DYES

Tetramethyldiaminodiphenyl-	Leuco Bases: M.P.,[a] °C.	Yield, %	Analyses: Found C	H	S	Hal	Calcd. C	H	S	Hal.	Complexes[b] Analyses: Calcd. N	Found N
(3-Thianaphthenyl)-methane	148–149	84.8	78.01	7.40	8.34		77.71	6.74	8.30		5.27	4.85
(2-Thianaphthenyl)-methane	142–143	80.4	77.34	6.69	7.96		77.71	6.74	8.30		5.27	5.11
(3-Methyl-2-thianaphthenyl)methane	157–158	34.3	77.68	6.59	7.66		78.00	7.00	8.00		5.15	4.94
(3-Bromo-2-thianaphthenyl)methane	126–127	39.8	64.25	5.45		17.40	64.50	5.38		17.21	4.60	5.22
(3-Chloro-2-thianaphthenyl)methane	139–140	61.3	71.19	5.89			71.35	5.95			6.40	5.82

[a] All melting points are uncorrected. [b] For 3 $C_{25}H_{25}ClN_2R°S\cdot 2ZnCl_2\cdot 3H_2O$ where R° is a substituent on the thianaphthene ring.

TABLE VI

CARBINOL BASES OF THE THIANAPHTHENE MALACHITE GREEN DYES

Tetramethyldiaminodiphenyl-	M.P.,[a] °C.	Analyses: Found C	H	S	Calculated C	H	S
(3-Thianaphthenyl)methanol	170	74.95	6.47	7.78	74.63	6.47	7.96
(2-Thianaphthenyl)methanol	193–194	74.57	6.82	8.16	74.63	6.47	7.96
(3-Methyl-2-thianaphthenyl)methanol	182–183	75.00	6.73	7.69	74.61	6.54	7.69
(3-Bromo-2-thianaphthenyl)methanol	212–213	62.79	5.40	7.30	62.38	5.20	6.65
(3-Chloro-2-thianaphthenyl)methanol	188	69.13	6.01		68.71	5.73	

[a] All melting points are uncorrected.

taken at every mμ. Solutions of the dyes were made by dissolving weighed amounts of analytically pure carbinols in glacial acetic acid. The molarities of the dye solutions were between 1×10^{-5} and 1×10^{-3}.

Acknowledgments. This investigation was aided by grants from the National Science Foundation and the U.S. Public Health Service. The thianaphthene used was obtained through the courtesy of Dr. W. J. Coppoc of the Texas Company, Beacon, N. Y.

NEW YORK 58, N. Y.

[CONTRIBUTION NO. 248 FROM THE RESEARCH DIVISION, ORGANIC CHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

Tetra-2-benzimidazolylethylene, a New Yellow Chromophore

R. G. ARNOLD, R. S. BARROWS, AND R. A. BROOKS

Received August 12, 1957

Tetra-2-benzimidazolylethylene (I) has been prepared and its ultraviolet, visible, infrared, and x-ray diffraction spectra determined. Nitro, chloro, bromo, sulfo, methyl, and methoxyl derivatives of I have been made.

In the course of an investigation of novel dye structures, tetra-2-benzimidazolylethylene (I) was prepared and found to be a strong yellow chromophore. The visible spectrum in dimethylformamide is shown in Fig. 1. The molar extinction coefficient is 24,000 at 3800 Å. I is insoluble in water at any *p*H and in most organic solvents. It can be dissolved to a small extent in dimethylformamide and is completely soluble in 100% sulfuric acid from which it is recovered unchanged by dilution with water. I is crystalline and is characterized by an x-ray diffraction pattern having seven peaks at the following interplanar spacings:

d, Å.	I/I_{max}
13.5	40
12.4	100
6.20	20
5.85	30
5.42	20
3.80	20
3.65	15

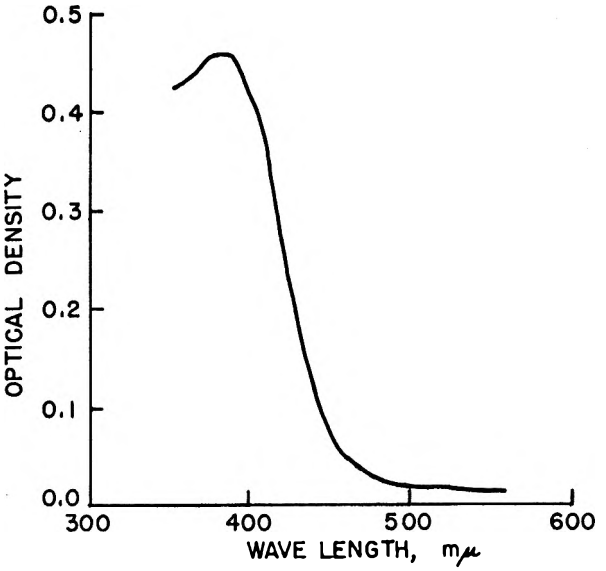


Fig. 1. Visible spectrum of tetra-2-benzimidazolylethylene. One centimeter dimethylformamide solution, 0.0093 gram per liter

The ultraviolet and infrared spectra of I are reproduced in Figs. 2 and 3, respectively. From a study of molecular models, it is concluded that I should be hydrogen-bonded between the 4 adjacent nitrogen pairs.

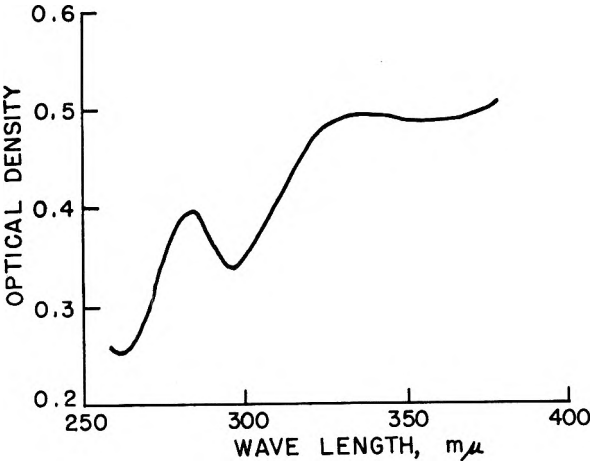


Fig. 2. Ultraviolet spectrum of tetra-2-benzimidazolylethylene. One centimeter dimethylformamide solution, 0.0180 gram per liter

Two routes to I were found. The first is reaction of tetramethyl ethane-1,1,2,2-tetracarboxylate with *o*-phenylenediamine to give 1,1,2,2-tetra-2-benzimidazolylethane which is subsequently oxidized to I.

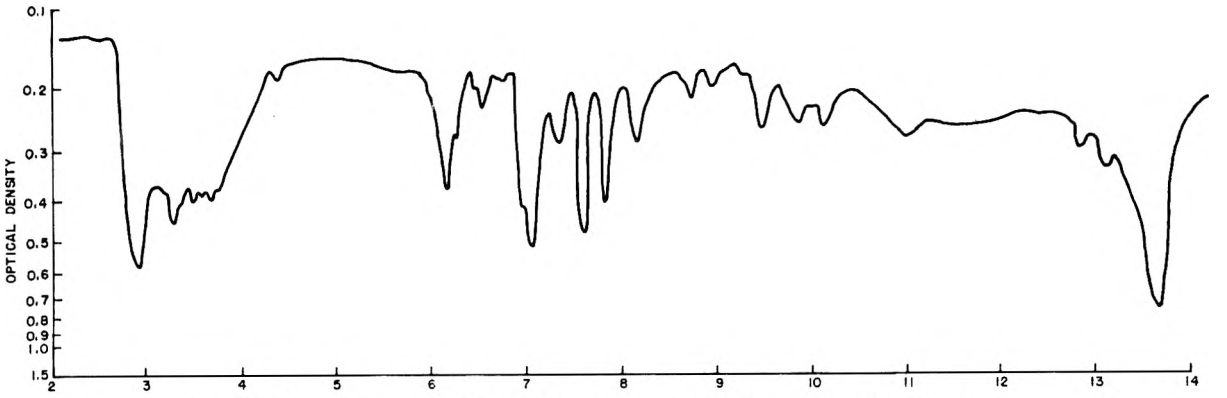
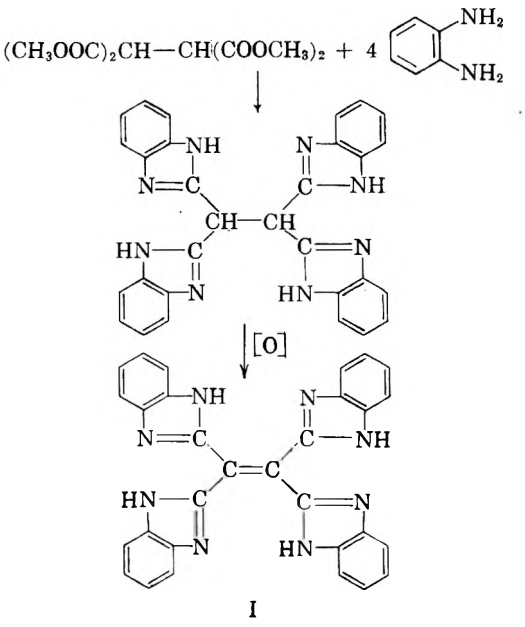


Fig. 3 Infrared spectrum of tetra-2-benzimidazolylethylene, KBr Disk, NaCl Prism



I

Oxidation may be achieved in air at 210–250°, refluxing nitrobenzene, aqueous hydrogen peroxide, alkaline sodium hypochlorite, chlorine, bromine, or nitric acid. Chlorine, bromine, and nitric acid produce chloro, bromo, and nitro derivatives of I, respectively. Nitrobenzene is preferred for ease of operation, yield, and purity. Acidic potassium permanganate or chromic acid cannot be used since they destroy the product.

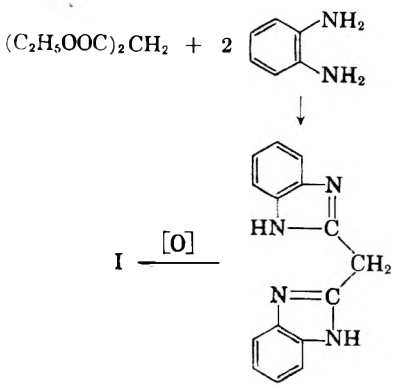
The second preparative route is reaction of diethylmalonate with *o*-phenylenediamine to give di-2-benzimidazolylmethane, followed by bimolecular oxidation to I with air, nitrobenzene, sulfur, sodium hypochlorite, chlorine, or bromine. Chlorine and bromine give halogenated products.

Both routes are generally successful with *o*-phenylenediamine substituted with alkyl or alkoxyl groups. Halogen or nitro substituents, on the other hand, prevent reaction.

Chlorination and bromination of I are readily effected by direct reaction with the elements in alcohol or acetic acid. As expected,[1] an appreciable amount of halogen is bound by the imidazole rings and is difficult to remove even by pasting in sulfuric acid. For this reason it is best to chlorinate with sulfuryl chloride and to brominate in a mixture of bromine, sulfuryl chloride, and trichlorobenzene. Products obtained in this way appear to be free of removable halogen and are characterized by very low solubility in nitrobenzene, a solvent for many of the *N*-halogenated compounds. A product containing approximately 11 nuclear chlorine atoms was found to be too insoluble in dimethylformamide to permit determination of the visible spectrum in that solvent. Determination of the spectrum on a mineral oil dispersion showed a maximum at 3600 Å. The infrared spectrum of this chlorinated derivative is reproduced in Fig. 4.

I and its derivatives are not affected noticeably by mild alkalies and weak acids. Strong alkalies and strong mineral acids cause shade changes, greener with alkalies, redder with acids. An exception is the completely chlorinated derivative which shows no sensitivity to either acids or bases.

The strong color and stability of I and its derivatives make these novel substances potentially useful as dyes and pigments.[2]



(1) J. B. Wright, *Chem. Revs.*, **48**, 397 (1951).

(2) R. G. Arnold, U. S. Patents **2,697,711**, **2,697,712**, and **2,697,713** (1954) [*Chem. Abstr.*, **49**, 14036 (1955)].

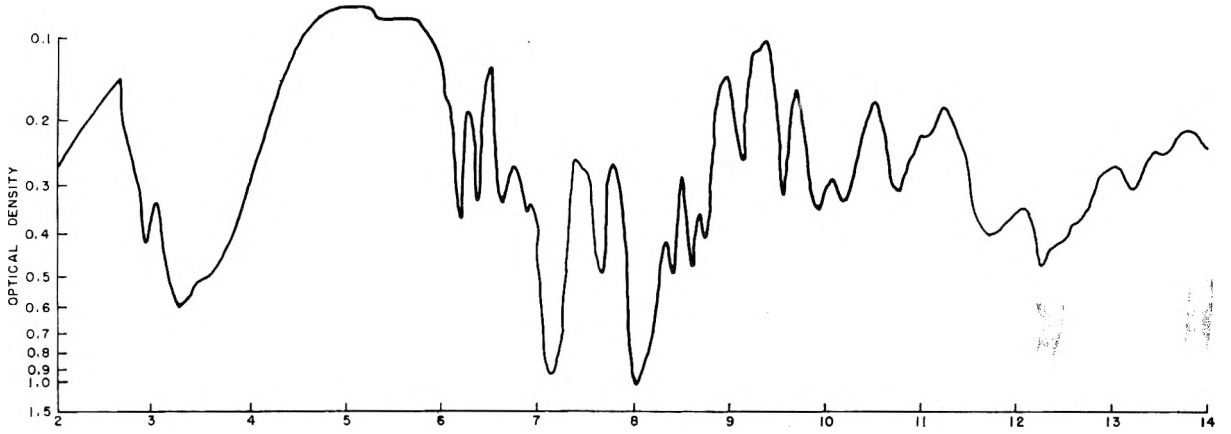


Fig. 4. Infrared spectrum of polychlorotetra-2-benzimidazolylethylene, KBr disk, NaCl prism

EXPERIMENTAL

The ultraviolet and visible spectra were determined with a Cary Model 11 Recording Spectrophotometer. The infrared spectrum was obtained with a Perkin-Elmer Model 12-C Spectrophotometer.

1,1,2,2-Tetra-2-benzimidazolylethane dihydrate. One hundred grams (0.378 mole) of tetramethyl ethane-1,1,2,2-tetracarboxylate and 180 g. (1.66 mole) of *o*-phenylenediamine were dissolved in 750 ml. of trichlorobenzene at 85°. This solution was then added to 300 ml. of boiling trichlorobenzene at such a rate that the temperature did not drop below 180°. The reaction mixture was then boiled for 3 hr. The mixture was cooled to room temperature which caused a crystalline product to precipitate. After cooling, the mass was poured into several volumes of alcohol and filtered. The product was washed free of trichlorobenzene with alcohol and dried. The yield was 131.5 g. (65.5%).

Anal. Calcd. for $C_{30}H_{22}N_8(H_2O)_2$: C, 67.9; H, 4.92; N, 21.2. Found: C, 67.7, 67.3; H, 5.3, 5.3; N, 20.8, 20.9.

Tetra-2-benzimidazolylethylene monohydrate. A slurry of 70 g. (0.132 mole) of 1,1,2,2-tetra-2-benzimidazolylethane dihydrate and 5 g. of potassium carbonate in 150 ml. of nitrobenzene was heated at reflux for 1 hr. The mixture, which became thick during heating, was cooled to room temperature and filtered. The filter cake was washed with benzene, then with alcohol, and dried. It was next dissolved in 30 ml. of 98% sulfuric acid at 10°, reprecipitated with water, filtered, and washed free of acid. When dry the bright orange product weighed 30 g. (44.7%).

Anal. Calcd. for $C_{30}H_{20}N_8(H_2O)$: C, 70.5; H, 4.31; N, 21.7. Found: C, 70.4, 70.5, 70.8; H, 4.25, 4.25, 4.23; N, 21.6, 21.9.

Oxidation of 1,1,2,2-tetra-2-benzimidazolylethane dihydrate with nitric acid. A fine slurry was produced by ball-milling 56.4 g. (0.106 mole) of 1,1,2,2-tetra-2-benzimidazolylethane dihydrate in 1 l. of water. An additional 1 l. of water was added, followed by 450 ml. of 70% nitric acid added in a slow stream. Stirring was continued for 30 min. and then the red reaction mass was made basic with 30% sodium hydroxide. The product was filtered, washed free of alkali, and dried. This material was dissolved in 15 parts of 96% sulfuric acid, reprecipitated with water, filtered, washed free of acid, and dried. The yield was 42 g. (71.3%) of a bright yellow solid.

Anal. Found: C, 63.2, 63.8; H, 3.74, 4.08; N, 22.6, 22.8; H_2O by weight loss at 200°, 3.14. This corresponds to a mixture of nitro derivatives with an average content of 1.2 nitro groups.

This product can be further nitrated with fuming nitric acid in 96% sulfuric acid at 25° to give a tetranitro derivative.

Oxidation of 1,1,2,2-tetra-2-benzimidazolylethane dihydrate with bromine. Five grams (0.0094 mole) of 1,1,2,2-tetra-2-benzimidazolylethane dihydrate was suspended in 100 ml. of carbon tetrachloride containing 5 g. of dissolved bromine. After standing for 48 hr. at room temperature, the mixture was filtered. The product was washed with carbon tetrachloride and then with alcohol. When dry it was dissolved in 10 parts of 96% sulfuric acid, reprecipitated with water, washed free of acid, and dried again. The final product was a bright orange solid. The yield was 5.5 g. (87.3%).

Anal. Calcd. for $C_{30}H_{18}N_8Br_2(H_2O)$: C, 53.8; H, 2.99; N, 16.8; Br, 23.9. Found: C, 53.5, 54.0; H, 3.21, 3.41; N, 17.0, 17.4; Br, 23.5, 24.0.

Tetrakis(5[or 6]methyl-2-benzimidazolyl)ethylene. This product was made in 56% yield by condensing 4-methyl-*o*-phenylenediamine with tetramethyl ethane-1,1,2,2-tetracarboxylate, followed by oxidation with nitric acid. The product was not nitrated and contained no water of crystallization.

Anal. Calcd. for $C_{34}H_{28}N_8$: C, 74.4; H, 5.14; N, 20.4. Found: C, 72.9, 73.0; H, 5.17, 5.21; N, 21.1, 21.0.

Tetrakis(5[or 6]methoxy-2-benzimidazolyl)ethylene dihydrate. This product was prepared in 30% yield by condensing 4-methoxy-*o*-phenylenediamine with tetramethyl ethane-1,1,2,2-tetracarboxylate followed by oxidation with sodium hypochlorite.

Anal. Calcd. for $C_{34}H_{28}N_8O_4(H_2O)_2$: C, 62.9; H, 4.93; N, 17.3. Found: C, 62.1, 62.5; H, 5.04, 5.23; N, 17.0, 17.1.

Di-2-benzimidazolylmethane monohydrate. A mixture of 1,000 g. (9.25 moles) of *o*-phenylenediamine and 2,500 ml. of trichlorobenzene was heated to 170° in a flask equipped with an azeotroping head, and 740 g. (4.62 moles) of diethylmalonate was added over 90 min. The temperature was allowed to rise to 185° during addition of the malonate, and finally was maintained at 185–190° for 2 hr. more. During the reaction period, volatile material amounting to 641 g. was collected. The mixture was cooled to 25° whereupon a crystalline product precipitated. The product was filtered and the filter cake washed twice with 250-ml. portions of benzene, and then with 250 ml. of alcohol and 250 ml. of water. The sand-like yellow product was dried at 110°. The yield was 1,040 g. (84.5%).

Anal. Calcd. for $C_{15}H_{12}N_4(H_2O)$: N, 21.4. Found: N, 21.6, 21.6.

Tetra-2-benzimidazolylethylene monohydrate by oxidation of the corresponding methane. Two hundred g. (0.806 mole) of di-2-benzimidazolylmethane monohydrate, 200 g. of potassium carbonate, and 1200 ml. of nitrobenzene were heated at 160° for 4 hr. After cooling at room temperature, the reaction mass was poured into 2 l. of alcohol, filtered, and the filter cake washed with alcohol until free of nitrobenzene. The product was then stirred with 2 l. of water at 50°, filtered, washed with water until alkali-free, and dried at 110°. The yield was 160 g. (77.8%) of a bright yellow solid.

Anal. Calcd. for $C_{30}H_{20}N_8(H_2O)$: C, 70.5, H, 4.31; N, 21.7. Found: C, 70.2, 70.3, 70.8; H, 4.13, 3.95; N, 21.9, 21.9.

This product was identical with that prepared by oxida-

tion of the corresponding ethane with nitrobenzene. A small sample was dried for 3 days at 110° and analyzed before moisture could be regained.

Anal. Calcd. for $C_{30}H_{20}N_8$: C, 73.2; H, 4.10; N, 22.8. Found: C, 73.6, 73.7; H, 3.70, 3.80; N, 22.3, 22.5.

Chlorination of tetra-2-benzimidazolylethylene with sulfuryl chloride. Fifty g. (0.098 mole) of tetra-2-benzimidazolylethylene was finely ground and suspended in 650 ml. of trichlorobenzene. One g. of iodine was added, the mixture was heated to 150° and maintained at 150–155° while 200 ml. (2.47 moles) of sulfuryl chloride was added over 4 hr. The mixture was held at 155° for an additional 30 min., cooled, and poured into 2 l. of water. The product was filtered, washed with alcohol, and dried. The yield of crude material was 85 g. This was ground and extracted for 7 hr. in a Soxhlet extractor with benzene. The residue was then extracted twice with 500-ml. portions of nitrobenzene at 90°, washed free of nitrobenzene with alcohol, and dried. The yield was 59.5 g. (69.3%) of bright orange solid.

Anal. Found: C, 40.1, 40.6; H, 1.60, 1.70; N, 12.7, 12.7; Cl, 42.3, 42.4.

This corresponds to a mixture of monohydrates with an average content of 10.6 chlorine atoms.

This product can be further chlorinated to a chlorine content of 53.4% by autoclaving at 150° for 10 hr. with excess sulfuryl chloride.

Bromination of tetra-2-benzimidazolylethylene. A mixture of 10.5 g. (0.065 mole) of bromine and 10.5 g. (0.077 mole) of sulfuryl chloride was slowly added to a suspension of 4 g. (0.008 mole) of tetra-2-benzimidazolylethylene in 100 ml. of trichlorobenzene. The temperature rose to 31°. The mixture was heated to 80°, held one hour, then heated to 130° and held one hour. After cooling, the mixture was filtered and the filter cake washed with alcohol. The dry product weighed 8 g., was insoluble in nitrobenzene, and contained 70.2% bromine, corresponding to 14 bromine atoms. No chlorine was found.

Sulfonation of tetra-2-benzimidazolylethylene. A mixture of 93 ml. of 100% sulfuric acid and 8 ml. of 65% oleum was cooled to 19°. Ten g. (0.203 mole) of finely ground tetra-2-benzimidazolylethylene was added slowly at 20–25°. The mixture was heated at 70° until a drop was just soluble in dilute sodium hydroxide (45 min.). The solution was then cooled and poured slowly into 200 ml. of water. Fifty ml. of 30% sodium hydroxide was added and, after filtration to remove any insoluble material, the filtrate was mixed with 150 ml. of 30% sodium hydroxide. After cooling again to room temperature, the product was filtered, redissolved in 400 ml. of water, and reprecipitated with 7 g. of potassium chloride. The product weighed 35 g. when dry.

Anal. Found: N, 4.63, 4.39; Organic S, 2.04, 2.04. This corresponds to a mixture of sulfonated derivatives averaging 1.5 sulfonic acid groups admixed with sodium and potassium salts.

This product dyes wool from a weakly acidic dyebath in red-yellow shades.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Dialkylaminoalkyl Ethers of Some 2,6-Dialkylphenols

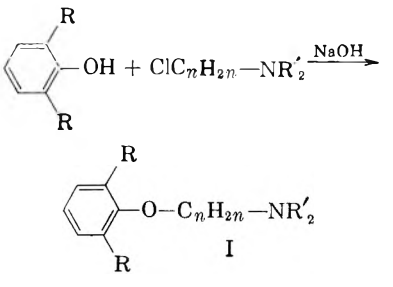
WILLIAM B. WHEATLEY AND CHARLES T. HOLDREGE

Received August 28, 1957

A number of dialkylaminoalkyl ethers of some 2,6-dialkylphenols, particularly 2,6-diisopropylphenol, have been prepared in good yields by the Williamson synthesis using dialkylaminoalkyl chlorides. Attempts to prepare other ethers, *e.g.*, β-hydroxyethyl and β-haloethyl ethers, were almost completely unsuccessful, probably because of steric hindrance.

2,6-Dialkylphenols have recently become available on a scale such that their use as intermediates is now feasible.[1] Because of the fact that certain basic ethers of substituted phenols have shown utility as therapeutic agents, we set out to prepare some dialkylaminoalkyl ethers of these 2,6-dialkylphenols. This particular type of compound has received little attention, due in part to the previous accessibility of only the simpler dialkylphenols such as 2,6-xylenol, and of the 2,4,6-trialkylphenols.

The majority of compounds to be described are ethers of 2,6-diisopropylphenol (DIP), and most of the discussion which follows refers to this phenol. The presence of two branched ortho substituents causes this phenol to be cryptophenolic, being insoluble in aqueous alkali, but soluble in Claisen's alkali. It does form a sodium salt quite readily on treatment in boiling toluene with either sodium hydride or sodium hydroxide.[2] This sodium 2,6-diisopropylphenoxide is not typical, however, since it participates in the Williamson ether synthesis in widely varying degrees, depending on the nature of the halide used as the other reactant.



I

With dialkylaminoalkyl chlorides, the desired basic ethers (I) were obtained in quite acceptable yields. With other halides, the results were often negative. All attempts to prepare β-hydroxyethyl 2,6-diisopropyl ether were unsuccessful; neither ethylene chlorohydrin nor ethylene carbonate[3] could be caused to react with DIP under a variety

(1) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).

(2) T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *J. Am. Chem. Soc.*, **79**, 5019 (1957).

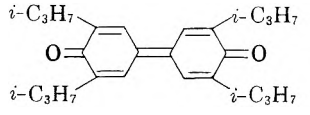
(3) W. W. Carlson, U. S. Patent 2,448,767 (1948).

of conditions. Ethyl chloroacetate also failed to react with the sodium salt of DIP.

An alternate synthesis of basic ethers would involve the preparation of an ω-haloalkyl ether and subsequent reaction of this halide with an amine. The only successful preparation was that of the β-chloroethyl ether, from DIP and β-chloroethyl *p*-toluenesulfonate, although in only 26% yield. Because of the low yield, this approach was not investigated further. Neither ethylene dibromide or ethylene chlorobromide reacted with DIP in the presence of sodium hydroxide.

The facile conversion of DIP to its sodium salt in nonaqueous medium and the inconsistent reactivity of this sodium salt toward alkylating agents pose an interesting question. The answer probably includes both polar and steric factors. The fact that DIP is more difficult to etherify than other phenols not having large alkyl groups in the 2 and 6 positions suggests steric hindrance. A polar effect is indicated in that the only really good reactions observed are those with basic alkyl chlorides, in which cyclic quaternary imonium ions are known to be involved.[4]

In order to ascertain the effect of groups in the 4-position, a few 4-substituted-2,6-dialkylphenols were prepared. The 4-bromo- and 4-chloro-2,6-diisopropylphenol were prepared easily and in high yield by halogenation with bromine and sulfuryl chloride, respectively. Friedel-Crafts reactions of DIP with benzyl alcohol and phenylmethylcarbinol yielded the 4-benzyl- and 4-α-methylbenzyl-2,6-diisopropylphenols. An attempted nitration of DIP apparently resulted in oxidation to a diphenoquinone (II), a reaction which has been recorded for analagous 2,6-dialkyl-phenols with a variety of oxidizing agents.[5]



II

A few basic ethers of phenols having *t*-butyl groups in the ortho positions were made, using 2-methyl-6-*t*-butylphenol, 2,6-di-*t*-butylphenol (DTB), and 2,6-di-*t*-butyl-p-cresol (DBPC). Under the experimental conditions used, we could detect no noticeable difference in reactivity. This is interesting in relation to the work of Stillson, Sawyer, and Hunt,[6] who studied the properties of hindered phenols containing ortho *t*-alkyl groups. These workers found that DBPC and 2,4,6-tri-*t*-butylphenol were insoluble in both aqueous and alcoholic alkali, and failed to form sodium salts on refluxing with sodium in ether or petroleum ether. We likewise found DTB to be insoluble in Claisen's alkali, but it must form a sodium salt in the course of the conversion to the basic ether. As with DIP, DTB failed to react with ethylene carbonate.

A recent paper by Coffield, Filbey, Ecke, and Kolka[2] discusses further reactions of these 2,6-dialkylphenols.

EXPERIMENTAL[7]

Basic ethers. In a typical experiment, 0.3 mole of the 2,6-dialkylphenol, 0.4 mole of the dialkylaminoalkyl chloride hydrochloride, and 0.8 mole of flake sodium hydroxide were stirred together for 24 hr. in refluxing toluene. After treatment of the cooled reaction mixture with water to dissolve inorganic material, the toluene solution was extracted three times with dilute hydrochloric acid. Basification of the acid extracts and ether extraction, followed by distillation of the dried ether solution yielded the basic ether I. As noted in Table I, most of these were converted to crystalline acid addition salts for ease in pharmacological evaluation.

In working up a significant number of experiments, it was found that extraction with dilute acid failed to transfer the basic ether from the toluene to the aqueous phase. If this occurred, the toluene layer was concentrated to an oil under reduced pressure. This residual oil was taken up in Skellysolve B and extracted with acid. Basification and ether extraction of the acid aqueous extracts then yielded the basic ether as described above. This modification is noted in Table I.

2,6-Diethylphenol. Diazotization and hydrolysis of 2,6-diethylaniline afforded 2,6-diethylphenol in 88% yield, b.p. 100–105° at 8 mm. The concomitant hydrolysis and steam distillation as described by Lambooy[8] proved highly effective in this instance.

4-Chloro-2,6-diisopropylphenol. A total of 2.5 moles of sulfuryl chloride was added to 2.0 moles of 2,6-diisopropylphenol in two equal portions. After 4 hr. on the steam bath, the mixture was distilled to give 370 g. (89% yield) of pale orange liquid, b.p. 94–97° at 1 mm.,[1] n_D^{25} 1.5279.

4-Bromo-2,6-diisopropylphenol. To a solution of 357 g. (2.0 moles) of 2,6-diisopropylphenol in 300 ml. of carbon tetrachloride was added dropwise 320 g. (2.0 moles) of bromine, maintaining the temperature at 15–20° by occasional cooling. Hydrogen bromide was evolved copiously. The solution was stirred for one hour at room temperature, then heated on the steam bath to drive off solvent and remaining hydrogen bromide. Distillation gave 498 g. (97% yield) of liquid, b.p. 101–107° at 1 mm., n_D^{25} 1.5465.

Anal. Calcd. for $C_{12}H_{17}BrO$: C, 56.1; H, 6.7. Found: C, 55.9; H, 6.8.

4-Benzyl-2,6-diisopropylphenol. Aluminum chloride (67 g. 0.5 mole) was added portionwise over a two-hour period to a stirred solution of 222 g. (1.25 moles) of 2,6-diisopropylphenol and 108 g. (1.0 mole) of benzyl alcohol in 200 ml. of Skellysolve B, keeping the temperature at 30–35° by cooling as needed. After standing overnight at room temperature, the dark red reaction mixture, which contained much oily solid, was hydrolyzed with ice–hydrochloric acid. The Skellysolve layer was separated and the aqueous layer extracted three times with ether. After evaporation of the solvent from the dried organic extracts, distillation gave 112 g. of recovered DIP, followed by 91.5 g. (34% yield) of 4-benzyl-2,6-diisopropylphenol, b.p. 156–162° at 1 mm., n_D^{25} 1.5553.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.0; H, 9.0. Found: C, 85.4; H, 9.0.

2,6-Diisopropyl-4-(α-methylbenzyl)phenol. Similarly, 2,6-diisopropylphenol and phenylmethylcarbinol gave 2,6-diisopropyl-4-(α-methylbenzyl)phenol in 67% yield, b.p. 158–163° at 1 mm., n_D^{25} 1.5496.

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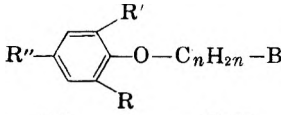
TABLE I

DIALKYLAMINOALKYL ETHERS OF 2,6-DIALKYLPHENOLS



R	R′	R″	C_nH_{2n}	B[a]	% Yield	BP. °C./mm.	n_D^{25}	M.P. of salt	Recrystallization Solvent[n]	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	H	$-CH_2CH_2-$	$N(CH_3)_2$	74	116–120/8	1.4972[b]	191.0–195.0	iPrOH	$C_{12}H_{19}NO\cdot HCl$	62.7	63.2	8.8	8.2
CH_3	t-C_4H_9	H	$-CH_2CH_2-$	$N(CH_3)_2$	82	122–127/1.5	1.4994[c]	128.5–130.5	iPrOH	$C_{15}H_{25}NO\cdot C_6H_8O_7$[e]	59.0	59.1	7.8	7.9
CH_3	t-C_4H_9	H	$-CH_2CH_2-$	$N(iC_3H_7)_2$	84	137–140/1.4	1.4904	[d]		$C_{19}H_{33}NO$	78.3	78.2	11.4	10.9
C_2H_5	C_2H_5	H	$-CH_2CH_2-$	$N(CH_3)_2$	70	129–133/9	1.4960	135.0–137.0	MIBK	$C_{14}H_{23}NO\cdot HCl$	65.2	65.4	9.4	9.1
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(CH_3)_2$	88	110–113/0.6	1.4908[f]	203.0–205.0	MEK	$C_{16}H_{27}NO\cdot HCl$	67.2	67.8	9.9	9.9
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(C_2H_5)_2$	86	130–140/1	1.4866	149.0–151.0	MIBK	$C_{18}H_{31}NO\cdot HCl$	69.1	69.3	10.3	10.4
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_4H_8	74	[g]		210.0–213.0	MIBK	$C_{18}H_{29}NO\cdot HCl$	69.3	69.3	9.7	9.7
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_5H_{10}	75	[g,h]		212.0–215.0	MIBK	$C_{19}H_{31}NO\cdot HCl$	70.0	70.2	9.9	10.1
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(iC_3H_7)_2$	78	123–126/1		154.0–156.0	Benzene-Skellysolve	$C_{20}H_{35}NO\cdot HCl$	70.2	70.6	10.6	10.5
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_4H_8O	24[m]	[g]		198.0–200.0	MIBK	$C_{18}H_{29}NO_2\cdot HCl$	65.8	66.0	9.2	9.3
iC_3H_7	iC_3H_7	H	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	78	146–151/8	1.4884[i]	80–157[k]	MIBK	$C_{17}H_{29}NO\cdot HCl$	68.1	68.3	10.1	10.1
iC_3H_7	iC_3H_7	H	$-CH_2C(CH_3)_2CH_2-$	NC_5H_{10}	49[m]	174–180/1		206.0–210.0	MIBK	$C_{22}H_{37}NO\cdot HCl$	71.7	71.9	10.4	10.4
iC_3H_7	iC_3H_7	$C_6H_5CH_2$	$-CH_2CH_2-$	$N(CH_3)_2$	59[m]	[g]		206.0–209.0	iPrOH	$C_{23}H_{33}NO\cdot HCl$	73.4	73.6	9.1	9.3
iC_3H_7	iC_3H_7	$C_6H_5CH(CH_3)-$	$-CH_2CH_2-$	$N(CH_3)_2$	74[m]	162–166/0.5	1.5265	[d]		$C_{24}H_{35}NO$	81.5	81.7	10.0	9.8
iC_3H_7	iC_3H_7	Cl	$-CH_2CH_2-$	$N(CH_3)_2$	62	154–160/8	1.5060	223.0–226.0	MIBK	$C_{16}H_{26}ClNO\cdot HCl$	60.1	60.2	8.5	8.6
iC_3H_7	iC_3H_7	Cl	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	70	144–148/1	1.5028	205.0–208.0	nBuOH	$C_{17}H_{25}ClNO\cdot HCl$	61.1	60.7	8.7	8.6
iC_3H_7	iC_3H_7	Br	$-CH_2CH_2-$	$N(CH_3)_2$	78	133–140/1	1.5238	230.0–232.0	nBuOH	$C_{16}H_{26}BrNO\cdot HCl$	52.7	52.3	7.4	7.2
iC_3H_7	iC_3H_7	Br	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	85	144–154/1	1.5204	205.0–208.0	nBuOH	$C_{17}H_{28}BrNO\cdot HCl$	53.8	53.7	7.7	7.7
tC_4H_9	tC_4H_9	H	$-CH_2CH_2-$	$N(CH_3)_2$	80	[g]		169.0–171.0	MeOH	$C_{18}H_{31}NO\cdot C_6H_8O_7$	61.4	61.8	8.4	8.6
tC_4H_9	tC_4H_9	CH_3	$-CH_2CH_2-$	$N(CH_3)_2$	52[m]	130–137/0.6	1.4990[l]	171.5–172.5	MeOH	$C_{19}H_{33}NO\cdot C_6H_8O_7$	62.1	62.4	8.6	8.5

[a] NC_4H_8 = 1-pyrrolidino; NC_5H_{10} = 1-piperidino; N C_4H_8O = 4-morpholino. [b] Base prepared by Hey and Willey [*Brit. J. Pharmacol*, **9**, 471 (1954)] from 2-(2,6-xylyloxyl)ethyl bromide and dimethylamine. [c] Base: Calcd. for $C_{15}H_{25}NO$: C, 76.5; H, 10.7; Found: C, 76.5; H, 10.5. [d] Crystalline salt not obtained; analysis for base given in table. [e] $C_6H_8O_7$ = citric acid. [f] Base: Calcd. for $C_{16}H_{27}NO$: C, 77.1; H, 10.9. Found: C, 76.5; H, 11.1. [g] Base not distilled; yield is that of crude salt. [h] Hydrochloride crystallized out on extraction with dilute hydrochloric acid. [i] Base: m.p. 44.5–47.0° (dilute ethanol): Calcd. for $C_{20}H_{25}NO$: C, 78.6; H, 11.6. Found: C, 79.0; H, 11.3. [j] Base: Calcd. for $C_{17}H_{29}NO$: C, 77.5; H, 11.1. Found: C, 77.9; H, 11.1. [k] In spite of repeated recrystallizations, this wide melting range persisted. [l] Base: Calcd. for $C_{19}H_{33}NO$: C, 78.3; H, 11.4. Found: C, 78.4; H, 11.3. [m] The modified working up procedure involving evaporation of the toluene and subsequent acid extraction from Skellysolve solution was used; see Experimental. [n] MIBK = methyl isobutyl ketone; MEK = methyl ethyl ketone.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.1; H, 9.3. Found: C, 85.4; H, 9.1.

2-(2,6-Diisopropylphenoxy)ethyl chloride. A solution of 53.5 g. (0.3 mole) of 2,6-diisopropylphenol in 300 ml. of toluene was added dropwise to a stirred suspension of 7.1 g. (0.3 mole) of sodium hydride in 150 ml. of toluene. The mixture was then stirred at reflux for one hour. To this thick suspension was added in five portions 70.7 g. (0.31 mole) of β-chloroethyl-*p*-toluenesulfonate. After refluxing overnight, the reaction mixture was treated while hot with 25 ml. of 20% sodium hydroxide, and when cool, with 200 ml. of water. The toluene layer was separated, dried, and distilled. A fraction boiling at 130–140° at 8 mm. appeared to be essentially the desired product: 18.7 g. (26% yield) was obtained, n_D^{25} 1.5070. A considerable amount of DIP was recovered as forerun.

Anal. Calcd. for $C_{14}H_{21}ClO$: C, 69.8; H, 8.8. Found: C, 70.1; H, 8.8.

3,3',5,5'-Tetraisopropyldiphenoquinone (II). To a stirred solution of 220 g. (1.23 moles) of 2,6-diisopropylphenol in 450 ml. of benzene and 320 ml. of glacial acetic acid, held at 0–5°, was added dropwise 90 ml. of concentrated nitric acid. Some brown fumes were evolved during the addition and appeared to have ceased at the end. After standing overnight at room temperature, the reaction mixture was poured into one liter of water, shaken well, and the aqueous layer discarded. The benzene layer was extracted in turn with 10% urea solution and saturated sodium bicarbonate solution. Evaporation of the solvent from the dried benzene solution left a semisolid residue, which on trituration with 250 ml. of cold methanol gave 55.1 g. of purplish red solid, m.p. 185–198°. Three recrystallizations from isopropyl alcohol gave material melting at 199–203°: red plates with a purple luster (lit.[1] m.p. 196–198°).

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SYRACUSE 1, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Synthesis of Amino Compounds in the Sugar Series by Phenylhydrazone Reduction[1,2]

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It has been shown that the reduction of the phenylhydrazone function provides a convenient method for the synthesis of a variety of amino compounds in the sugar series. These include: the 1-amino-1-deoxy derivatives of D-arabinitol, D-galactitol, D-glucitol, D-gulitol, and D-xylitol; the diaminodideoxyalditols 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol, 1,4-diamino-1,4-dideoxy-D-threitol, 1,2-diamino-1,2-dideoxy-D-glucitol, and 1,2-diamino-1,2-dideoxy-D-mannitol; and 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose. All of these compounds have been isolated as crystalline salicylaldehyde Schiff bases and some of them have been further characterized as their hydrobromide and *N*-(2,4-dinitrophenyl) derivatives.

Reduction of the condensation products of carbohydrates with nitrogen bases provides a general route for the synthesis of a variety of amino sugars. Thus, many of the 1-amino-1-deoxyalditols have been prepared through the sodium amalgam reduction of the corresponding oximes.[3] These compounds can also be prepared by the reduction of the aldoses in the presence of ammonia[4,5] or by the hydrogenation of glycosylamines[6] and of 1-deoxy-1-benzylaminoalditols.[5] Other methods are based on the reduction of the aldonamides with lithium aluminum hydride[7] and the reduction of hydrazine derivatives. The latter method was employed by Fischer and Groh[8] for converting the phenylhydrazones of certain keto acids to the corresponding amino acids, a process which has been employed for the identification and estimation of the keto acids in plant products.[9] Emil Fischer also prepared (as the acetate salt) 1-amino-1-deoxy-D-fructose, "isoglucosamine," by the reduction of D-glucose phenylosazone with zinc and acetic acid.[10] Maurer and Schiedt[11] increased the yield in this reaction to 60% through employment of catalytic

(1) Carried out in part under contracts DA-33-019-ord-2042 (Office of Ordnance Research) and DA-33-019-ord-2025 (Aberdeen Proving Ground) between the U. S. Army Ordnance Corps (technical supervising agency, Ballistic Research Laboratories, Aberdeen Proving Ground, Md.) and The Ohio State University Research Foundation (Projects 679 and 675).

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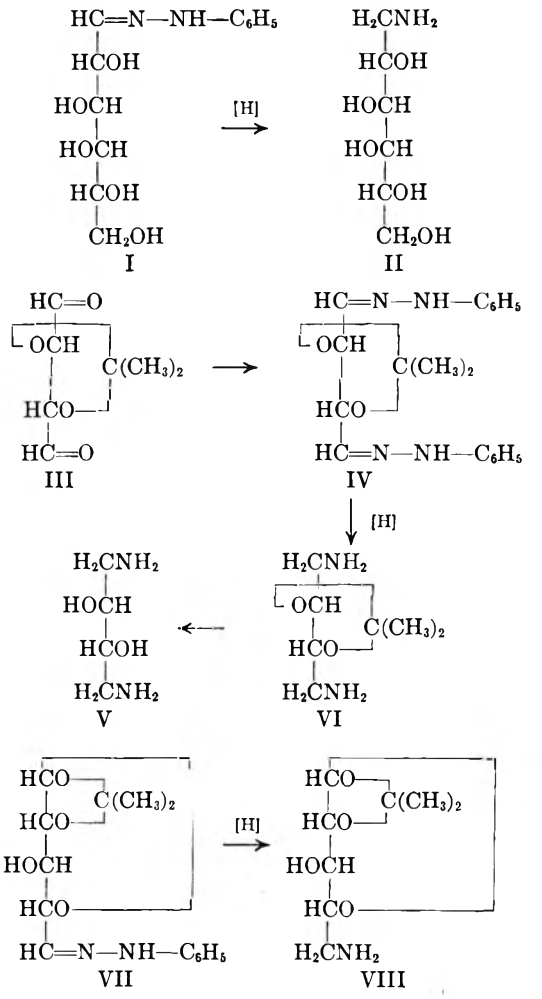
hydrogenation with a palladium catalyst in acetic acid.

The carbohydrate hydrazone derivatives provide a class of readily available and often highly crystalline compounds. Thus, their reduction should be of interest. Despite this, applications in carbohydrate chemistry[12,13] have been sporadic. We have found that this reaction provides a convenient method for the synthesis of a variety of amino sugar derivatives, some of which have been prepared for the first time.

The catalytic reduction of the aldose hydrazone derivatives with Raney nickel proceeds under mild conditions and provides a good yield of the expected 1-amino-1-deoxyalditol. Thus, the reduction of a hot concentrated solution of D-galactose phenylhydrazone, which is known to exist in the acyclic form (I)[14,15] in the Parr hydrogenation apparatus provides 1-amino-1-deoxy-D-galactitol (II) and presumably aniline, which can be extracted from the aqueous solution with benzene. We have isolated the product, 1-amino-1-deoxy-D-galactitol, as a crystalline hydrobromide salt, salicylaldehyde Schiff base, and *N*-(2,4-dinitrophenyl) derivative. 1-Deoxy-1-salicylideneamino-D-galactitol[2] is a useful intermediate for the isolation of the amino alditol. This compound has recently been recorded by Kagan and associates.[5] The amino alditol can also be isolated from the reaction mixture as the hydrochloride or hydrobromide salt. However, the salt obtained through this method is contaminated with an unknown impurity which can be separated by fractional crystallization. The physical constants and properties of this material are in agreement with those reported for the substance designated "didulcitylamine" by Kagan and co-workers.[5]

Derivatives of 1-amino-1-deoxy-D-arabinitol, 1-amino-1-deoxy-D-gulitol, (6-amino-6-deoxy-L-glucitol), 1-amino-1-deoxy-D-glucitol, and 1-amino-1-deoxy-D-xylitol have been similarly prepared through the catalytic reduction of the corresponding phenylhydrazones. The above reaction has been extended to the phenylhydrazone derivatives prepared from the product of glycol cleavage of some carbohydrate acetals. Thus, 2,3-*O*-isopropylidene-*dialdehydo*-D-*threo*-tetrodiose (III), first prepared by the lead tetraacetate oxidation of 3,4-*O*-isopropylidene-D-mannitol[16] and later by the periodate oxidation of 3,4-*O*-isopropylidene-D-glucitol,[17] has been converted to the bis(phenylhydrazone) derivative[16] (IV) and subsequently hydrogenated. The product, 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol (VI) has been isolated as a crystalline dipicrate salt and bis(salicylaldehyde Schiff base). Acid hydrolysis of the isopropylidene group gave 1,4-diamino-1,4-dideoxy-D-threitol (V), isolated as the crystalline bis(salicylaldehyde Schiff base). In similar manner, the phenylhydrazone derivative of 1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodiofuranose (VII), produced by lead tetraacetate[18] or periodate[19,20] oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose, was converted to 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (VIII). This product was isolated as the crystalline hydrobromide salt and salicylaldehyde Schiff base. Since our first report on this subject,[2] the isolation of the above compound, as the free base and *p*-toluenesulfonate salt, has been recorded by other investigators.[21] The hydrobromide and hydrochloride salts of the above compound are unstable and grad-



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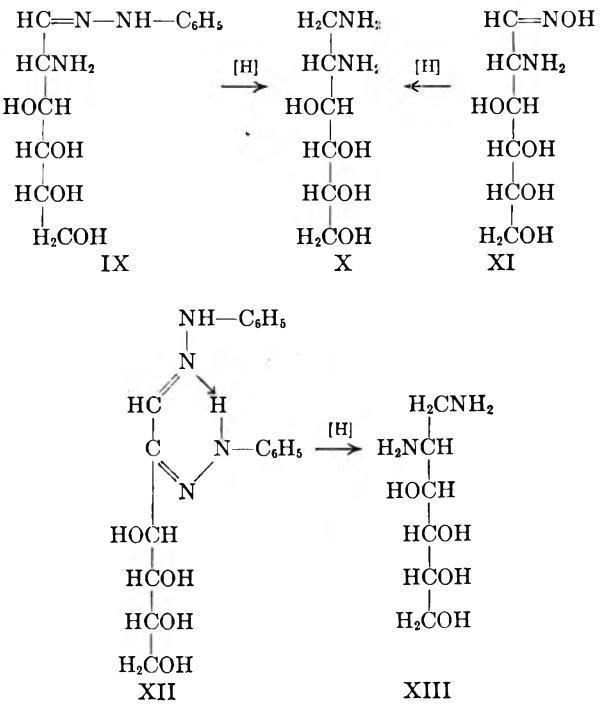
ually decompose with the evolution of acetone. Attempts to prepare the free 5-amino-5-deoxy-D-xylose by the acid hydrolysis of the above compound led to the extensive decomposition with the formation of a product resembling the "browning" polymers formed in the Maillard reaction.[22]

The reduction of the phenylhydrazine derivatives of carbohydrates has been herein extended to the synthesis of 1,2-diamino-1,2-dideoxyalditols which constitute a unique class of carbohydrate derivatives. Thus, 2-amino-2-deoxy-D-glucose hydrochloride was treated with phenylhydrazine and the reaction mixture, containing 2-amino-2-deoxy-D-glucose phenylhydrazone (IX), was hydrogenated with Raney nickel catalyst. The reduction product was isolated, in low yield, as the crystalline bis-(salicylaldehyde Schiff base), identical with the product (X) obtained by the hydrogenation of 2-amino-2-deoxy-D-glucose oxime (hydrochloride)[23] (XI) with palladium-charcoal catalyst. This demonstrates that X bears the D-glucose structure. An isomeric substance (XIII) was obtained, in low yield, by the reduction of D-*arabino*-hexose phenylosazone ("glucosazone"; XII) with palladium-charcoal catalyst, in the presence of hydrochloric acid. This compound must therefore possess the D-mannose configuration.

It has been noted that the reduction of D-*arabino*-hexose phenylosazone, in the presence of acetic acid according to Emil Fischer[10] and Maurer and Schiedt,[11] results in the formation of 1-amino-1-deoxy-D-fructose. This is in contrast with the properties of acetophenone ketazine, $C_6H_5(CH_3)C{=}N{-}N{=}C(CH_3)C_6H_5$, which on catalytic hydrogenation gives 1,2-bis(α-methylbenzyl)hydrazine, $C_6H_5(CH_3)CHNHNHCH(CH_3)C_6H_5$, without cleavage, and with benzil phenylosazone which remains unchanged.[13] Kuhn and Kirschenlohr[24] have isolated the *N*-acetyl derivatives of 2-amino-2-deoxylactose and 1-amino-1-deoxylactulose by chromatographic separation of the mixture obtained from the catalytic reduction of lactose phenylosazone in the presence of acetic acid. According to these authors,[24] the acidic conditions cause one of the phenylhydrazone functions to be hydrolyzed and subsequent reduction gives a mixture of 2-amino-2-deoxyaldose and 1-amino-1-deoxyketose, in which the latter product predominates. These considerations reflect the complexity of the reduction products of D-*arabino*-hexose phenylosazone (XII) which is stabilized in the acyclic structure[25,26] by the formation of a chelate ring,[26,27] and may provide an explanation for the low yield of 1,2-diamino-1,2-dideoxy-D-mannitol.



EXPERIMENTAL

1-Deoxy-1-salicylideneamino-D-galactitol. D-Galactose phenylhydrazone[28] (15 g.) was dissolved in 150 ml. of hot water and hydrogenated in the Parr apparatus at 3-atm. pressure for 17 hr., using Raney nickel catalyst. The reaction mixture was filtered and extracted with five 100-ml. portions of benzene. The aqueous solution containing 1-amino-1-deoxy-D-galactitol was then treated with 7 g. of salicylaldehyde and 5 g. of sodium bicarbonate. After shaking for 2 hr., the product, 1-deoxy-1-salicylideneamino-D-galactitol, was filtered and recrystallized from 50% aqueous ethanol; yield 12.1 g., m.p. 202°; no suitable solvent was found for the determination of optical rotation.

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.58; H, 6.86; N, 4.91.

1-Amino-1-deoxy-D-galactitol hydrobromide. A suspension of 1-deoxy-1-salicylideneamino-D-galactitol (10 g.) in 200 ml. of abs. ethanol was treated with 6 g. of 48% aqueous hydrogen bromide. The resulting colorless precipitate of 1-amino-1-deoxy-D-galactitol hydrobromide was filtered and recrystallized from hot aqueous methanol; yield 6.8 g., m.p. 136°, $[\alpha]_D^{20}$ −10.5° (*c* 4.59, water).

Anal. Calcd. for $C_6H_{16}BrNO_5$: C, 27.49; H, 6.15; Br, 30.49; N, 5.34. Found: C, 27.66; H, 6.25; Br, 30.21; N, 5.50.

This compound, as well as the hydrochloride salt, could be isolated directly from the benzene-extracted hydrogenation mixture described above, by concentration to a sirup and addition of methanolic hydrogen bromide or hydrogen chloride and repeated fractional crystallization from aqueous methanol. The less soluble fraction, which crystallized first, is a by-product which was obtained as the hydrochloride salt, after two more recrystallizations from the same solvent; m.p. 241–242° (the reported[5] m.p. of "didulcitylamine hydrochloride" is 240–241°).

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Anal. Calcd. for $C_{12}H_{28}ClNO_{10}$: C, 37.75; H, 7.39; N, 3.67. Found: C, 36.92; H, 7.04; N, 3.67.

1-Deoxy-1-(2,4-dinitroanilino)-D-galactitol. A solution of 150 mg. of 1-amino-1-deoxy-D-galactitol hydrobromide in 3 ml. of water was treated with 140 mg. of 2,4-dinitrofluorobenzene and 300 mg. of sodium bicarbonate. The reaction mixture was heated briefly at 100° with continuous stirring. After cooling, the orange colored precipitate of 1-deoxy-1-(2,4-dinitroanilino)-D-galactitol was filtered and recrystallized from aqueous methanol; yield 138 mg., m.p. 195–196°.

Anal. Calcd. for $C_{12}H_{17}N_3O_9$: C, 41.49; H, 4.89; N, 12.1. Found: C, 41.43; H, 4.85; N, 11.98.

1-Deoxy-1-salicylideneamino-D-gulitol. D-Gulose phenylhydrazone[29] (3 g.) was dissolved in 90 ml. of water and hydrogenated as described above for D-galactose phenylhydrazone. The resultant aqueous solution of 1-amino-1-deoxy-D-gulitol was treated with 1.3 g. of salicylaldehyde and 3 g. of sodium bicarbonate. Evaporation of the reaction mixture gave 1-amino-1-deoxy-D-gulitol salicylaldehyde Schiff base as a sirup which crystallized on standing. The product was filtered, washed with small amounts of water and ether, and recrystallized from ethanol; yield 1.58 g., m.p. 157.5–158°, $[\alpha]_D^{20}$ −11.5° (*c* 2.24, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.69; H, 6.74; N, 4.88.

1-Amino-1-deoxy-D-arabinitol hydrobromide, salicylaldehyde Schiff base and N-2,4-dinitrophenyl derivative. D-Arabinose phenylhydrazone[30] (10 g.) was hydrogenated as described above and the product was converted to 1-amino-1-deoxy-D-arabinitol salicylaldehyde Schiff base; yield 5.5 g., m.p. 184–185°, $[\alpha]_D^{20}$ +25° (*c* 2.24, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.26; H, 6.52; N, 5.56.

A suspension of 2 g. of 1-amino-1-deoxy-D-arabinitol salicylaldehyde Schiff base in 50 ml. of methanol, on treatment with 1.6 g. of 48% aqueous hydrogen bromide, gave a colorless solution containing 1-amino-1-deoxy-D-arabinitol hydrobromide. This product was precipitated by the gradual addition of ether and was recrystallized from 95% ethanol; yield 0.75 g., m.p. 166–167°, $[\alpha]_D^{20}$ +11° (*c* 4.14, water).

Anal. Calcd. for $C_5H_{14}BrNO_4$: C, 25.58; H, 6.08; Br, 34.43; N, 6.03. Found: C, 26.12; H, 5.84; Br, 34.56; N, 5.80.

The above product was converted to 1-deoxy-1-(2,4-dinitroanilino)-D-arabinitol, m.p. 174–175°.

Anal. Calcd. for $C_{11}H_{15}N_3O_8$: C, 41.64; H, 4.77; N, 13.25. Found: C, 41.52; H, 5.35; N, 13.07.

1-Deoxy-1-salicylideneamino-D-glucitol. This compound (3.8 g.) was prepared from the reduction product of 8 g. of D-glucose phenylhydrazone (α-form),[28] m.p. 177–177.5°, $[\alpha]_D^{23}$ −20° (*c* 2.58, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.86; H, 6.55; N, 4.86.

1-Amino-1-deoxy-D-xylitol salicylaldehyde Schiff base and hydrobromide. The Schiff base (14.5 g.) was prepared from the reduction product of 20 g. of D-xylose phenylhydrazone;[31] m.p. 128–129°, $[\alpha]_D^{23}$ −20° (*c* 2.79, *N,N*-dimethylformamide) Kagan and co-workers,[5] quote the m.p. 131–133°.

The above compound (12 g.) was converted to 1-amino-1-deoxy-D-xylitol hydrobromide (9.2 g.), m.p. 167–168°, $[\alpha]_D^{23}$ −13° (*c* 4.33, water).

Anal. Calcd. for $C_5H_{14}BrNO_4$: C, 25.58; H, 6.08; N, 6.03. Found: C, 25.85; H, 5.93; N, 6.14.

1,4-Diamino-1,4-dideoxy-2,3-O-isopropylidene-D-threitol dipicrate. 2,3-*O*-Isopropylidene-*dialdehydo*-D-*threo*-tetrodiose bis(phenylhydrazone)[16,17] (664 mg.) was dissolved in 67% aqueous ethanol and hydrogenated with freshly prepared Raney nickel catalyst at atmospheric pressure for 18 hr. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure. Treatment of the residue with a hot concentrated solution of 910 mg. of picric acid in ethanol gave 870 mg. of 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate, which was purified by several recrystallizations from aqueous ethanol and from water; m.p. 217–218° (dec.).

Anal. Calcd. for $C_{19}H_{22}N_8O_{16}$: C, 36.90; H, 3.58; N, 18.12. Found: C, 36.99; H, 3.54; N, 18.72.

1,4-Dideoxy-2,3-O-isopropylidene-1,4-bis(salicylideneamino)-D-threitol. 1,4-Diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate (100 mg.) was dissolved in 2 ml. of saturated sodium bicarbonate solution and sufficient water was added to keep the resulting sodium picrate in solution. The warmed reaction mixture was treated with 0.04 ml. of salicylaldehyde and the resulting precipitate of 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol bis(salicylaldehyde Schiff base) (55 mg.) was isolated after standing at 0° for 15 hr. The product was purified by several recrystallizations from aqueous methanol; m.p. 111°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.61. Found: C, 68.48; H, 6.43; N, 8.11.

1,4-Dideoxy-1,4-bis(salicylideneamino)-D-threitol. 1,4-Diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate (200 mg.) was suspended in 10 ml. of water containing one drop of concentrated hydrochloric acid and the mixture was heated for 2 hr. over the steam bath. It was then neutralized to *p*H 8 with sodium bicarbonate and sufficient water was added to keep the resulting sodium picrate in solution. The reaction mixture was then treated with 0.11 ml. of salicylaldehyde, heated briefly, and allowed to stand at 0° for 18 hr. The resulting precipitate of 1,4-diamino-1,4-dideoxy-D-threitol bis(salicylaldehyde Schiff base) (100 mg.) was recrystallized from 18 ml. of methanol; m.p. 228–231° (dec.). This compound was poorly soluble in most of the organic solvents and in water.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.70; H, 6.18; N, 8.46.

5-Amino-5-deoxy-O-isopropylidene-α-D-xylofuranose hydrobromide, hydrochloride, and salicylaldehyde Schiff base. 1,2-*O*-Isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodiofuranose phenylhydrazone[18] (4.5 g.) was suspended in 200 ml. of water and hydrogenated in the Parr apparatus at 3-atm. pressure, using Raney nickel as catalyst. After 17 hr., the reaction mixture was filtered and extracted with benzene as before. Evaporation of the aqueous layer furnished 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose as a thick sirup. This was dissolved in ethanol and neutralized with hydrogen chloride to *p*H 4.5. The resultant hydrochloride was precipitated by the addition of ether and was recrystallized from aqueous ethanol; yield 1.68 g., m.p. 130° dec., $[\alpha]_D^{20}$ −12° (*c* 3.2, water).

Anal. Calcd. for $C_8H_{16}ClNO_5$: C, 42.6; H, 7.09; N, 6.2. Found: C, 42.07; H, 7.71; N, 6.33.

The hydrobromide salt was prepared in like manner; m.p. 170° (dec.).

Anal. Calcd. for $C_8H_{16}BrNO_4$: C, 35.55; H, 5.90; N, 5.2. Found: C, 35.60; H, 5.54; N, 5.09.

Both of the above salts were unstable and decomposed gradually with the evolution of acetone.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose on treatment with salicylaldehyde furnished a crystalline Schiff base; m.p. 155°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.48; N, 4.77. Found: C, 61.40; H, 6.45; N, 4.78.

Attempted isolation of the free 5-amino-5-deoxy-D-xylose through the acid hydrolysis of the isopropylidene group was unsuccessful and resulted in rapid browning of the reaction mixture and the formation of a gummy dark brown product.

1,2-Dideoxy-1,2-bis(salicylideneamino)-D-glucitol. A solution of 5 g. of 2-amino-2-deoxy-α-D-glucose (α-D-glucosamine) hydrochloride, 2.5 g. of phenylhydrazine, and 0.5 ml. of acetic acid in 2.0 ml. of water was heated with stirring until the initial formation of D-glucose phenylosazone. The reaction mixture was then cooled and filtered from the small precipitate of D-glucose phenylosazone, and the filtrate was

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(30) G. Chavanne, *Compt. rend.*, **134**, 661 (1902).

(31) C. Tanret, *Bull. soc. chim. (France)*, **27**, 392 (1902).

hydrogenated in the Parr apparatus at 3-atm. pressure, using Raney nickel as catalyst. After 18 hr., the reaction mixture was filtered and extracted with benzene in the manner described above. The aqueous solution containing the 1,2-diamino-1,2-dideoxy-D-glucitol was treated with 2 g. of sodium bicarbonate and 4.68 g. of salicylaldehyde and the mixture was heated over the steam bath, with stirring, for 3 hr. The product, 1,2-diamino-1,2-dideoxy-D-glucitol bis(salicylaldehyde Schiff base), was recrystallized from 95% ethanol; yield 2.34 g., m.p. 208–208.5°, $[\alpha]_D^{20}$ −83° (c 4.04, *N*,*N*-dimethylformamide), x-ray powder diffraction data:[32] 15.17w, 11.87m, 8.04w, 5.93m, 5.55vw, 5.15s(3), 4.90vs(1,1), 4.62s, 4.47s, 4.14vs(1,1), 3.85vw, 3.71vw, 3.53vw, 2.72 vw.

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.65; H, 6.01; N, 7.00.

2-Amino-2-deoxy-D-glucose oxime hydrochloride[23] (11.5 g.) was dissolved in 200 ml. of 75% ethanol and the solution was hydrogenated as in the above experiment, but with palladium-charcoal catalyst. The reaction mixture was then evaporated under reduced pressure and a portion of the product (10%) was converted to 1,2-dideoxy-1,2-bis(salicylideneamino)-D-glucitol. This compound had the same x-ray powder diffraction pattern and physical properties as the product synthesized above from 2-amino-2-deoxy-D-glucose phenylhydrazone.

1,2-Dideoxy-1,2-bis(salicylideneamino)-D-mannitol. D-*arabino*-Hexose phenylosazone (3.6 g., 10 millimoles) was dissolved in 100 ml. of 95% ethanol containing 40 millimoles of hydrogen chloride and the solution was hydrogenated in the Parr apparatus at 3-atm. pressure, using palladium-charcoal as catalyst. The reaction mixture was filtered and the filtrate was concentrated to 25 ml., diluted with 100 ml. of water, neutralized with sodium bicarbonate, and extracted with four 100-ml. portions of benzene. The aqueous solution of the reduction product was treated with 4 g. of sodium bicarbonate and 1 ml. of salicylaldehyde and heated over the steam bath with stirring for 2 hr. The resulting yellow precipitate of 1,2-diamino-1,2-dideoxy-D-mannitol bis(salicylaldehyde Schiff base) was purified by three recrystallizations from 95% ethanol; yield 0.15 g., m.p. 223–224°, $[\alpha]_D^{23}$ +54.2° (*c* 2.15, *N*,*N*-dimethylformamide), x-ray powder diffraction data:[32] 14.98w, 11.33m, 8.67m, 6.71w, 5.40m, 5.10vs(1), 4.80m, 4.60vs(2), 4.31vw, 4.00s(3), 3.73vw, 3.48vw, 3.29vw, 3.14w.

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 62.02; H, 6.46; N, 7.17.

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(32) Interplanar spacing, Å, CuK_α radiation. Relative intensity, estimated visually; s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

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Synthesis of β-(4-Pyridyl)-DL-alanine and of β-(4-Pyridyl-1-oxide)-DL-, D-, and L-alanine[1]

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A practical synthesis of β-(4-pyridyl)-DL-alanine, suitable for application on a gram scale, has been developed. β-(4-Pyridyl-1-oxide)-DL-alanine has been prepared in good yield, by a procedure capable of being employed on a much larger scale, and a satisfactory resolution of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine has been achieved.

Two methods have been reported for the synthesis of β-(4-pyridyl)-DL-alanine. The first[3] was based upon the sequence, 4-pyridylcarbinol→4-pyridylmethyl bromide→diethyl benzamido-(4-pyridylmethyl)malonate→β-(4-pyridyl)-DL-alanine and the second[4] upon the sequence, 4-picoline→ethyl α-oximino-β-(4-pyridyl)propionate→α-oximino-β-(4-pyridyl)propionic acid→β-(4-pyridyl)-DL-alanine. Both syntheses involved a step in which poor yields were obtained. The malonic ester condensation gave but a 4% yield, and the Claisen condensation a 12% yield. It was decided to study the malonic ester condensation with the aim of improving the yield.

The starting material for the malonic ester condensation, 4-pyridylmethyl bromide hydrobromide, was obtained in 85% yield from 4-pyridylcarbinol. This hydrobromide, and its parent amine, are severe vesicants.

The principal competing side reaction in the malonic ester condensation is the polymeric quaternization of 4-pyridylmethyl bromide. This quaternization has been studied by Sorm and Sedivy,[5] who also observed that 2-pyridylmethyl bromide quaternized at a slower rate. The quaternization of 4-bromopyridine is much faster than that of 2-bromopyridine,[6] the difference in rate being attributed to steric effects.[7] Presumably the same effects are operative in the case of 2- and 4-pyridylmethyl bromide. Examination of various modifi-

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(2) To whom inquiries regarding this article should be sent.

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cations of the malonic ester condensation,[8] such as using 4-pyridylmethyl tosylate, in lieu of the bromide, did not lead to a significant increase in the yield of desired product.

Considering the nature of the competing reactions, it would be predicted that use of a less polar solvent, *e.g.*, benzene instead of ethanol, would favor the rate of condensation and retard that of quaternization.[9] It was determined that approximately 50% benzene in ethanol was the most satisfactory solvent for effecting condensation.

It was necessary to neutralize the hydrobromide of 4-pyridylmethyl bromide. The rapid quaternization of the free base led to the use of an excess of the sodium salt of the acylamidomalonic ester in the neutralization reaction, which was conducted by adding the hydrobromide to a solution of the sodium salt. This procedure had the added effect of providing a higher concentration of the attacking group during the early part of the reaction and thus minimized the possibility of ether formation due to attack of the halide by alkoxide ion.

One would expect the rate of condensation of 4-pyridylmethyl bromide with the malonic ester to be reasonably fast, if the usual comparison of nitrophenyl and pyridyl groups can be made.[10] Dornow and Winter[11] obtained at least a 60% yield of the desired product from the condensation of *p*-nitrobenzyl chloride with diethyl formamidomalonate and it has been shown that *p*-nitrobenzyl bromide is about 400 times more reactive than *n*-butyl bromide in S_N2 reactions.[12] On the other hand, *p*-nitrobenzyl bromide exhibited the slowest rate of several *p*-substituted benzyl bromides in a quaternization reaction with triethylamine.[13] There are no data that afford comparison of the rate of an S_N2 reaction with that of quaternization.

The addition of the dry hydrobromide to the sodio-acylamidomalonic ester was abandoned for two reasons. One, the salt was hygroscopic, which complicated its addition. Two, high local concentration of 4-pyridylmethyl bromide formed when the addition was conducted with the dry salt favored quaternization. Since the hydrobromide was soluble only in water, it was necessary to add it as a slurry in benzene-ethanol.

As a result of studying the effect of time, temperature, solvent, mode of addition of the hydrobromide, and concentration of reactants, on the yields obtained in sixteen preparations, a procedure was devised which gave consistent 60–70% yields of diethyl acetamido(4-pyridylmethyl)malonate on a 0.02-mole scale. However, when scaled up to 0.08-mole quantities, the yield dropped to 30%, largely because of slurrying problems.

The diethyl acetamido(4-pyridylmethyl)malonate was hydrolyzed and decarboxylated with 48% hydrobromic acid to give 76% of the dihydrobromide of β-(4-pyridyl)-DL-alanine. Treatment of this salt with "Amberlite IR-4B" resin gave the desired α-amino acid in 90% yield. β-(4-Pyridyl)-DL-alanine reacted rapidly in the cold with ninhydrin to give a red color,[3,4] and was soluble in water to the extent of 3.4 g. per 100 ml. at 25°.

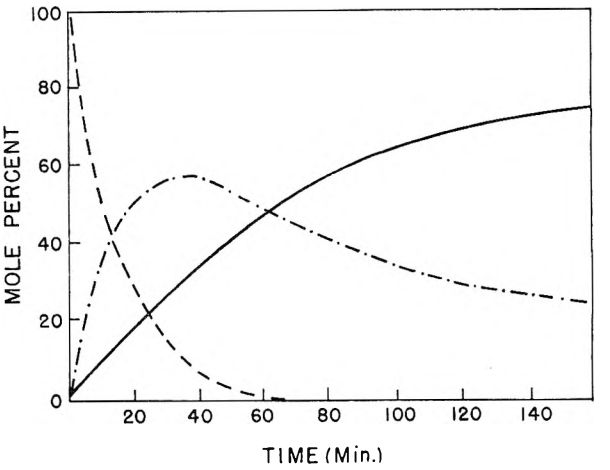

Fig. 1. The catalytic hydrogenation of β-(4-pyridyl-1-oxide)-DL-alanine: --- β-(4-pyridyl-1-oxide)-DL-alanine; -·- β-(4-pyridyl)-DL-alanine; — β-(4-piperidyl)-DL-alanine

Another route to β-(4-pyridyl)-DL-alanine that was considered was from isonicotinaldehyde *via* the azlactone. However, the aldehyde is stable only as a hydrate, the anhydrous compound being very sensitive to air oxidation.[14] It also readily undergoes a Cannizzaro reaction in the presence of air.[15] No product could be isolated from a standard Erlenmeyer synthesis[16] using the anhydrous aldehyde, or its diacetate, prepared from the hydrate by reaction with acetic anhydride. A modified Erlenmeyer synthesis involving rhodanine[17] gave only non-characterizable products.

One possible route that was not investigated was the Knoevenagel condensation of isonicotinaldehyde with nitroacetonitrile. The yield of 1-γ-pyridyl-2-cyano-2-nitroethylene has been reported as 35%.[18] The reaction of ethyl nitroacetate with picolinaldehyde gave an 81% yield of diethyl

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α,α-dinitro-γ-(4-pyridyl)glutarate[19] and probably could be controlled to give a 1:1 condensation product. It appears that the double bond and nitro group of 1-γ-pyridyl-2-cyano-2-nitroethylene could be reduced without reducing the pyridine ring on the basis of work done by Walter *et al.* on the reduction of the pyridine acrylic acids.[20]

Although the goal of raising the yield in a series of reactions leading to β-(4-pyridyl)-DL-alanine was achieved, the improved synthesis was not useful for the preparation of large quantities of this amino acid. While there was no reason to expect that the yield obtained by Elliott, Fuller, and Harington[4] could be improved, more recent studies indicated that the electron deficiency at the methyl group of 4-picoline was greatly enhanced in 4-picoline-1-oxide[21] thus implying that a Claisen condensation based upon 4-picoline-1-oxide would be considerably more successful than one based on 4-picoline. This was shown to be the case by Adams and Miyano,[22] who obtained a 48% yield of ethyl β-(4-pyridyl-1-oxide)pyruvate from the condensation of ethyl oxalate and 4-picoline-1-oxide, in the presence of potassium ethoxide. The α-keto ester was isolated *via* aqueous hydrolysis of its potassium salt and extraction with chloroform. A modification of this reaction, conducted in these laboratories, involved aqueous hydrolysis of the sodium salt of the keto ester and, after cooling, isolation of the crystalline solid that had formed. This product was impure, and was found to contain a component that was insoluble in chloroform. Recrystallization of the impure material from water gave a 48% yield of the α-keto ester. Concentration of the filtrate gave a yellow crystalline light sensitive solid, m.p. 186–187°, of unknown constitution. This latter compound was insoluble in chloroform, and would not form a water insoluble oxime, as would the α-keto ester or α-keto acid.

The oxime of the α-keto ester was prepared by Adams and Miyano[22] in 57% yield, and this result was confirmed in these laboratories. A modification of the method for the preparation of the oxime, not involving isolation of the α-keto ester, gave consistent 55–60% yields of recrystallized ethyl α-oximino-β-(4-pyridyl-1-oxide)propionate, directly from 4-picoline-1-oxide.

Oximes are readily reduced to amines, but α-oximino esters require rather strenuous conditions. Hartung and co-workers[23] have examined the catalytic reduction of a number of α-oximino esters. Generally, five grams of palladium on charcoal plus one to five grams of palladium chloride with 150 p.s.i. of hydrogen at room temperature was used for 0.15 mole of oximino ester. In addition, a threefold excess of concentrated hydrochloric acid was necessary to prevent formation of secondary amines. Hartung and Waters[24] have shown that α-amino acids poison the catalytic reduction of α-oximino acids. In the case of oximinomalonic ester, 1500 p.s.i. of hydrogen were necessary to obtain reduction with the palladium catalyst.[25] With Adam's catalyst the reduction of 3-oximino-1-dimethylaminobutane gave a 25% yield of the diamine.[26] Shivers and Hauser[27] found that reduction of α-oximino esters with Raney nickel gave 85% yields of the amino esters and Ried and Schiller[28] employed Raney nickel in glacial acetic acid for the reduction of ethyl α-oximino-β-(2-quinolyl)-propionate. In the latter instance, considerable amounts of β-(2-tetrahydroquinolyl)-DL-alanine were obtained and in other cases only the α-hydroxylamino ester was isolated.[29]

In all of the above procedures it would be expected that concurrent reduction of a pyridine nucleus would occur. This has been shown to be the case for α-oximino-β-(4-pyridyl)propionic acid by Elliott, *et al.*,[4] and for its *N*-oxide in this investigation.

Other methods used for the reduction of oximes, such as lithium aluminum hydride, or sodium amalgam, are not applicable to the case at hand. The use of sodium borohydride was investigated, but no reduction was obtained.

Elliott, Fuller, and Harington[4] found that their oximino acid could be reduced with stannous chloride in concentrated hydrochloric acid. The tin salts were removed by precipitation with hydrogen sulfide after dilution of the reaction mixture with water. A more satisfactory procedure was developed in this investigation and was based upon removal of most of the hydrochloric acid by distillation *in vacuo* and neutralization of the residue to *p*H 6.7 with ammonium hydroxide. The precipitation of stannous and stannic hydroxides was so complete that no further precipitate could be obtained with hydrogen sulfide. The aqueous solution was evaporated to dryness to give a mixture of ammonium chloride and the amino acid, in a ratio of about four to one. The ammonium chloride was removed by extraction of the powdered mixture with methanol, the salt being soluble in methanol to the extent of 3.35 g. per 100 g. at

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19°.[30] The residue analyzed correctly for β-(4-pyridyl-1-oxide)-DL-alanine.

The amino acid reacted very slowly at room temperature with an aqueous solution of ninhydrin to give an orange color. It was soluble in water to the extent of 47 g. per 100 ml. at 25° and was essentially insoluble in the usual organic solvents.

In the preparation of acylated β-(4-pyridyl-1-oxide)-DL-alanines, one potential complicating factor has to be considered, *i.e.*, that amine oxides occasionally react with anhydrides and acid chlorides. In the case of heterocyclic aromatic amine oxides, the literature, while consistent, is difficult to explain. Thus, 4-nitroquinoline-1-oxide reacted with acetyl chloride at room temperature to give 4-chloroquinoline-1-oxide while reaction with benzoyl chloride gave 4-chlorocarbostyril.[31] The reaction of 4-aminopyridine-1-oxide with benzoyl chloride under Schotten-Baumann conditions gave a dibenzoyl derivative, which was converted to 4-benzamidopyridine-1-oxide upon recrystallization.[32] Acylation of 4-aminoquinoline-1-oxide with benzoyl chloride under Schotten-Baumann conditions gave a dibenzoate, a monobenzoate, and a carbostyril.[33] Treatment of the same amine with acetic anhydride or benzoic anhydride at room temperature gave only the 4-acylamidoquinoline-1-oxides.[33] Both anhydrides reacted with pyridine-1-oxide at temperatures near 140° to give α-pyridone.[34] With the 2-and 4-picoline-1-oxides, reaction with acetic anhydride at room temperature gave the pyridylcarbinol acetates.[35] However, reaction of acetyl chloride with 4-nitro-2-picoline-1-oxide gave 4-chloro-2-picoline 1-oxide, with no evidence of rearrangement.[36]

The attempted acylation of β-(4-pyridyl-1-oxide)-DL-alanine with benzoyl chloride under Schotten-Baumann conditions gave only red oils, from which no single product could be isolated.[37] However, benzoic anhydride in the presence of triethylamine gave *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine in 74% yield. The product was separated from benzoic acid by acidifying the reaction mixture until it was 2*N* in hydrochloric acid. The precipitated benzoic acid was removed and the solution then adjusted to *p*H 2.3, to precipitate the product. *N*-Benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine was also obtained in 70% yield from the oximino acid by reduction with stannous chloride, precipitation of stannous and stannic ions with sodium hydroxide, and benzoylation of the filtrate after removal of the stannous and stannic hydroxides.

The pK_A' of the 1-hydroxypyridinium ion derived from β-(4-pyridyl-1-oxide)-DL-alanine was determined to be 1.15 by the spectrophotometric method of Flexser, Hammett, and Dingwall.[38] This value is in good agreement with the values for this type of ion obtained by Jaffe and Doak.[39] With a value of 3.5 for the pK_A' of the carboxyl function,[40] the above value of 1.15 was used to calculate the *p*H for the minimum solubility of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine noted above, *i.e.*, 2.3.

It was found that β-(4-pyridyl-1-oxide)-DL-alanine could be acylated with acetic anhydride under Schotten-Baumann conditions in 87% yield. A unique feature of this acetylation was that no excess of the anhydride was required. In fact, an excess led to the immediate formation of colored products, presumably arising from the reaction of the anhydride with the *N*-oxide function. This observation suggests that the amino group is more nucleophilic than the *N*-oxide oxygen with its formal negative charge. *N*-Acetyl-β-(4-pyridyl-1-oxide)-DL-alanine was so soluble in water, about 50 g. per 100 ml. at 25°, and so insoluble in organic solvents that it could not be separated from sodium chloride. This property led to the use of triethylamine as the base in the Schotten-Baumann acetylation, for after acidification of the solution to *p*H 2 and evaporation to dryness, the triethylamine hydrochloride that was formed could be removed by extraction of the solid residue with chloroform since its solubility in this solvent was 17.4 g. per 100 g. at 25°.[41] As no free amino acid could be detected in the extracted residue, it may be inferred that the acylation was quantitative.

In order to determine whether the apparent low order of reactivity of anhydrides toward the *N*-oxide function could be observed under more drastic conditions equimolar amounts of β-(4-pyridyl-1-oxide)-DL-alanine and phthalic anhydride were heated in the dry state at 140°. *N*-Phthaloyl-β-(4-pyridyl-1-oxide)-DL-alanine was isolated in 64% yield. This compound was characterized by its

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(37) Attempts to benzoylate β-(4-pyridyl)-DL-alanine with benzoyl chloride under Schotten-Baumann conditions led to the same result. However, benzoic anhydride in the presence of triethylamine gave *N*-benzoyl-β-(4-pyridyl)-DL-alanine.

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strong ultraviolet absorption at 260 mμ,[42] its failure to give a positive ninhydrin reaction, and by its ability to give a positive ferric hydroxamate test.

The methyl esters of *N*-benzoyl- and *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alanine, and the ethyl ester of the former compound were prepared by the thionyl chloride procedure of Brenner and Huber.[43] The product first isolated was the hydroxypyridinium chloride which was converted to the free ester by reaction with ammonia in chloroform at ice temperatures.[44] The acetyl ester was soluble in water at room temperature to the extent of 50 g. per 100 ml. at 25° and the benzoyl ester to the extent of 8 g. per 100 ml. at 25°.

The resolution of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine methyl ester with α-chymotrypsin was conducted at *p*H 7.9, the solution acidified to *p*H 2.2, and after standing for one hour at 4°, the *N*-benzoyl-β-(4-pyridyl-1-oxide)-L-alanine was recovered by filtration. The filtrate was neutralized to *p*H 7 and saturated with salt, whereupon the *N*-benzoyl-β-(4-pyridyl-1-oxide)-D-alanine methyl ester precipitated. The L-acid was purified by solution in aqueous sodium bicarbonate, at *p*H 7, filtration, reprecipitation at *p*H 2.2, and recrystallization from water. The compound appeared to be a monohydrate. Esterification of the L-acid with methanol and thionyl chloride[43] gave *N*-benzoyl-β-(4-pyridyl-1-oxide)-L-alanine methyl ester, with the same melting point and the same rotation, but of opposite sign, as the D-ester.

In the attempted resolution of *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alanine methyl ester, solubility problems were encountered. Because of the high water solubility of both the ester and parent acid, the attempted separations were based on differing solubilities in organic solvents. Both compounds had rather low solubilities in methanol or ethanol. However, the ester was soluble in chloroform, while the acid was only slightly soluble in this solvent. Since the resolution was conducted in aqueous solution at *p*H 7.9, it was necessary to add base to maintain a constant *p*H. Two choices were available, sodium hydroxide or triethylamine. When sodium hydroxide was used, the sodium salt of the L-acid was formed, and this compound was only slightly in methanol or ethanol. When the solution containing the D-ester and L-acid salt was acidified, sodium chloride was formed. It was not possible to separate the salt from the L-acid. When triethylamine was used the solution again had to be acidified because the triethylammonium salt of the L-acid was soluble in chloroform. Acidification of the solution produced triethylammonium chloride which is soluble in chloroform. Evaporation of the acidified solution to dryness gave a dry powder only a small portion of which would dissolve in chloroform. The low solubility of this product in chloroform was due to the fact that enzyme was present in the dry powder. The dry enzyme is very hygroscopic. Also, triethylammonium chloride is very hygroscopic in the presence of an excess of hydrochloric acid. These two features led to the wetting of the methyl ester, which then was insoluble in chloroform.

An alternative method considered for the resolution of *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alanine was *via* a papain catalyzed synthesis of the phenylhydrazide. This method is based on the formation of a water-insoluble phenylhydrazide, which for the case at hand would not be likely, since *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alaninamide was prepared and found to be very water soluble.

Since the original aim of this study was an improved route to β-(4-pyridyl)-DL-, D-, and L-alanine, it was necessary to consider the problem of removal of the *N*-oxide group. Aliphatic amine *N*-oxides or those represented by dimethylaniline-*N*-oxide are readily reduced to the corresponding tertiary amine. On the other hand, aromatic heterocyclic amine *N*-oxides are characterized by a marked resistance to reduction. The oxide oxygen of pyridine- and quinoline-*N*-oxide is not readily removed by catalytic hydrogenation at ordinary temperatures and pressures.[45] For example 4-benzyloxypyridine-1-oxide can be hydrogenolyzed to 4-hydroxypyridine-1-oxide.[32] However, the use of acetic acid–acetic anhydride as a solvent apparently led to reduction of the *N*-oxide group.[46] Raney nickel at elevated temperatures gave a fair yield of the tertiary amine but also a large amount of by-products.[47] Of the many chemical reducing agents that have been investigated, few have proved successful. One of the most useful, *i.e.*, phosphorus trichloride,[48] has obvious limitations. Hertog, *et al.*, has reported the use of iron and glacial acetic acid.[49]

A catalytic reduction would be the most desirable. However, one is handicapped by the ease of reduction of the pyridine nucleus. Exploratory studies were based on the reduction of 4-picoline-1-oxide with platinum and palladium on charcoal. The extent of reduction at room temperature was followed by means of pressure-drop in a low pressure hydrogenation apparatus. The presence of secondary amine was determined by means of the

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nickel chloride–carbon bisulfide reagent described by Shriner and Fuson.[50] With 5% palladium on charcoal, no reduction was obtained using absolute ethanol or 1*N* hydrochloric acid in absolute ethanol. With glacial acetic acid and one mole equivalent of acetic anhydride, reduction of the pyridine nucleus was extensive. With Adams' catalyst, and the above three solvents, reduction of the nucleus proceeded concomitantly with that of the *N*-oxide.

It was decided to study the catalytic reduction of β-(4-pyridyl)-DL-alanine and of the corresponding *N*-oxide spectrophotometrically, using the method outlined by Friedel and Orchin.[51] The conditions employed involved the use of platinum dioxide at 40 p.s.i. of hydrogen at room temperature in water. The results are summarized in Figure 1. Although the data are not precise, there is good evidence that concomitant reduction of β-(4-pyridyl-1-oxide)-DL-alanine and β-(4-pyridyl)-DL-alanine was encountered under the above conditions.

In conjunction with the previous study, a sample of β-(4-pyridyl-1-oxide)-DL-alanine was hydrogenated at 40 p.s.i. and room temperature over a platinum dioxide catalyst, allowing 2.5 equivalents of hydrogen to be absorbed instead of the 4 equivalents required for complete reduction. These conditions should have led to a 1:1 mixture of β-(4-pyridyl)-DL-alanine and β-(4-piperidyl)-DL-alanine. A sample of the latter compound was prepared and was found to be very soluble in absolute methanol. The reduction product was isolated, dried, and extracted with methanol. The ultraviolet absorption spectra of the dried product exhibited about one-half of the theoretical molar absorption for β-(4-pyridyl)-DL-alanine and gave a blue-purple ninhydrin reaction, in contrast to the red color given by β-(4-pyridyl)-DL-alanine. The same product was isolated after a second methanol extraction. This product appears to be the β-(4-piperidyl)-DL-alanine salt of β-(4-pyridyl)-DL-alanine.

Other methods for the reduction of the amine oxide group that were investigated involved the use of hypophosphorous acid and triphenyl phosphine. In both cases no reduction was obtained. Horner and Hoffmann[52] recently reported the failure of attempted reductions of pyridine- and quinoline-1-oxides with triethyl- and triphenylphosphine. Because of the similarity of the semi-polar N→O bond in heterocyclic aromatic amine *N*-oxides to that of the N→O bond in aromatic nitro compounds, it was hoped that the use of hydrazine and Raney nickel in alcohol, a method which works well for aromatic nitro compounds,[53] would be applicable to the N-oxides. No reduction was obtained with 4-picoline-1-oxide. A reduction of the same compound was attempted, using sulfur in morpholine under the conditions of the Willgerodt reaction. The product obtained was thioisonicotinyl morpholine. These conditions appear to be too strenuous for application to more complex compounds.

This investigation has resulted in the development of a synthesis of β-(4-pyridyl)-DL-alanine which is satisfactory if quantities of 1 to 2 grams of this α-amino acid are all that are required. An alternative synthesis has been developed to the point where substantial quantities of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-, D-, and L-alanine may be prepared with relative ease. The problem of transforming these latter compounds to β-(4-pyridyl)-DL-, D-, and L-alanine in good yield has not been solved.

EXPERIMENTAL[54,55]

4-Pyridylmethyl bromide hydrobromide. A solution of 20 g. of 4-pyridylcarbinol in 180 ml. of 48% hydrobromic acid was held at reflux for 4 hr. The reaction mixture was concentrated *in vacuo* to a thick paste, diluted with 100 ml. of absolute ethanol, filtered at ice temperature, and the residue washed with 20 ml. of absolute ethanol. The product, colorless needles, was dried *in vacuo* to give 38.7 g. of the hydrobromide (84%), m.p. 185–187° with dec., lit., 145–150°[3], 187°[5].

Diethyl acetamido-(4-pyridylmethyl)malonate. As a result of sixteen preparations of this compound under varying conditions, the procedure given below was found to be optimal for a 0.02-mole scale.

A 500-ml. three-necked round-bottomed flask, equipped with a Teflon-bladed Trubore stirrer, reflux condenser, drying tube, and a slurrying device containing a separate Teflon-bladed stirrer, was purged with dry nitrogen. After 0.92 g. (0.04 g.-atom) of sodium had been dissolved in 70 ml. of a 1:1 mixture of benzene and anhydrous ethanol, 8.46 g. (0.04 mole) of diethyl acetamidomalonate was added and the resultant solution heated to reflux. With the stopcock on the slurrying device closed, 100 ml. of the benzene-ethanol solvent was added to the bulb of the slurrying device with its stirrer on, followed by 5.06 g. (0.02 mole) of 4-pyridylmethyl bromide hydrobromide. With the stirrer in motion in the reaction flask, the stopcock of the slurrying device was opened. The slurry was added to the reaction flask over 40 min., the rate of addition being controlled by the stirring rate in the slurrying device. The resultant red reaction mixture was held at reflux for 2 hr., then allowed to stand overnight at room temperature. The solvent was removed by evaporation under a stream of air, leaving a brick red solid. The solid was extracted with 100 ml. of dry chloroform, and the chloroform solution extracted with 40 ml. of 4*N* hydrochloric acid. The acid phase was neutralized at ice temperatures with 30% aqueous sodium hydroxide to *p*H 6. The resultant precipitate was recovered by filtration, and combined with a small amount of material obtained by chloroform extraction of the filtrate to give *ca.* 4 g. of product (70%). The ester was recrystallized from water; m.p. 121.7–122.0°.

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(53) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

(54) All melting points are corrected.

(55) Microanalyses by Dr. A. Elek.

Anal. Calcd. for $C_{15}H_{20}O_5N_2$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.5; H, 6.5; N, 9.1.

This procedure gave only 30% yields when 0.08-mole quantities of the bromide-hydrobromide were used.

β-(4-Pyridyl)-DL-alanine. A solution of 15 g. of recrystallized diethyl acetamido(4-pyridylmethyl)malonate in 75 ml. of 48% hydrobromic acid was held at reflux for 6 hr. The solvent was removed *in vacuo* until a dense white solid separated. The crystalline material was recovered by filtration and washed with 20% hydrobromic acid. The filtrates were concentrated to 10 ml., and another batch of crystals obtained. The combined solids were dried *in vacuo* to give 12.2 g. (76%) of β-(4-pyridyl)-DL-alanine dihydrobromide, m.p. 250–252° (dec.).

Anal. Calcd. for $C_8H_{12}O_2N_2Br_2$: C, 29.0; H, 3.7; H, 8.5; Br, 48.4. Found: C, 29.1; H, 3.6; N, 8.7; Br, 48.5.

An aqueous solution of 11.2 g. of dihydrobromide was shaken with water washed Amberlite IR-4B until the solution was neutral. The resin was removed by filtration, and the yellow solution treated with Norit to give a colorless filtrate. The water was removed *in vacuo* to yield after recrystallization from water, 5.11 g. (90%) of β-(4-pyridyl)-DL-alanine, m.p. 234–235° with dec., lit.,[3] 235–236°.

Anal. Calcd. for $C_8H_{10}O_2N_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.5; H, 6.1; N, 16.2; Br, 0.3.

The addition of ninhydrin to an aqueous solution of the amino acid resulted in the formation of a red color.[3,4] The amino acid is soluble in water to the extent of 3.4 g. per 100 ml. at 25°, and is slightly soluble in pyridine.

N-Benzoyl-β-(4-pyridyl)-DL-alanine. To 0.5 g. (3.02 mmole) of β-(4-pyridyl)-DL-alanine dissolved in 20 ml. of water at 10° was added 0.835 ml. of triethylamine (6.04 mmole) and 0.75 g. (3.32 mmole) of benzoic anhydride. The suspension was stirred for 18 hr., filtered to remove residual anhydride, the filtrate acidified to *p*H 1 with concd. hydrochloric acid, the precipitated benzoic acid removed, and the filtrate adjusted to *p*H 4.3 with aqueous sodium bicarbonate. A ter standing overnight at 4°, the crystalline product was recovered and recrystallized from 50% aqueous methanol to give 0.67 g. of the acylated amino acid, m.p. 246° with dec.

Anal. Calcd. for $C_{15}H_{14}O_3N_2$: C, 66.7; H, 5.2; N, 10.4. Found: C, 66.4; H, 5.3; N, 10.3.

Ethyl β-(4-pyridyl-1-oxide)pyruvate. To a solution of 28 g. (1.22 g.-atom) of sodium in 300 ml. of absolute ethanol was added 109.2 g. (1.00 mole) of 4-picoline-1-oxide dissolved in 300 ml. of absolute ethanol. The solution was stirred at reflux for 15 min. to give a clear red solution. To this solution was added 146.2 g. (1.00 mole) of ethyl oxalate over a period of 5 min. After about 2 min., the yellow sodium salt of the keto ester began to precipitate. Heating was discontinued and the resultant yellow paste stirred for 2 hr. The solvent was removed *in vacuo* to leave a yellow paste, which was dissolved in water to give a dark red solution. The solution was neutralized with 12*N* aqueous hydrochloric acid, the precipitate recovered and recrystallized from water to give 100 g. of product A, yellow needles, m.p. 140.2–141.5°. Concentration of the aqueous filtrate gave 20 g. of product B, yellow prisms, m.p. 182.8–183.0°. Analyses of both samples showed neither to be pure keto ester. B would not dissolve in chloroform, while A dissolved nearly completely. Recrystallization of A from water after prior solution in chloroform and removal of the insoluble material, *i.e.*, B, gave 95 g. of keto ester, m.p. 129° with dec., lit.,[22] 122–123°. Another 5.0 g. was obtained from a chloroform extract of B to give a total yield of 48%.

Recrystallization of B from water, after prior extraction with chloroform, gave a pale yellow solid, m.p. 187–188° with dec. This compound was an acid of molecular weight *ca.* 300 and would not form an oxime. When heated, the compound suddenly decomposed and evolved a purple vapor. The compound turned bright yellow after prolonged exposure to light. No consistent analyses could be obtained but it was shown that the compound contained nitrogen.

Ethyl-α-oximino-β-(4-pyridyl-1-oxide)propionate. The condensation of 4-picoline-1-oxide and ethyl oxalate was conducted as described above. However, the solvent was not removed *in vacuo*. Instead, the yellow paste was washed from the reaction flask into a 4-l. beaker with 2 l. of 50% aqueous ethanol. The resultant red solution heated to *ca.* 60°, and 85 g. (1.22 mole) of hydroxylamine hydrochloride and 100 g. (1.22 mole) of sodium acetate were added. The reaction mixture was allowed to cool overnight, the crystals which had formed collected, the filtrate concentrated to one-half its original volume, and a second crop of crystals recovered. The two crops were combined and recrystallized from water to give 136 g. (60%) of oximino ester, m.p. 210° with dec., lit.,[22] 221–222°. Although the oximino ester was dried over phosphorus pentoxide at 65° and 100 mm., the low melting point and the analysis indicated that a hydrate had been obtained.

Anal. Calcd. for $C_{10}H_{12}O_4N_2 \cdot H_2O$: C, 49.6; H, 5.8; N, 11.6. Found: C, 49.7; H, 5.6; N, 11.7.

The same product was obtained from ethyl β-(4-pyridyl-1-oxide)pyruvate. To a hot solution of 15 g. (0.0702 mole) of keto ester in 100 ml. of water was added 4.9 g. (0.0702 mole) of hydroxylamine hydrochloride, 2.8 g. (0.0702 mole) of sodium hydroxide, and 5.75 g. (0.0702 mole) of sodium acetate. A white flocculent precipitate formed as the solution cooled. The precipitate was recrystallized from water to give 8.2 g. (52%) of fibrous needles, m.p. 210° with dec.

α-Oximino-β-(4-pyridyl-1-oxide)propionic acid. A solution of 20 g. (0.0893 mole) of the ester and 7.15 g. (0.1786 mole) of sodium hydroxide in 180 ml. of water was held at the boiling point for 5 min. The reaction mixture was cooled to about 50°, neutralized with 14.9 ml. of concd. hydrochloric acid, diluted with 25 ml. of water, kept in an ice bath for 4 hr., the solid which had formed recovered and washed with a small amount of cold water. The product was dried *in vacuo* to give 14.3 g. (82%) of acid, m.p. 140–141° with dec. Recrystallization from water gave the acid, clusters of fine needles, m.p. 139.8–140° with dec.

Anal. Calcd. for $C_8H_8O_4N_2$: C, 49.0; H, 4.1; N, 14.3. Found: C, 49.2; H, 4.2; N, 14.4.

β-(4-Pyridyl-1-oxide)-DL-alanine. To 1 l. of concd. hydrochloric acid and 260 g. (1.15 mole) of stannous chloride dihydrate was added, in portions, 100 g. (0.51 mole) of α-oximino-β-(4-pyridyl-1-oxide)propionic acid. The clear solution was allowed to stand at room temperature overnight and then concentrated *in vacuo* to a thick paste. The paste was dissolved in 750 ml. of water and the solution neutralized to *p*H 6.8 with *ca.* 375 ml. of 28% aqueous ammonia. The precipitate was removed and washed with 200 ml. of water. The filtrate was evaporated to dryness *in vacuo*, and the granular residue ground to pass an 80-mesh screen. This powder was extracted with 6 l. of absolute methanol to give 90 g. of crude product. Further extraction with two 500 ml. portions of methanol gave 78 g. (84%) of β-(4-pyridyl-1-oxide)-DL-alanine, m.p. 238.2° with dec. An aqueous solution of the product did not give a positive test with silver nitrate.

Anal. Calcd. for $C_8H_{10}O_3N_2$: C, 52.7; H, 5.5; N, 15.4. Found: C, 52.7; H, 5.6; N, 15.4.

The product could be obtained more rapidly, but in a lower yield, *i.e.*, *ca.* 45%, by removing the solid, formed on partial evaporation of the filtrate obtained by adjustment of the acidic reaction mixture to *p*H 6.8 with aqueous ammonia followed by filtration, and continuing this process until the volume of the filtrate was reduced to *ca.* 150 ml. The filtrate was then evaporated to dryness and the residue, mainly product, extracted with methanol to remove residual ammonium chloride.

The amino acid gave an orange color, preceded by a violet-blue color, with ninhydrin solution. The reaction was very slow. The amino acid was soluble in water to the extent of 45 g. per 100 ml. at 25° and was slightly soluble in pyridine.

N-Benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine. To a solution of 61.0 g. (0.33 mole) of β-(4-pyridyl-1-oxide)-DL-alanine in

600 ml. of ice cold water and 92 ml. (0.66 mole) of triethylamine was added 82.2 g. (0.363 mole) of finely ground benzoic anhydride. The mixture was stirred for 18 hr., filtered, and the filtrate acidified with 246 ml. of 12*N* aqueous hydrochloric acid. The precipitated benzoic acid was removed, washed with a small amount of 2*N* aqueous hydrochloric acid, and the combined filtrate and washings adjusted to *p*H 2.3 with 91.2 g. of sodium hydroxide in 200 ml. of water. The resultant paste was cooled to 4°, the product collected, washed with 250 ml. of water, and dried to give 73 g. (77%) of acid, m.p. 228.5–229.2° with dec. The acid was recrystallized from 60% aqueous ethanol to give 70 g. (74%) of acid, m.p. 229.5° with dec.

Anal. Calcd. for $C_{15}H_{14}O_4N_2$: C, 62.9; H, 4.9; N, 9.8. Found: C, 62.9; H, 5.0; N, 9.8.

The compound was soluble in water to the extent of 0.5 g. per 100 ml. at 25°.

N-Acetyl-β-(4-pyridyl-1-oxide)-DL-*alanine*. To 30 g. (0.165 mole) of the amino acid dissolved in 165 ml. of water was added 23.1 ml. (0.165 mole) of triethylamine. The solution was cooled to *ca.* 0° and portions, each of 5.8 ml (0.041 mole) of triethylamine and 3.85 ml. (0.041 mole) of acetic anhydride, were added in that order with vigorous stirring and at 10-min. intervals. When a few drops of the fifth portion of acetic anhydride was added, the solution became bright orange, and no further addition was made. The solution was acidified with 100 ml. of 4*N* hydrochloric acid and concentrated *in vacuo*. The residual paste was dried *in vacuo* over potassium hydroxide and phosphorus pentoxide for two days. The dried material was powdered in a dry box, shaken with 400 ml. of dry chloroform for 20 min. to remove the triethylamine hydrochloride, and then filtered to give 32.9 g. of crude product. An additional 3.6 g. separated from the filtrate to give a total yield of 36.5 g. The crude product was stirred with 100 ml. of dry chloroform for 10 min., filtered, and dried to give 32.3 g. (87%) of chloride-free product. This product was recrystallized from absolute ethanol to give the acid, m.p. 210.2° with dec.

Anal. Calcd. for $C_{10}H_{12}O_4N_2$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.5; H, 5.1; N, 12.5.

The acid was soluble in water to the extent of 60 g. per 100 ml. at 25°.

N-Phthaloyl-β-(4-pyridyl-1-oxide)-DL-*alanine*. β-(4-Pyridyl-1-oxide)-DL-alanine, 1.0 g., (5.5 mmole) and phthalic anhydride, 0.816 g., (5.5 mmole) were thoroughly mixed and heated at 140° for one hour. The yellow paste was cooled and treated with saturated aqueous sodium bicarbonate. The residual anhydride was removed and the filtrate acidified with hydrochloric acid to give an oil which crystallized upon trituration with water. The crystalline solid was collected to give 1.06 g. (64%) of product, m.p. 253–254° with dec. This product was recrystallized from 200 ml. of water to give the acid, rhombs, m.p. 254.5–255.0° with dec. The ultraviolet spectrum of the acid exhibited a characteristic *N*-oxide absorption at 260 mμ and the acid did not give a positive ninhydrin reaction. It gave a positive ferric hydroxamate test, similar to that observed with *N*-phthaloyl-DL-phenylalanine.

Anal. Calcd. for $C_{16}H_{12}N_2O_5$: C, 61.5; H, 3.9; N, 9.0. Found: C, 61.5; H, 4.0; N, 9.1.

N-Benzoyl-β-(4-pyridyl-1-oxide)-DL-*alanine methyl ester*. To 200 ml. (4.88 mole) of absolute methanol, cooled in an ice-salt bath and stirred, was added over a period of 15 min., 26.7 ml. (0.366 mole) of thionyl chloride. To this solution was added, in portions, over a period of 20 min., 70.0 g. (0.244 mole) of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine. The clear solution was warmed to 40°, and after about 15 min., a white solid began to precipitate. The slurry was stirred overnight at room temperature, filtered, and the filtrate evaporated to dryness. The residues from the filtration and evaporation were combined and dried *in vacuo* to give 77 g. (94%) of ester hydrochloride. The dry hydrochloride was suspended in 600 ml. of ice cold dry chloroform and treated with 150 ml. of 1.8*N* ammonia in chloroform (0.270 mole). The ammonium chloride that formed was removed and the filtrate evaporated to dryness. The residue was washed with ligroin and dried *in vacuo* to give 63.5 g. (86%) of ester, m.p. 190.0–190.5°. The melting point was not raised by recrystallization of the ester from chloroform. The ester was soluble in water to the extent of 8.0 g. per 100 ml. at 25°.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: C, 64.0; H, 5.4; N, 9.3. Found: C, 63.9; H, 5.4; N, 9.5.

N-Benzoyl-β-(4-pyridyl-1-oxide)-DL-*alanine ethyl ester*. This ester, m.p. 141–143°, was prepared from the acid and anhydrous ethanol as described for the methyl ester.

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 65.0; H, 5.8; N, 8.9. Found: C, 65.2; H, 5.6; N, 9.0.

N-Acetyl-β-(4-pyridyl-1-oxide)-DL-*alanine methyl ester*. This ester was prepared in 75% yield from *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alanine in a manner identical with that used for the *N*-benzoyl-compound. The ester was very soluble in chloroform and water, soluble in methanol, less soluble in ethanol and 2-propanol, and insoluble in ethyl acetate and toluene. The ester was recrystallized from absolute ethanol to give clusters of hygroscopic needles, m.p. 193.5–194.2° with dec.

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.4; H, 6.0; N, 11.7.

The ester was also obtained in a 47% yield from α-oximino-β-(4-pyridyl-1-oxide)propionic acid as follows: The oximino acid was reduced with stannous chloride and the tin salts removed as described previously. Following concentration, the filtrate was acetylated with acetic anhydride and sodium hydroxide. The resultant solution was acidified to *p*H 2.0 and evaporated to dryness. Treatment of the residue with thionyl chloride and methanol gave a solution of the ester hydrochloride and a precipitate of sodium chloride. Following filtration, the solution was treated as described above.

The determination of the pK_A of the N-benzoyl-β-(4-pyridyl-1-hydroxy)-DL-*alanine ion*. A stock solution, $0.930 \times 10^{-2}M$ in *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine in *ca.* 0.3*N* hydrochloric acid was prepared. The ultraviolet spectrum of 1.00 ml. of the stock solution, diluted to 50.00 ml. with 4*N* hydrochloric acid, was taken to obtain a value for A_{BH}. The ultraviolet spectrum of 1.00 ml. of the stock solution, made basic with sodium hydroxide and diluted to 100.00 ml. with water (*p*H 10.6), was determined to obtain a value for A_B. From extinction coefficients determined at 260 mμ and proceeding as described by Flexser, Hammett, and Dingwall,[38] the following values were obtained or derived; $A_{BH} = 1.013$, $A = 1.438$, $A_B = 1.648$, $C_{BH} = 1.86 \times 10^{-4}M$, $C = 1.86 \times 10^{-4}M$, $C_B = 0.93 \times 10^{-4}M$, $C_H = 0.309M$, $C_{BH}/C_B = 4.37$, $k'_{BH} = 0.545 \times 10^4$ cm. M^{-1} $k' = 0.773 \times 10^4$ cm. M^{-1}, $k'_B = 1.772 \times 10^4$ cm. M^{-1} $K'_A = 0.0707$ and $pK'_A = 1.15$.

β-(4-Pyridyl-1-oxide)-DL-*alanine methyl ester*. The amino acid was suspended in absolute methanol and the mixture saturated with dry hydrogen chloride, allowing the temperature to rise to *ca.* 60°. The clear solution was evaporated *in vacuo*, and the residue neutralized with methanolic sodium methoxide. The sodium chloride was removed, the filtrate concentrated, filtered, and the filtrate evaporated to dryness *in vacuo*. The product, a hard glass, was soluble in chloroform if initially wet with methanol. It was completely insoluble in anhydrous chloroform once exposed to a trace of moisture. The product was deliquescent in air, and it was impossible to obtain a pure sample, even when working in a dry box.

β-(4-Pyridyl-1-oxide)-DL-*alaninhydrazide*. Approximately 1.0 g. of the above ester was dissolved in 5 ml. of absolute methanol, 0.5 ml. of anhydrous hydrazine added, the solution held at reflux for one hour and then evaporated in a stream of dry nitrogen to give a viscous oil which crystallized when triturated with chloroform. The solid was collected and dried *in vacuo* to give 0.71 g. (70%) of a hygroscopic product,

TABLE I

SPECTRAL AND RATE DATA FOR HYDROGENATION OF β-(4-PYRIDYL)-DL-ALANINE AND ITS N-OXIDE

Optical Density *vs.* Concentration

β-(4-Pyridyl)-DL-alanine			β-(4-Pyridyl-1-oxide)-DL-alanine		
Concn. $M \times 10^{-3}$	O.D.260 mμ	O.D250 mμ	Concn. $M \times 10^{-4}$	O.D.260 mμ	O.D.250 mμ
0.120	0.258	0.246	0.209	0.328	0.213
0.240	0.526	0.498	0.418	0.660	0.434
0.480	1.042	0.981	0.835	1.343	0.878
0.959	2.056	1.947	1.044	1.692	1.106
1.199	2.619	2.416	1.225	2.053	1.402

Optical Density *vs.* Time

β-(4-Pyridyl)-DL-alanine $c_0 = 1.199 \times 10^{-2} M$ Pt = 0.265 g./l.			β-(4-Pyridyl-1-oxide)-DL-alanine $c_0 = 1.074 \times 10^{-2} M$ Pt = 0.265 g./l.		
Time, min.	O.D.260 mμ $\times 10^{-1}$	O.D.250 mμ $\times 10^{-1}$	Time, Min.	O.D.260 mμ $\times 10^{-2}$	O.D.250 mμ $\times 10^{-2}$
0	2.619	2.416	0	1.724	1.185
5	2.323	2.147	10	0.983	0.672
10	2.167	2.010	23	0.504	0.362
21	2.010	1.838	39	0.263	0.213
46	1.767	1.648	64	0.1250	0.118
63	1.672	1.605	109	0.0730	0.0730
91	1.616	1.477	155	0.0581	0.0578
298	1.010	0.990	1130	0.0149	0.0151

Mole Percent *vs.* Time[a]

β-(4-Pyridyl)-DL-alanine		β-(4-Pyridyl-1-oxide)-DL-alanine			
Time, Min.	Mole % PA[b]	Time, Min.	Mole %, POA[c]	Mole %, PA[d]	Mole %, PIA[d]
0	100	0	100	0	0
5	89	10	51	44	5
10	82	23	22	49	29
21	76	39	6.5	63.5	30
46	68	64	1	46	53
63	65	109	0	32.5	67.5
91	61	155	0	25.5	74.5
298	40	1130	0	6.5	93.5

[a] Based upon the relations: at 260 mμ, $O.D._{POA}/c_{POA} = 1.604 \times 10^4 M^{-1}$, $O.D._{PA}/c_{PA} = 2.183 \times 10^3 M^{-1}$; at 250 mμ $O.D._{POA}/c_{POA} = 1.058 \times 10^4 M^{-1}$, $O.D._{PA}/c_{PA} = 2.017 \times 10^3 M^{-1}$. [b] β-(4-pyridyl)-DL-alanine. [c] β-(4-pyridyl-1-oxide)-DL-alanine. [d] β-(4-piperidyl)-DL-alanine.

which was recrystallized from ethanol to give large rhombs, m.p. 147–148°.

Anal. Calcd. for $C_8H_{12}O_2N_4$ (196): C, 49.0; H, 6.2; N, 28.6. Found: C, 48.9; H, 6.0; N, 28.4.

N-Acetyl-β-(4-pyridyl-1-oxide)-DL-alaninamide. A solution of 5.0 g. of *N*-acetyl-β-(4-pyridyl-1-oxide)-DL-alanine methyl ester in 120 ml. of dry methanol saturated with ammonia at room temperature was allowed to stand overnight. The solution was evaporated to dryness *in vacuo*, the residue suspended in absolute ethanol and filtered to give 4.0 g. (86%) of product. This substance was recrystallized from 300 ml. of absolute ethanol to give 3.4 g. of amide, m.p. 235–236° with dec. The amide was soluble in water to the extent of about 50 g. per 100 ml. at 25°.

Anal. Calcd. for $C_{10}H_{13}O_3N_3$: C, 53.8; H, 5.9; N, 18.8. Found: C, 53.8; H, 5.8; N, 18.8.

N-Benzoyl-β-(4-pyridyl-1-oxide)-L-alanine. α-Chymotrypsin, 20 mg., was added to a solution of 10 g. of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine methyl ester in 100 ml. of water maintained at *p*H 7.9 by the addition of 1*N* aqueous sodium hydroxide. The asymmetric hydrolysis was complete in one hour. The clear solution was acidified to *p*H 2.3 with 6*N* aqueous hydrochloric acid, the solution held for one hour at 4°, the precipitated L-acid collected, and recrystallized from water to give 2.73 g. (58%) of L-acid, $[\alpha]_D^{25°}$ −45.1° to −43.4° (c, 1.5% in acetic acid), m.p., 216–220°, with oil formation at 145–150°. Analyses for this compound were never satisfactory even after repeated recrystallization. A similar behavior was observed with resolutions conducted with the ethyl ester.

Anal. Calcd. for $C_{15}H_{14}O_4N_2 \cdot H_2O$ (316): C, 60.7; H, 5.1; N, 8.9. Found: C, 59.5; H, 5.2; N, 10.1.

N-Benzoyl-β-(4-pyridyl-1-oxide)-D-alanine methyl ester. The acidified filtrate from the above resolution was adjusted to *p*H 7.0 with saturated aqueous sodium bicarbonate and the solution saturated with sodium chloride. The D-methyl ester precipitated. The crude ester was collected, dried, dissolved in chloroform, the solution filtered and the filtrate evaporated to give 2.82 g. (56%) of the D-methyl ester, m.p. 207° with dec., $[\alpha]_D^{25°}$ +95.5° (c, 3.3% in methanol).

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: C, 64.0; H, 5.4; N, 9.3. Found: C, 63.9; H, 5.3; N, 9.2.

N-Benzoyl-β-(4-pyridyl-1-oxide)-D-alanine ethyl ester. This ester was recovered from a resolution of the DL-ethyl ester which was conducted as described for the D-methyl ester. The crude product was recrystallized from 300 ml. of ethyl acetate containing 3 ml. of water to give 3.7 g. (74%) of D-ester, m.p. 181.0–182.0, $[\alpha]_D^{25°}$ +87.6° (c, 1.5% in methanol).

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 65.0; H, 5.8; N, 8.9. Found: C, 65.0; H, 5.9; N, 8.8.

N-Benzoyl-β-(4-pyridyl-1-oxide)-L-alanine methyl ester. This ester was prepared from the L-acid by reaction with methanol and thionyl chloride. The recrystallized product,

m.p. 208°, $[\alpha]_D^{25}$° −95.5° (c, 4% in methanol), was obtained in 88% yield.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: C, 64.0; H, 5.4; N, 9.3. Found: C, 63.9; H, 5.4; N, 9.3.

N-Benzoyl-β-(4-pyridyl-1-oxide)-L-alanine ethyl ester. This ester was prepared as described for the DL-ester. Recrystallization of the crude product from wet ethyl acetate gave 86% of the L-ester, m.p. 181.0–182.5°, $[\alpha]_D^{25}$° −87.3° (c, 1.5% in methanol).

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 65.0; H, 5.8; N, 8.9. Found: C, 64.9; H, 5.9; N, 8.9.

4-(Pyridyl-1-oxide)carbinol. To 23 g. of 4-pyridylcarbinol dissolved in 200 ml. of glacial acetic acid was added 30 ml. of 30% aqueous hydrogen peroxide, the solution held at 70° for three hours, another 30 ml. of hydrogen peroxide added and the solution held at 70° overnight. The solvent was removed *in vacuo* and the residue recrystallized from a mixture of ethanol and ethyl acetate to give 19.6 g. (74%) of fine needles, m.p. 111.5–112.0°.

Anal. Calcd. for $C_6H_7NO_2$ (125): C, 57.6; H, 5.6; N, 11.2. Found: C, 57.6; H, 5.6; N, 11.1.

4-(Pyridyl-1-oxide)methyl bromide hydrobromide. A solution of 10.0 g. of 4-(pyridyl-1-oxide)carbinol in 50 ml. of 48% hydrobromic acid was heated twice to the boiling point and allowed to stand overnight. The acid was removed *in vacuo*, 50 ml. of absolute ethanol added, and the solution cooled to 0° to give a paste, which was recrystallized from absolute ethanol to give 8.2 g. of the hydrobromide of 4-(pyridyl-1-oxide)carbinol, m.p. 93–95°. This material, 6.53 g., was dissolved in 25 ml. of hydrobromic acid and held at reflux for 18 hr. The acid was removed *in vacuo*. The addition of absolute ethanol to the residue caused the formation of a white crystalline solid, which was collected, washed with absolute ethanol, and dried *in vacuo* to give 7.2 g. (88%) of a hygroscopic product, m.p. 170.5–171.8°.

Anal. Calcd. for $C_6H_6ONBr \cdot HBr$: C, 26.8; H, 2.6; N, 5.3; Br, 59.4. Found: C, 26.9; H, 2.6; N, 5.2; Br, 59.4.

4-(Pyridyl-1-oxide)methyl bromide. Five g. of the above bromide hydrobromide was dissolved in the minimum amount of water and solid sodium bicarbonate was added until the solution was adjusted to *p*H 7.0. The solution was saturated with salt and extracted with chloroform. The extracts were dried and the solvent removed to give the theoretical amount of solid, m.p. 138–138.5°. No analysis was obtained as the compound becomes colored and decomposes within several hours.

Thioisonicotinyl morpholine. A suspension of 9.6 g. (0.3 g.-atom) of sulfur in a mixture of 10.9 g. (0.1 mole) of 4-picoline-1-oxide and 13.1 g. (0.15 mole) of morpholine was heated at 170° for 12 hr. The reaction mixture was cooled, diluted with 50 ml. of absolute ethanol, the precipitate collected and recrystallized twice from ethanol to give 11.4 g. (55%) of product, m.p. 150–152° lit.,[56] 150–151°.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.6; H, 5.8; N, 13.4.

Catalytic hydrogenation of β-(4-pyridyl)-DL-alanine and its N-oxide. The reductions were conducted in the same manner for both compounds. A weighed sample of each compound was dissolved in 25 ml. of water, the weighed platinum dioxide catalyst added, and the mixture hydrogenated at 40 p.s.i. and 25°. At selected time intervals the hydrogenation was interrupted, a 2.5-ml. aliquot removed, filtered and a 1.0-ml. aliquot of the filtrate diluted 1:10 for β-(4-pyridyl)-DL-alanine and 1:100 to 1:5 for the *N*-oxide. The spectra were taken at 260 and 250 mμ. The data are summarized in Table I. The data for the mole percentage of β-(4-pyridyl)-DL-alanine and β-(4-piperidyl)-DL-alanine in the reduction of β-(4-pyridyl-1-oxide)-DL-alanine have error in them estimated at ± 10 mole percent through the fifth point, and about ± 2 mole percent in the last points. This is due to the fact there is approximately a factor of 10 between the molar extinction coefficients of β-(4-pyridyl-1-oxide)-DL-alanine and β-(4-pyridyl)-DL-alanine and small errors in the concentration of the former component are reflected by *ca.* 10 times that error in the concentration of the latter. β-(4-Piperidyl)-DL-alanine has no absorption in this region.

To a solution of 5.0 g. (.0275 mole) of β-(4-pyridyl-1-oxide)-DL-alanine in 25 ml. of water was added 0.5 g. of platinum dioxide and the mixture hydrogenated at 40 p.s.i. and 25° until 0.069 mole of hydrogen had been absorbed. The catalyst was removed and the solution evaporated in dryness *in vacuo*. The solid was extracted with 25 ml. of dry methanol and the residue, 2.82 g., dried *in vacuo*. An oily solid was isolated from the methanol extract. β-(4-Piperidyl)-DL-alanine is very hygroscopic. A determination of the extinction coefficient at 256 mμ, assuming the absence of β-(4-pyridyl-1-oxide)-DL-alanine, gave a value of 311 ± 16 for the molecular weight of the solid product. After a second extraction with methanol, a value of 380 ± 10 was obtained. The molecular weight of β-(4-piperidinium)-DL-alanine β-(4-pyridyl)-DL-alaninate is 338. The solid decomposed at 250–280° and gave a blue-purple color with ninhydrin. The yield of 2.8 g. compares favorably with the yield of 2.5 g. expected on the basis of hydrogen uptake.

PASADENA, CALIF.

(56) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).

[CONTRIBUTION FROM INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of the Dicarboxylic Acid $C_{12}H_{14}O_4$—Degradation Product of Picrotoxin

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γ-(2-Carboxy-6-methylphenyl)butyric acid, a degradation product of picrotoxin, has been synthesized following an unambiguous procedure. The synthetic compound possesses properties similar to those described for the product from natural sources.

Picrotoxin is a molecular compound of picrotin and picrotoxinine. Each of these compounds when boiled with phosphorus and hydriodic acid produces picrotic acid.[1] The latter, on hydrolytic fission produces acetone and a dibasic acid, $C_{12}H_{14}O_4$.[2] Out of the two possible structures for this dibasic acid,

(1) F. Angelico, *Gazz. chim. ital.* **42**, ii, 337 (1911).

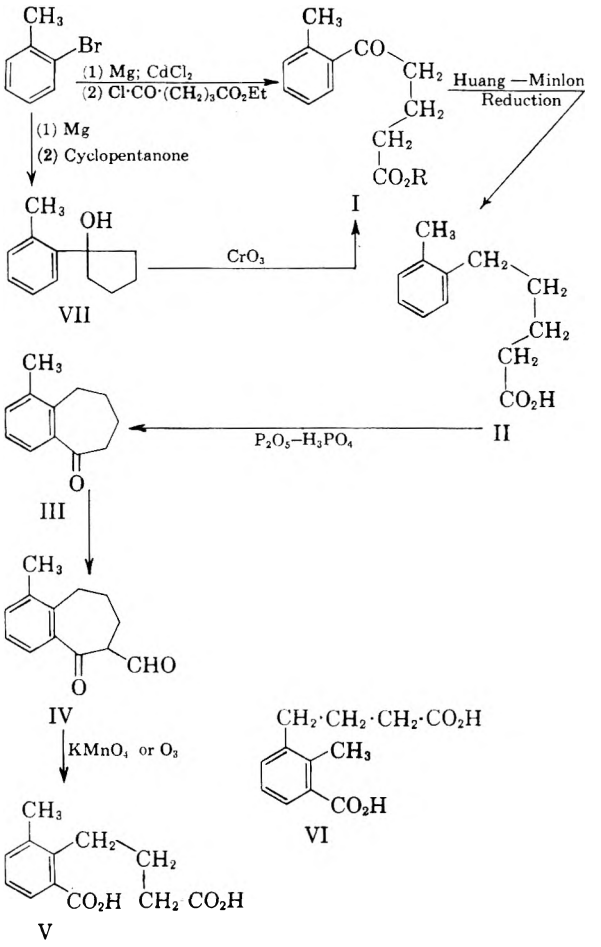
(2) F. Angelico and F. Monforte, *Gazz. chim. ital.*, **53**, 800 (1923).

Robertson has chosen structure (V) on the basis of its transformation to 5-methyltetralone.[3]

The acid (V) has been synthesized by an unambiguous method shown in the flow sheet.

γ-(2-Methylbenzoyl)butyric acid (I, R = H) was prepared following two different routes. In the first method *o*-tolylcadmium bromide was made to react with γ-carbethoxybutyroyl chloride resulting in the formation of ethyl γ-(2-methylbenzoyl)butyrate (I, R = Et)[4] which gave acid (I, R = H) on hydrolysis with alkali. In the second method the Grignard complex of *o*-bromotoluene was reacted with cyclopentanone and the resulting mixture of tertiary alcohol (VII) and the corresponding dehydrated product was oxidized with chromic acid to acid I (R = H).[5]

Huang-Minlon reduction of compound I (R = Et) gave δ-*o*-tolylvaleric acid (II) in satisfactory yield. Cyclization of acid II with polyphosphoric acid gave 1′-methylbenzocyclohepten-3-one (III) in almost quantitative yield. Compound III was converted into the formyl derivative (IV) which on oxidation with potassium permanganate or on ozonolysis furnished a dibasic acid which gave analytical figures agreeing with the molecular formula $C_{12}H_{14}O_4$ and melted at 136–136.5° (uncorrected). Robertson *et al.*[3] report melting point 135–136° for the degradation product of picrotoxin. A direct comparison of the synthetic specimen was not possible owing to unavailability of a sample from natural sources. The synthetic acid, however, could be converted to 5-methyltetralone according to the method of Robertson *et al.*[3] This definitely shows that the synthetic acid is identical with the acid from natural sources.



EXPERIMENTAL

Melting and boiling points are uncorrected.

Ethyl γ-(2-methylbenzoyl)butyrate (I, R = Et). A solution of *o*-bromotoluene (45 g.) in a mixture of dry ether (132 ml.) and thiophene-free benzene (44 ml.) was added with stirring in the course of 1.5 hr. to magnesium turnings (6.5 g.) covered with ether containing a little methyl iodide maintaining gentle reflux of the reaction mixture. The Grignard solution was then cooled in an ice bath and anhydrous cadmium chloride (29 g.) was added. The resulting mixture was heated under reflux with stirring for 45 min. The ether in the mixture was then distilled off until the mixture in the flask became a thin slurry and the distillation became slow. Thiophene-free benzene (176 ml.) was added and 22 ml. of benzene were distilled off.

A solution of γ-carbethoxybutyroyl chloride (47.1 ml.) dissolved in thiophene-free benzene (44 ml.) was added with vigorous stirring to the hot mixture (kept in nitrogen atmosphere) as quickly as possible. An exothermic reaction ensued, and cadmium halide precipitated out. The mixture was then heated under reflux for 1 hr., and processed in the usual manner. Ethyl γ-(2-methylbenzoyl)butyrate (19 g.) b.p. 157.5° (4.0 mm.) was obtained.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.38; H, 7.80.

The *2,4-dinitrophenylhydrazone* crystallized from alcohol, m.p. 100°.

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: N, 13.53. Found: N, 13.41.

The ester (1.3 g) was hydrolyzed with sodium hydroxide (1 g.) in a mixture of ethanol (6 ml.) and water (4 ml.). γ-(2-Methylbenzoyl)butyric acid (I, R = H) was obtained as a white solid which was purified with the help of sodium bicarbonate and then crystallized from water containing a few drops of acetic acid; m.p. 80°, which did not rise on further crystallization. Yield—0.7 g.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 69.61; H, 6.93.

1-o-Tolylcyclopentanol. (VII) To a Grignard solution prepared from *o*-bromotoluene (105.5 g.), magnesium (14.5 g.), ether (310 ml.), and methyl iodide (1 ml.) cooled in ice was added cyclopentanone (50.0 g.) in 175 ml. of ether with stirring. A white solid was precipitated. The reaction mixture was left overnight, and then refluxed for 3 hr. It was then cooled in an ice bath and decomposed with saturated ammonium chloride solution and worked up in the usual manner. On distillation a clear liquid (12.5 g.), b.p. 110–115°/6 mm., was obtained.

γ-(2-Methylbenzoyl)butyric acid (I, R = H). The above Grignard product (12.5 g.) was dissolved in acetic acid (375 ml.) and chromic acid solution (7*N*, 165 ml.) was added gradually in the course of 1 hr. The temperature of the reaction mixture was kept below 25°. Excess chromic acid was decomposed with sodium bisulfite. Acetic acid was removed by distillation under reduced pressure below 100°. The residue was treated with 10% sulfuric acid and extracted with ether. The ethereal extract was treated with 5% sodium

(3) D. Mercer, A. Robertson, and R. S. Cahn, *J. Chem. Soc.*, 997 (1935).

(4) J. Cason and P. Prout, *J. Am. Chem. Soc.*, 66, 46 (1944).

(5) L. F. Fieser and J. Szmuszkovicz, *J. Am. Chem. Soc.*, 70, 3352 (1948).

bicarbonate solution and the alkaline layer acidified. The precipitated acid was purified by sublimation under low pressure. When the product (1.6 g.), m.p. 72–73°, was crystallized from water containing a few drops of acetic acid the melting point rose to 80°. Mixed m.p. with the acid previously described was undepressed.

δ-(o-tolyl)valeric acid (II). To a solution of sodium hydroxide (4 g.) in diethylene glycol (42 ml.) was added ethyl γ-2-methylbenzoyl butyrate (5.9 g.) followed by hydrazine hydrate (50%, 8.5 ml.). The mixture was refluxed on an oil bath kept at 140° for 1 hr. The system was then connected to a distilling arrangement and the temperature was raised to 200°. Brisk evolution of nitrogen set in, and a few milliliters of water distilled out. After 3 hr. the reaction mixture was cooled, diluted with water, and acidified with hydrochloric acid (1:1) in the cold. The precipitated white solid (3.9 g.) had m.p. 57–58° which rose to 58.5–59° on crystallization from petroleum ether (b.p. 40–60°).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.10; H, 8.60.

1-Methylbenzosuber-5-one. (III). To a mixture of phosphorus pentoxide (153 g.) and phosphoric acid (89%, 97.5 ml.), maintained at 100°, δ-(*o*-tolyl)valeric acid (5 g.) was gradually added with stirring. In 7 min., the reaction mixture turned an amber color which gradually deepened. The temperature was maintained at 100° for 2 hr. Then the reaction mixture was decomposed with ice water, and allowed to stand for 15 min. The separated solid was filtered, and washed with dilute ammonia; yield, 4.9 g., m.p. 62–63°, which rose to 65° on sublimation in high vacuum and crystallization from methanol.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.52; H, 8.11.

The *2,4-dinitrophenylhydrazone* crystallized from benzene–ethyl acetate mixture, m.p. 240°.

Anal. Calcd. for $C_{18}H_{18}O_4N_4$: C, 61.02; H, 5.08. Found: C, 61.12; H, 5.22.

6-Formyl-1-methylbenzosuber-5-one (IV). To an ice-cold suspension of sodium ethoxide from sodium (0.55 g.) and ethanol (1.4 ml.) in thiophene-free benzene (26 ml.) was added a mixture of compound III (2.1 g.) and ethyl formate (1.8 g.) in benzene (13 ml.) under nitrogen. After keeping overnight in a nitrogen atmosphere, the reaction mixture was decomposed with ice water. The benzene layer was separated and washed twice with 3% alkali, and mixed with the water layer. The combined aqueous solution was extracted once with ether, and then acidified with 80% acetic acid. The formyl derivative was extracted with ether and distilled to yield 1.8 g., b.p. 133°/0.4 mm. With ferric chloride it gave a reddish violet color turning greenish violet.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.65; H, 7.12.

γ-(2-Carboxy-6-methylphenyl)butyric acid (V). (*a*) *By oxidation with permanganate:* To an ice-cold solution of the formyl derivative (IV, 1.65 g.) in 3% sodium hydroxide, powdered potassium permanganate (3.9 g.) was added slowly with stirring. After 2 hr., the solution was treated with sufficient hydrochloric acid (1:1) and saturated sodium bisulfite solution when a tarry mass separated. This was removed and washed several times by decantation with water and then dissolved in hot sodium bicarbonate solution. The alkaline solution was acidified and left in a refrigerator overnight. Black and white particles of solid separated, the latter melting at 129–130°. This was subjected to evaporative distillation and the distillate crystallized twice from benzene to yield 0.3 g., m.p. 136–136.5°.

(*b*) *By ozonolysis:* Sufficient ozonized oxygen was passed through a solution of the formyl derivative (IV, 0.2 g.) in a mixture of ethyl acetate (5 ml.) and glacial acetic acid (5 ml.) chilled in an ice-salt bath. Three such lots were combined and treated with water (4.5 ml.) and hydrogen peroxide (30%, 1.5 ml.). The mixture was then kept overnight. Ethyl acetate and acetic acid were removed under reduced pressure and the residue was treated with water and then taken up in ether. The ether solution was thoroughly extracted with saturated sodium bicarbonate solution. The combined bicarbonate solutions were acidified and extracted with ether. Removal of ether and trituration of the residue with petroleum ether (b.p. 40–60°) gave a solid having an indefinite melting point. Evaporative distillation followed by two crystallizations from benzene gave colorless crystals having m.p. 136–136.5° which was not depressed on admixture with the product prepared according to the method (a).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.80; H, 6.16.

CALCUTTA, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

A Comparison of Rates of Precipitation of Substituted Hippuric Anilides Formed by Papain-Catalyzed Reactions between Hippuric Acid and Substituted Anilines at Approximately *p*H 4.6

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The rates of precipitation of twelve substituted hippuric anilides have been studied, in papain-catalyzed reactions between hippuric acid and substituted anilines at pH ≅ 4.6. Six of these are new compounds. A comparison of these rates permits a reasonable interpretation of results in terms of steric hindrance, electrostatic effects and resonance. In the absence of steric effects, the reaction of substituted anilines appears to increase with increasing basicity.

Preliminary to a series of enzymatic resolutions being instigated in this laboratory, it was important to study the relative rates of precipitation of a few well-chosen substituted hippuric anilides, formed by papain-catalyzed reactions between hippuric acid and appropriately substituted anilines. The general procedure given by Bergmann and Fraenkel-Conrat,[1] as subsequently adapted by

(1) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, 119, 707 (1937).

Bennett and Niemann[2] and others, was followed. L-Cysteine was used as a promotor.

$$C_6H_5CONHCH_2COOH + NH_2C_6H_4X \xrightarrow[pH \cong 4.6;\ 40°]{\text{papain, L-cysteine}} C_6H_5CONHCH_2CONHC_6H_4X + H_2O$$

Reactions between acylated amino acids and aniline,[1] or phenylhydrazine[1] or even substituted anilines[3] have been reported without regard to effects of the position of substituents on the benzene nucleus of the base reactant. A few studies have been made with respect to dependence of yield[1,4] on *p*H, which have revealed that amide formation usually proceeds fastest in the *p*H range of about 4.5 to 5.0. All of the reactions in the present investigation were carried out at *p*H $\cong$ 4.6, with convenient usage of an acetic acid–sodium acetate buffer.

Since the substituted anilines were not all of equal molar solubility, five were selected for graphic comparison from the entire group studied. All five had an initial concentration of 0.05 mole in 250 ml. of buffered solution. These were the *o*-, *m*- and *p*-aminophenols (Fig. 1) and the *m*- and *p*-amino-

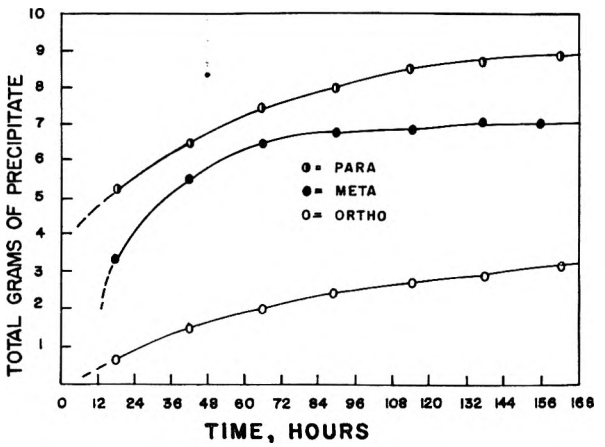

Fig. 1. Comparative rates of precipitation of hippuric *o*-, *m*- and *p*-hydroxyanilides formed from hippuric acid and aminophenols. 0.050 mole hippuric acid; 0.050 mole aminophenol; 1.00 g. L-cysteine hydrochloride monohydrate; 0.50 g. Schwarz Papain; buffered at *p*H $\cong$ 4.6, HOAc–NaOAc; total volume of solution, 250 ml.

acetophenones (Fig. 2). Although the rates are qualitative, there is sufficient consistency to draw certain conclusions. Hydroxyl ortho to the amino group provides steric hindrance and decreases the rate of reaction, compared with the same substit-

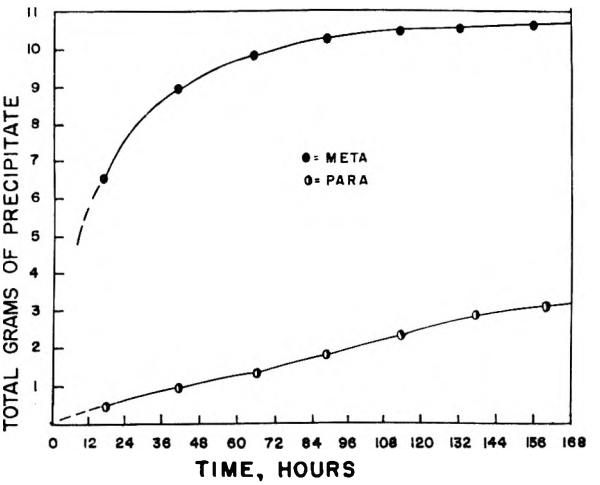

Fig. 2. Comparative rates of precipitation of hippuric *m*- and *p*-acetylanilides formed from hippuric acid and aminoacetophenones. 0.050 mole hippuric acid; 0.050 mole aminoacetophenone; 1.00 g. L-cysteine hydrochloride monohydrate; 0.50 g. Schwarz papain; buffered at *p*H $\cong$ 4.6, HOAc–NaOAc; total volume of solution, 250 ml.

uent in a meta or para position (Fig. 1). If the hydroxyl is para the reaction is faster than if it is meta, since with the hydroxyl in the para position resonance tends to keep the electron pair available on nitrogen for amide formation. *m*-Aminoacetophenone reacts faster than *p*-aminoacetophenone because the acetyl group is an electron-attracting group and electrons are withdrawn from the amino group by a resonance effect when the acetyl is para, but not when it is meta.

A comparison between *p*-aminophenol and *m*-aminoacetophenone shows that the latter reacts at a somewhat faster rate in these experiments. The implication made by these qualitative rate comparisons is that the reactivity of the substituted anilines is proportional to their basicities in the absence of steric effects in similarly substituted compounds.

Although methyl *p*-aminobenzoate was reported elsewhere[3] not to undergo a reaction with hippuric acid, it did under the conditions of our experiment. The low yield can be attributed to the low solubility of methyl *p*-aminobenzoate. Methyl anthranilate and *p*-nitroaniline were very low in solubility, anthranilic acid was of moderate solubility and both metanilic acid and sulfanilic acid were of substantial solubility. None reacted with hippuric acid. Six new substituted hippuric anilides are reported here. Two substituted anilines not previously investigated gave no product under conditions of this study.

(2) (a) E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **70**, 2610 (1948); (b) *J. Am. Chem. Soc.*, **72**, 1798 (1950); (c) *J. Am. Chem. Soc.*, **72**, 1800 (1950).

(3) E. Waldschmidt-Leitz and K. Kuhn, *Z. physiol. Chem.*, **285**, 23 (1950).

(4) Unpublished results from this laboratory.

TABLE I

SUBSTITUTED HIPPURIC ANILIDES FROM HIPPURIC ACID AND SUBSTITUTED ANILINES

Substituted Aniline Reactant	Reaction Product	Melting Point of Product, °C.	Yield of Product in Grams for Consecutive Periods of Incubation					
			0–18 hr.	18–42 hr.	42–66 hr.	66–90 hr.	90–114 hr.	114–138 hr.
m-Phenylenediamine	Hippuric *o*-Aminoanilide	260–262°[4]	1.4904	1.8545	0.5185	0.2259	0.2238	0.1350
p-Phenylenediamine	Hippuric *p*-Aminoanilide	326°[4]	2.305	2.103	0.667	0.372	0.205	0.140
o-Aminophenol	Hippuric *o*-hydroxyanilide	202–203°	0.462	1.105	0.563	0.327	0.238	0.209
m-Aminophenol	Hippuric *m*-hydroxyanilide[a]	223–225°	3.2715	2.3599	0.8683	0.3086	0.1006	0.0729
p-Aminophenol	Hippuric *p*-hydroxyanilide	243–244°	5.264	1.320	0.820	0.605	0.379	0.251
Anthranilic acid	No Precipitate		Similarly methyl anthranilate, metanilic acid,[a] sulfanilic					
m-Aminobenzoic acid	*m*-Hippuramidobenzoic acid[2]	283–284°	3.2731	0.8647	0.4106	0.2412	0.1384	0.1004
p-Aminobenzoic acid	*p*-Hippuramidobenzoic acid	278–279°	0.704	0.925	0.085	0.027	0.0140	0.0130
m-Aminoacetophenone	Hippuric *m*-acetylanilide[a]	229–230°	6.558	2.460	0.777	0.395	0.145	0.128
p-Aminoacetophenone	Hippuric *p*-acetylanilide[a]	198–199°	0.5552	0.5140	0.4174	0.3648	0.3458	0.2558
o-Anisidine	Hippuric *o*-methoxyanilide	120–121°	0.0000	1.6551	0.8012	0.6235	0.4330	0.3342
p-Anisidine	Hippuric *p*-methoxyanilide[a]	217–218°	4.8200	2.3905	1.2587	0.6905	0.4684	0.3196
Methyl *p*-aminobenzoate	Methyl *p*-hippuramidobenzoate[a]	194–195°	0.2959	0.2856	0.2286	0.2115	0.1403	0.1201

[a] Prepared or studied for the first time.

EXPERIMENTAL

Activation of papain. The papain used in this investigation was supplied by the Schwarz Laboratories, Mount Vernon, N. Y. A modification of the method of Grassmann[5] and Bennett and Niemann[2b] for activation of the enzyme was employed. Fifty grams of papain was ground rapidly to a paste in a mortar with a few milliliters of cold water and was then stirred mechanically with 200 ml. of water in an ice bath for 4 hr. The solution was removed by suction filtration. Hydrogen sulfide was passed into the filtrate, surrounded by an ice bath, for 18 hr. Suspended matter was removed by centrifugation at 2000 r.p.m. for 20 min. The papain was precipitated once by addition of enough methanol to give a 70 volume % of solution, followed by centrifuging for 20 min. at 2000 r.p.m. The precipitate was dried over phosphorus pentoxide in a vacuum desiccator and then crushed lightly to a powder. The coarse powder was stored in stoppered vials, kept in a large, air-tight, brown bottle, fitted with a screw cap, and refrigerated at about 5°.

Procedure for rate studies. A sodium acetate (0.25*M*)-acetic acid (0.25*M*) buffer was used. For each reaction, 0.050 mole of hippuric acid, 0.050 mole of the substituted aniline, 1.00 g. of L-cysteine hydrochloride monohydrate, and 0.50 g. of papain were employed, with enough buffer to make 250 ml. of solution. The *p*H was adjusted to and maintained at 4.6. Usually the hippuric acid and substituted aniline were dissolved in hot buffer solution, which was cooled to 40°. Then L-cysteine and papain were added, after first being dissolved in about 5 ml. of buffer, with further addition of enough buffer to give a total volume of 250 ml. The solution was filtered, followed by incubation at 40°. Filtration was then carried out at the end of 18 hr., subsequently at the end of each 24 hr. for 6 days, and finally 7 days later. The precipitate for each period was dried and weighed, and then the total amount of precipitate was collected and recrystallized from a suitable solvent. In general, two or more recrystallizations, with the use of decolorizing carbon, were necessary to bring the sample to sufficient purity for nitrogen analysis. Melting points were corrected in the usual way for those determined in a potassium sulfate–sulfuric acid bath. Other melting points were determined by means of a Fisher-Johns melting point apparatus. Nitrogen analyses were determined at the Oakwold Laboratories, Alexandria, Va., and The Microchemical Specialties Company, Berkeley, Calif. Results are summarized in Table I.

Acknowledgments. This work was supported by funds from the Research Corporation and a grant-in-aid from the Society of Sigma Xi and RSEA. Mr. David R. Schwarz of the Schwarz Laboratories, Mount Vernon, N. Y., generously donated the papain used in these experiments. Professor Charles D. Hurd of Northwestern University offered helpful suggestions with regard to possible systems of correct nomenclature of the hippuric anilides. Indebtedness is expressed to Professor Carl Niemann of the California Institute of Technology for help, through private communications, with respect to appropriate treatment of the papain. Mr. Jimmie Jimkawa drew the graphs and other assistance was given by Mr. Jerome Blank and Mr. Herbert Chelner.

FRESNO, CALIF.

(5) W. Grassmann, *Biochem. Z.*, 279, 131 (1935).

TABLE I (*Cont'd*)

SUBSTITUTED HIPPURIC ANILIDES FROM HIPPURIC ACID AND SUBSTITUTED ANILINES

tion in Hours 138–162 hr.	162–380 hr.	Solvent for Recrystallization	Nitrogen Analyses % Calcd.	% Found	Total Yield, Grams	Percentage Yield	Color of Product
0.0982	0.4076	Ethanol	15.51	See Ref. 4	4.9539	36.75	White
0.0850	0.5430	Ethanol	15.51	15.56	6.1500	45.62	White
0.161	0.725	Ethanol	10.37	10.45	3.7900	28.00	White
0.0026	0.0000	Ethanol or Methanol	10.37	10.26	6.9844	51.69	Cream
0.177	0.653	Ethanol	10.37	10.38	9.4690	70.09	White
acid, and *p*-nitroaniline[a] gave no precipitate							
0.0791	0.3305	Glacial HOAc; then addition of water	9.39	9.29	5.4380	36.47	Cream
0.0120	0.153	Glacial HOAC; then addition of water	9.39	9.32	1.9330	14.34	White
0.091	0.3162	Ethanol or acetophenone	9.46	9.40	10.8702	73.35	Cream
0.2111	1.1169	Ethanol	9.46	9.34	3.7810	25.51	White
0.2266	1.1611	Ethanol	9.86	9.87	5.2347	36.81	Cream
0.2437	1.0495	Ethanol	9.86	9.99	11.2409	79.05	White
0.0941	0.3942	Ethanol	8.97	8.96	1.7703	11.71	White

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralene I: Certain Reactions of Xanthotoxin*

MERVIN E. BROKKE AND BERT E. CHRISTENSEN

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A number of the chemical reactions of 9-methoxypsoralene and its derivatives are described. These include nitration, halogenation, reduction, thionation, demethylation, ozonation, and other degradation procedures. Degradation studies and unequivocal synthesis show that bromination occurs at the four position. The structures of the 2,3-dihydropsoralene derivatives were established by a comparison of the ultraviolet absorption spectra of psoralene and coumarin derivatives. Thionation of the 9-methoxypsoralenes proceeds in a manner analogous to that reported for coumarins.

In 1911, Priess[1] discovered a new piscicide in an alcoholic extract of *fagara zanthoxyloides Lam.* to which he gave the name zanthotoxin. Later Thoms[2] after determining the structure of this compound renamed it xanthotoxin and in 1936 Spath reproduced it synthetically.[3]

In addition to its toxic action on fish[4] xanthotoxin (9-methoxypsoralene or 9-methoxyfuro[3,2-*g*]coumarin I) has since been shown to possess a molluscicidal activity.[5] When administered in large doses to mammals it was found to produce fatty degeneration of the liver and adrenal hemorrhage,[6] while in humans the compound has found medical acceptance for the treatment of leukodermia.[7] The most recent applications have made use of the fact that I alters the erythermal response to ultraviolet light,[8a,b,c] a property which has been used clinically to prevent sunburn.[8a] There is some evidence that

* This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 327, School of Science, Department of Chemistry.

(1) H. Priess, *Ber. Pharm. Ges.*, 21, 227 (1911).
(2) H. Thoms, *Ber.*, 44, 3325 (1911).
(3) E. Spath and M. Pailer, *Ber.*, 69, 767 (1936).
(4) E. Spath and F. Kuffner, *Monatsh.*, 69, 75 (1936).
(5) A. Schönberg and N. Latif, *J. Am. Chem. Soc.*, 76, 6208 (1954).
(6) A. Elwi, *J. Roy. Egypt. Med. Assoc.*, 33, 773 (1950).
(7) I. Fahmy and H. Abu-Shady, *Quart. J. Pharm. and Pharmacol.*, 21, 499 (1948).
(8) (a) A. Lerner, *J. Invest. Dermatol.*, 20, 299 (1953). (b) A. Griffin, M. O'Neal, and T. Fitzpatrick, *Congress of intern. biochem.*, Brussels 1955, 121. (c) L. Musajo, G. Rotighiero and G. Caporale, *Chemica e industria*, 35, 13 (1953).

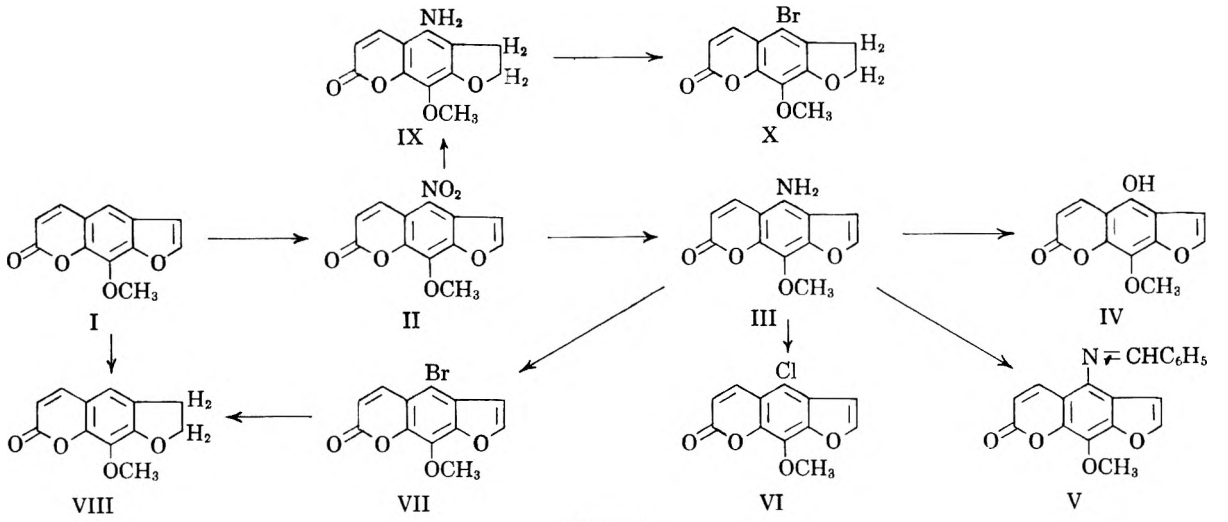

Figure 1

under certain conditions xanthotoxin may be carcinogenic.[8b]

Because of the wide-spread and increasing interest in xanthotoxin for its pharmacological action, this study was undertaken to investigate some of the chemical properties of the compound and to prepare new derivatives for biological testing.

Both Priess[1] and Thoms[2] prepared mononitro derivatives of I. Thoms and Baetcke[9] established that this nitro substituent was at the 4-position by reducing it to the corresponding amino compound, followed by oxidation to the quinone. This quinone was shown to be identical to that obtained from bergaptene (4-methoxypsoralene).

In the current study both the nitro and amino derivatives (see II and III, Fig. 1) were prepared in excellent yields. 4-Amino-9-methoxypsoralene III exhibited the normal behavior of an aromatic amine, for example, in the formation of an acetyl derivative and a Schiff's base.

Since III appeared to be a potential key compound for the preparation of other derivatives, it was subjected to a number of diazotization reactions. This type of reaction finds precedent in the work of Dey and Kutti[10] who diazotized and coupled a group of substituted coumarins; and in that of Noguchi and Kawanami[11] who prepared 9-hydroxy-4-methoxypsoralene from aminobergaptene. Analogous Sandmeyer reactions with III yielded the corresponding bromo and chloro derivatives while hydrolysis of the diazotized product yielded the phenol, 4-hydroxy-9-methoxypsoralene IV.

Spath has reported a phenol[12] which was shown to be either 4-hydroxy-9-methoxypsoralene or its isomer 9-hydroxy-4-methoxypsoralene. 9-Hydroxy-4-methoxypsoralene was shown to have a melting point of 198°,[11] while IV prepared in this laboratory melted at 220–226°. Since Spath found the melting point of his phenol to be 224–226° his compound was probably IV.

Schönberg and Sina[13] demethylated 9-methoxypsoralene to form the corresponding phenol, by the use of magnesium iodide and sulfuric acid. Later, Schönberg and Ayiz[14] reported that aniline hydrochloride was a superior cleaving agent. The latter work however, could not be confirmed in this laboratory. Cleavage with aniline hydrochloride was attempted both with the refluxing technique of Schönberg and by fusion in sealed tubes at various temperatures and heating times. In no case could any reaction be observed. Cleavage with the magnesium iodide procedure, on the other hand, was accomplished in small yield. Although other workers have reported cleavage of a butylfurocoumarin ether by mild treatment with mineral acid,[15] this reagent as expected was ineffectual with 9-methoxypsoralene.

In the original synthesis of I, Spath[3] prepared 2,3-dihydro-9-methoxypsoralene VIII which was subsequently dehydrogenated. In this laboratory it was found that the reverse reaction readily occurred; VIII was formed in good yield in palladium-catalyzed hydrogenation reactions.

That the hydrogenation product of 9-methoxypsoralene and the 2,3-dihydro-9-methoxypsoralene reported by Spath were identical structures was deduced from a consideration of the fact that their melting points were identical and from a study of the ultraviolet data given in Table I.

(9) H. Thoms and E. Baetcke, *Ber.*, **45**, 3705 (1912).
(10) B. Dey and V. Kutti, *Proc. Nat. Inst. Sci. India*, **6**, 641 (1940).
(11) T. Noguchi and M. Kawanami, *Ber.*, **71**, 1428 (1938).
(12) E. Spath, *Monatsh*, **72**, 179 (1938).
(13) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 4826–8 (1950).
(14) A. Schönberg and G. Ayiz, *J. Am. Chem. Soc.*, **75**, 3265–6 (1953).
(15) G. Pigulevskii and G. Kuznetrova, *Zhur. obshchei Khim.*, **23**, 1937 (1953).

TABLE I

ULTRAVIOLET ABSORPTION DATA OF CERTAIN COUMARIN AND PSORALENE DERIVATIVES

Compound	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ
A	<220	>4.04	...	...	275	4.04	315	3.76
B	<220	>4.04	270	3.30	275	3.30	...	...
C	225	4.11	255	3.70	295	3.76	350	4.07
D	<220	>4.08	250	3.48	290	3.60	...	...
E	245	4.08	275	3.45	282	3.48	...	...
F	<220	>3.6	282	3.52	289	3.48	...	...
G	243[a]	4.13	265	3.96	289	3.90	300	4.04
H	252[b]	3.28	262	3.44	284	3.40	335	4.08
I	240	4.30	246	4.29	290	3.98	>320	>3.90
J	225	4.24	258	3.67	295	3.88	>320	>4.21

A	Coumarin[16]	F	2,3-Dihydrobenzofuran[17]
B	3,4-Dihydrocoumarin[16]	G	9-Methoxypsoralene
C	6,7-Dihydroxycoumarin[16]	H	2,3-Dihydro-9-methoxypsoralene
D	3,4-Dihydro-6,7-dihydroxycoumarin[16]	I	4,5-Dimethylpsoralene[c]
E	Benzofuran[17]	J	2,3-Dihydro-4,5-dimethylpsoralene[c]

[a] This compound has a split peak at 243 and 248 each with same extinction coefficient. It also has a peak below 220. [b] This compound has a peak below 220. [c] These two compounds were synthesized in this laboratory and will be published elsewhere.

It is evident from the data presented in Table I that reduction of coumarin and 6,7-dihydroxycoumarin resulted in a lower extension of the conjugation with elimination of peaks above 300 mμ.; this same observation has been made in numerous other instances.[16] Furthermore since neither benzofuran, nor 2-3-dihydrobenzofuran shows an absorption spectrum above 300 mμ, it is reasonable to assume the benzofuran portion of the furocoumarin molecules would not be responsible for absorption in this region.

Therefore the peaks observed above 300 mμ, in the cases of G, H, I, and J must arise from the conjugation of the lactone carbonyl with the aromatic nucleus. For this reason the hydrogenation of 9-methoxypsoralene must have occurred in the 2,3-positions rather than the 5,6. It is to be noted that hydrogenation of the furan ring results in formation of a saturated ether which causes a bathochromic effect, offsetting the effect of the loss of conjugation due to reduction of the furan ring.

Nitration of 2,3-dihydro-9-methoxypsoralene VIII proceeded similarly to that of 9-methoxypsoralene yielding a mononitro derivative. This nitro derivative resisted dehydrogenation. Although this compound was hydrogenated further by both catalytic and chemical reduction no pure products were isolated from the reaction mixture.

On the other hand, 9-methoxy-4-nitropsoralene II was readily reduced by catalytic procedures to the corresponding 4-amino-2,3-dihydro-9-methoxypsoralene (IX). The position of the additional hydrogen atoms (2,3) was ascertained by converting the 4-amino substituent to the 4-bromo analog X and then comparing ultraviolet spectra of X with that of the known 4-bromo-9-methoxypsoralene. See Table II.

The presence of the peak at 330 mμ in the spectrum of 4-bromo-2,3-dihydro-9-methoxypsoralene is indicative of unsaturation in the 5,6 position thus extending conjugation of the carbonyl moiety to the aromatic nucleus. Despite the loss of conjugation due to reduction of the furan ring, the effect of the formation of the aliphatic ether causes a slight bathochromic shift in this instance.

Priess[18] reported that direct bromination of 9-methoxypsoralene in chloroform yielded a dibromo addition product which melted at 164°. He postulated that the addition took place either in the 2,3- or 5,6-positions. In this laboratory, the bromination in chloroform yielded a monobromo derivative VII, m.p. 185–186°, and a tribromo derivative XVII, m.p. 165°. Bromination with *N*-bromosuccinimide yielded the same monobromo substitution product VII as before. Under the various conditions of brominations which were tried, these were the only products ever isolated from the reaction. The tribromo derivative XVII, was readily converted to the monobromo derivative by the conventional method (treating it with an acetone solution of sodium iodide).

Horning and Risner[19] have reported the bromination of 5-methyl-2,3-dihydrofuro[3,2-*g*]coumarin with *N*-bromosuccinimide. Since their product could not be dehydrohalogenated and did not react with silver nitrate, these workers concluded that the bromine must be either on the lactone ring or the benzene nucleus.

The monobromo derivative of 9-methoxypsoralene VII was inert to aqueous base, silver nitrate, and Grignard formation under all conditions tested. It was however very labile to catalytic hydrogenation

(16) R. Goodwin and B. Pollock, *Arch. Biochem.*, **49**, 1 (1954).

(17) J. Jones and A. Lindsey, *J. Chem. Soc.*, 1836 (1950).

(18) H. Priess, *Chem. Zentralblatt* II, 94 (1911).

(19) E. Horning, and D. Risner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

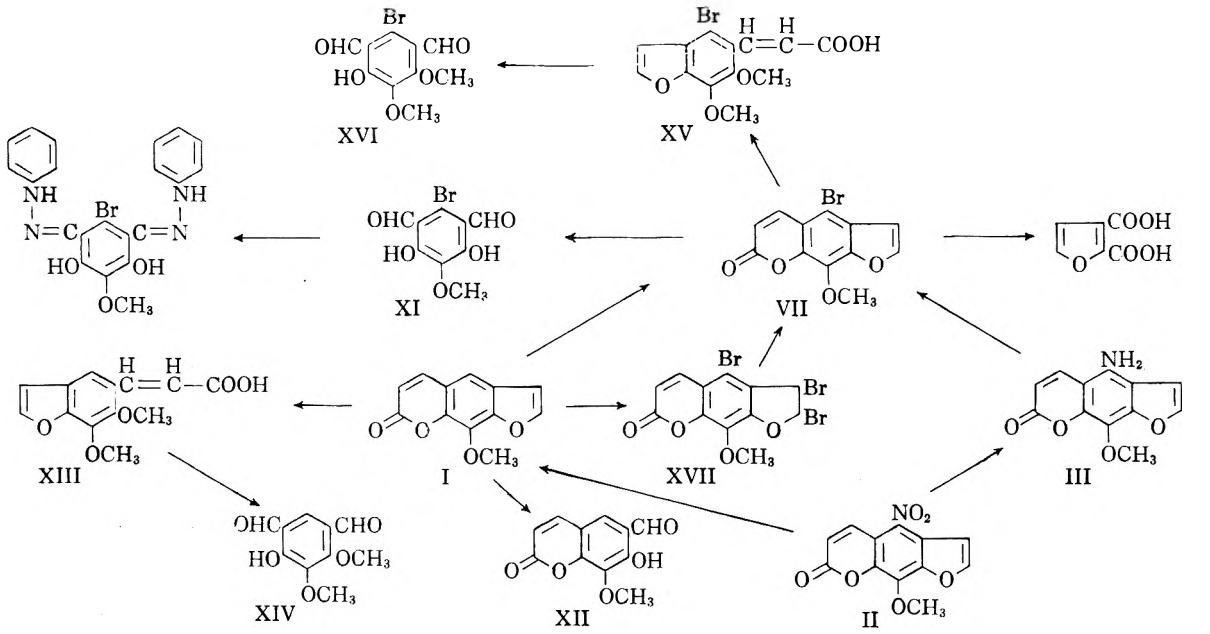

Figure 2

yielding VIII in 15 minutes at 40 lbs. hydrogen pressure in presence of palladized charcoal.

In order to establish the position of the bromo substituent, the monobromo derivative was oxidized with hydrogen peroxide[20] yielding furan-2,3-dicarboxylic acid, thus eliminating from consideration the 2- and 3-positions. Comparative ozonizations were carried out using 9-methoxypsoralene and bromo-9-methoxypsoralene, the former yielding the known 6-formyl-7-hydroxy-8-methoxycoumarin.[21] Final confirmation of this product was made by the preparation of the dinitrophenyl hydrazone derivative.

Bromo-9-methoxypsoralene on the other hand was cleaved in both hetero-rings yielding a substituted isophthalaldehyde (XI). The presence of two formyl substituents in XI; was established by the preparation and analysis of the bisphenylhydrazone derivative.

Although only one hetero ring in 9-methoxypsoralene was cleaved by direct ozonolysis, the corresponding isophthalaldehyde was obtained by opening the lactone ring with dimethyl sulfate.[2,22] Upon ozonolysis of the resultant product the same reactions were observed as in the instance of the bromo-9-methoxypsoralene. These reactions all pointed to the fact that the monobromo substituent must be in the 4- position. This observation was confirmed when the 4-bromo-derivative was synthesized unequivocally by the Sandmeyer procedure from 4-amino-9-methoxypsoralene. These series of reactions are given in Fig. 2.

(20) E. Spath and L. Kahovec, *Ber.*, **66**, 1146 (1933).

(21) G. Rodighiero and C. Antonello, *Ann. Chim. (Rome)*, **46**, 960 (1956); *Chem. Abstr.*, **56**, 6616 (1957).

(22) N. Shah and R. Shah, *J. Univ. Bombay*, **7**, Pt. 3, 213 (1938); *Chem. Abstr.* **33**, 3779 (1939).

The position of the remaining two bromo substituents in the tribromo-9-methoxypsoralene was established by the ultraviolet spectral data shown in Table II.

TABLE II

ULTRAVIOLET ABSORPTION DATA OF BROMINATED PSORALENE DERIVATIVES

	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ	$\lambda_{max.}$	Log ϵ
A	222	4.41	246[a]	4.01	268	4.28	308	4.14
B	<220	>4.62	254	4.42	266	4.43	330	4.52
C	<220	>4.27	246	3.98	268	4.27	310	4.14

A 4-Bromo-9-methoxypsoralene
B 4-Bromo-2,3-dihydro-9-methoxypsoralene
C 2,3-dihydro-9-methoxy-2,3,4-tribromopsoralene

[a] This compound has a split peak at 346 and 256 mμ

The fact that the two additional bromo substituents did not eliminate the adsorption above 300 mμ is indicative of addition in the 2,3-positions, for reasons mentioned previously.

2,3-Dihydro-9-methoxypsoralene was likewise observed to form a monobrominated product with bromine in chloroform solutions. *N*-bromosuccinimide however, gave a mixture which has not as yet been resolved. Although this bromo derivative resists dehydrohalogenation it was found to be labile in aqueous base yielding a hydroxy compound. A mixed melting point determination indicated that this monobrominated product was not identical with 4-bromo-2,3-dihydro-9-methoxypsoralene X.

Coumarin and its derivatives are known to react with phosphorus pentasulfide to produce thiocoumarins.[23] This reaction has been carried out

(23) A. Clayton and W. Godden, *J. Chem. Soc.* 210 (1912).

successfully with I, II, VII, and VIII to produce the corresponding furothiocoumarins (see Fig. 3).

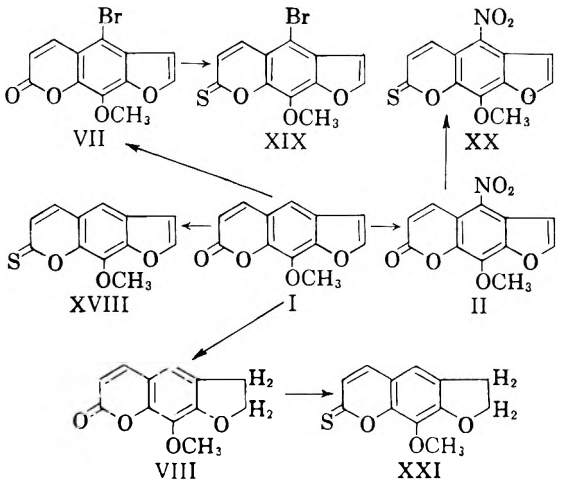

Figure 3

Under normal conditions coumarins are reduced by lithium aluminum hydride to give *o*-(3-hydroxy-1-propenyl)phenols.[24] This reaction proceeded in the same manner with I yielding 6-hydroxy-7-methoxy-5-(3-hydroxy-1-propenyl)benzofuran XXII. Furthermore, the lactone ring of I was also opened with hydrazine[25] to yield the corresponding hydrazide XXII.

Both of these reactions occurred simultaneously with I and VII to produce 6-(1,2-diphenylethyl)-7,8-dihydroxycoumarin and 5-bromo-6(1,2-diphenylethyl)-7,8-dihydroxycoumarin respectively (see Fig. 4).

EXPERIMENTAL

9-Methoxy-4-nitropsoralene (II). Ten g. of 9-methoxypsoralene was dissolved in 100 ml. of glacial acetic acid; while maintaining the temperature at 20°, 80 ml. of concd. nitric acid was added slowly with stirring. In a few seconds the mixture turned a deep red and then began to solidify. The mass was then poured onto 200 g. of ice. After the ice had melted the solution was filtered to yield 12.0 g. of a product which melted at 235–238° after recrystallization from ethanol.

4-Amino-9-methoxypsoralene (III). 9-Methoxy-4-nitropsoralene (10 g.) stannous chloride (20 g.) and tin granules (20 g.) were stirred at room temperature in 40 ml. of alcohol and 120 ml. of concd. HCl for 24 hr. (cooling was necessary at first). The material was then filtered, washed with sodium bicarbonate solution, and recrystallized from 95% ethanol to yield 5.6 g. of 4-amino-9-methoxypsoralene, m.p. 234–235°. Evaporation of the mother liquid yielded 2.3 g. of the product, raising the over-all yield to 89.3%. The identity of the product was confirmed by preparation of the acetyl derivative m.p. 244–245°.[9]

9-Benzalamino-9-methoxypsoralene V. 4-Amino-9-methoxypsoralene (0.10 g.) was warmed in 5 ml. of benzaldehyde and the mixture was poured into 25 cc. of 95% ethanol. After standing overnight in the refrigerator, pale yellow crystals, 0.079 g., m.p. 189–200° dec., were obtained.

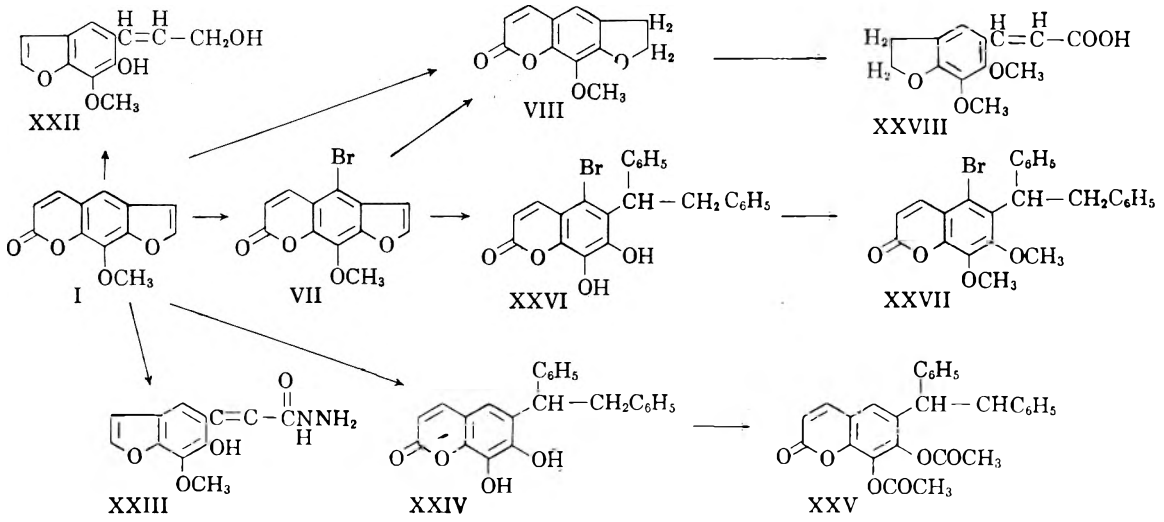

Figure 4

Angelicin and psoralene have been shown to add two moles of benzene in the presence of aluminum chloride to yield 1,2-diphenylethylhydroxycoumarins.[26] Aluminum chloride has also been found to act as an ether-cleaving agent in aromatic solvents.[27]

(24) P. Karrer and P. Banerjea, *Helv. Chim. Acta*, **32**, 1692 (1949).

(25) A. Darapsky, H. Berger and A. Neuhaus, *J. Prakt. Chem.* **147**, 145 (1936).

(26) B. Krishnaswamy and T. Seshadri, *Proc. Indian Acad. Sci.* **16A**, 151 (1942).

(27) B. Krishnaswamy and T. Seshadri, *Proc. Indian Acad.* **15A**, 437–40 (1942).

Anal. Calcd. for $C_{19}H_{13}O_4N$: C, 71.5; H, 4.07. Found: C, 71.5; H, 3.96.

4-Hydroxy-9-methoxypsoralene IV. One gram of 4-amino-9-methoxypsoralene, 0.3 g. sodium nitrite, and 10 ml. of concd. hydrochloric acid were mixed in 65 ml. 95% methanol at zero degrees and allowed to stand for 10 min. The mixture was then warmed to room temperature and 0.10 g. dark green material was removed at this point. This substance was found to melt at 220–226° after crystallization from 95% ethanol (reported m.p. 224–226°[12]).

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.2; H, 3.45. Found: C, 61.8; H, 3.50.

4-Chloro-9-methoxypsoralene VI. 4-Amino-9-methoxypsoralene (1.3 g.) was suspended in 30 ml. of concd. hydrochloric acid solution maintained in an ice-salt bath. An aqueous

solution containing 0.38 g. of sodium nitrite was then added slowly to the cooled solution. The mixture was permitted to stand in the cooling bath for 5 min. and then the reaction mixture was transferred to 50 ml. of boiling 6*N* hydrochloric acid which contained 1.5 g. of cuprous chloride. The product was collected, treated with Norite and recrystallized from ethanol, m.p. 187–188°, yield 0.35 g.

Anal. Calcd. for $C_{12}H_7O_4Cl$: C, 57.5; H, 2.79. Found C, 57.5; H, 2.80.

Attempted demethylation of 9-methoxypsoralene. Three grams of 9-methoxypsoralene were mixed intimately with twice the molar quantity of aniline hydrochloride and heated with stirring in a carbon dioxide atmosphere. The bath temperature was started at 180° and raised to 205° in 40 min. After cooling the mixture was extracted with water and the insoluble residue was recrystallized from dilute acetic acid.[14] After one crystallization, 2.36 grams of material remained m.p. 143–145°; mixed m.p. with 9-methoxypsoralene showed no depression.

4-Bromo-9-methoxypsoralene (VII). A. Five grams of 9-methoxypsoralene were mixed with a one molar excess of bromine in chloroform solution. The solvent was then stripped off on the steam bath and the residue was crystallized from 95% ethanol to yield 5.76 g., m.p. 185–186°.

Anal. Calcd. for $C_{12}H_7O_4Br$: C, 48.8; H, 2.38. Found: C, 48.8; H, 2.46.

B. 9-Methoxypsoralene (1.47 g.) and *N*-bromosuccinimide (1.21 g.) were suspended in 100 ml. of carbon tetrachloride. After refluxing for 2 hr., the solvent was evaporated and the residue was washed with hot water and crystallized from 95% ethanol; yield 1.15 g., m.p. 183–184.5°. Mixed melting point with A showed no depression.

C. 2,3-Dihydro-9-methoxy-2,3,4-tribromopsoralene (100 mg.) was dissolved in 25 ml. acetone and potassium iodide (0.5 gram) was added with stirring. After 2.5 hr. the solution was filtered, diluted with water, and cooled. The insoluble product was collected and crystallized from ethanol to yield 40 mg., m.p. 185–186°. A mixed melting point with 4-bromo-9-methoxypsoralene showed no depression.

D. 4-Amino-9-methoxypsoralene (1.3 g.) was suspended in 25 ml. 48% hydrobromic acid and then cooled in an ice-salt mixture. Sodium nitrite (0.388 g.) dissolved in a little water was added with stirring and the mixture was allowed to stand for 5 min. The mixture was then poured slowly into a boiling solution composed of 1.61 g. of cuprous bromide and 50 ml. 24% hydrobromic acid. The product was collected, dried, and then sublimed at 170° and 15 mm. pressure. This in turn was crystallized from methanol to yield 0.6 g., m.p. 185–186°. A mixed melting point with 4-bromo-9-methoxypsoralene obtained by direct bromination showed no depression.

4-Bromo-2,3-dihydro-9-methoxypsoralene (X). 4-Amino-2,3-dihydro-9-methoxypsoralene (150 mg.) was suspended in 25 ml. 48% hydrobromic acid and cooled in an ice-salt mixture. Sodium nitrite (45 mg.) dissolved in a little water was added and the solution was allowed to stand 5 min.; it was then poured into 50 ml. boiling 6*N* hydrobromic acid which contained cuprous bromide (160 mg.). This mixture was diluted with 100 ml. of water and cooled. The product was collected, treated with Norite, and crystallized from ethanol; yield 90 mg., m.p. 201–203°.

Anal. Calcd. for $C_{12}H_9O_4Br$: C, 48.6; H, 3.03. Found: C, 48.6; H, 3.16.

Furan-2,3-dicarboxylic acid. 4-Bromo-9-methoxypsoralene (2.0 g.) was dissolved in 200 ml. 4% methanolic potassium hydroxide and allowed to stand at room temperature overnight. One hundred ml. of water was added and the volume was reduced *in vacuo* to 100 ml. Then 100 ml. of 8% hydrogen peroxide was added and the solution was allowed to stand for 2 days at room temperature, whereupon the temperature was raised to 60–70° and the mixture heated for an additional 6 hr. The oxalic acid formed was removed with ammoniacal calcium chloride. The solution was acidified and extracted with ether. The yield was 0.1 g. of material, m.p. 217–220° dec. A mixed melting point with furan-2,3-dicarboxylic acid prepared by a similar oxidation of 9-methoxypsoralene showed no depression.

Anal. Calcd. for $C_6H_4O_5$: C, 46.2; H, 2.56; Found: C, 46.5; H 2.86.

2,3-Dihydro-9-methoxypsoralene (VIII). A. One gram of 9-methoxypsoralene was dissolved in 100 ml. of ethanol and 0.5 g. 10% palladium on charcoal was added. This mixture was then shaken for 2 hr. at room temperature under 40 pounds hydrogen pressure. The catalyst was then removed and the solvent was evaporated. The residue after crystallization from ethanol yielded 0.31 g. white needles melting at 160–161°. 2,3-Dihydro-9-methoxypsoralene synthesized by another procedure has been reported by Spath to melt at 163°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.59. Found: C, 66.2; H, 4.85.

B. One gram of 4-bromo-9-methoxypsoralene was suspended with 0.5 g. 10% palladium on charcoal in 75 cc. of 95% ethanol. This mixture was shaken for 15 min. under 30 pounds hydrogen pressure, the catalyst was removed, and the solution was reduced in volume, chilled, and filtered to yield 0.65 g. of crystals, m.p. 130–140°. This material was recrystallized three times from ethanol raising the melting point to 158–160°. A mixed melting point with 2,3-dihydro-9-methoxypsoralene showed no depression.

2,3-Dihydro-9-methoxy-x-nitropsoralene. One gram of 2,3-dihydro-9-methoxypsoralene was stirred into 25 ml. of a 50% solution of concentrated nitric acid in glacial acetic acid. The solution became cloudy after standing about one minute at room temperature and was immediately poured into 200 ml. of ice water. The product was filtered, washed with water, and recrystallized from ethanol to yield 1.2 g. of material, m.p. 192–198° dec.

Anal. Calcd. for $C_{12}H_9O_6N$: C, 54.7; H, 3.54. Found: C, 54.6; H, 3.53.

4-Amino-2,3-dihydro-9-methoxypsoralene (IX). One gram of 9-methoxy-4-nitropsoralene was suspended with 0.5 g. 10% palladium on charcoal in 150 ml. of 95% ethanol and shaken 2 hr. under 40 pounds hydrogen pressure at room temperature. The mixture was then heated to boiling and the catalyst removed. Upon cooling to 5° the product crystallized and was collected; yield 0.55 g., m.p. 214–216°.

Anal. Calcd. for $C_{12}H_{11}O_4N$: C, 61.7; H, 4.72. Found: C, 61.6; H, 4.63.

2-Bromo-4,6-dihydroxy-5-methoxy-m-phthalaldehyde (XI). One gram 4-bromo-9-methoxypsoralene was dissolved in 50 ml. methylene chloride. This solution was cooled in an ice bath whereupon a stream of approximately 3% ozone in oxygen was bubbled through it at the rate of about 50 ml. per minute, for 2 hr. The solution was then poured into 75 ml. of 30% acetic acid containing 0.5 g. zinc dust. The methylene chloride was evaporated on the steam bath and the remaining liquid decanted from the zinc. Upon cooling 0.25 gram product separated. The product was recrystallized from dilute acetic acid, m.p. 169–171°.

Anal. Calcd. for $C_9H_7O_5Br$: C, 39.3; H, 2.54. Found C, 39.3; H, 2.61. Bisphenylhydrazone; m.p. 263° dec.

Anal. Calcd. for $C_{21}H_{19}O_3N_4Br$: C, 55.4; H, 4.18. Found: C, 55.4; H, 4.34.

6-Formyl-7-hydroxy-8-methoxycoumarin (XII). One gram of 9-methoxypsoralene was dissolved in 50 ml. methylene chloride. The solution was cooled to zero degrees with an ice bath and approximately 3% ozonized oxygen was bubbled through for 3 hr. at the rate of about 50 ml. per minute. The solution was then added slowly to a suspension of 0.1 g. zinc dust in 75 ml. 30% acetic acid. After standing 1 hr. at room temperature, the methylene chloride was removed on the steam bath, the remaining solution was decanted and cooled. The product was collected and recrystallized from water to yield 0.41 g., m.p. 194–195.5°. Phenylhydrazone dec. 275°. Reported:[21] 195–196°, Phenylhydrazone derivative, 278–279° dec.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.1; H, 3.63. Found: C, 59.7, H, 3.76.

3-[5-(6,7-Dimethoxybenzofuryl)]propenoic acid (XIII). One gram of 9-methoxypsoralene was dissolved in 50 ml. of acetone and dimethyl sulfate (10 ml.) was added, followed by 50 ml. 20% potassium hydroxide. After refluxing for 15 min. another 10 ml. of dimethyl sulfate was added followed by 25 ml. of 20% potassium hydroxide. Reflux was continued for 2 hr. The solution was then cooled and acidified. The acetone was removed *in vacuo* and the product was collected. Recrystallization was effected from dilute acetic acid; yield 0.90 g., m.p. 112–114°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 63.0; H, 4.84. Found: C, 63.4; H, 4.87.

4,5-Dimethoxy-6-hydroxy-m-phthalaldehyde (XIV). One gram of the foregoing unsaturated acid was dissolved in 50 ml. of methylene chloride. The solution was cooled in an ice bath and a stream of approximately 3% ozone in oxygen was bubbled through at the rate of about 50 ml. per minute for 2 hr. The solution was then poured slowly into 75 ml. of 30% acetic acid containing 0.5 g. of zinc dust. The methylene chloride was removed using a steam bath and the remaining liquid was decanted from the zinc. Upon cooling 0.25 g. product separated. This was crystallized from dilute acetic acid, treated with Norite and recrystallized from water, m.p. 133–134°.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.2; H, 4.77. Found: C, 57.3; H, 4.76.

3-[5-(4-Bromo-6,7-dimethoxybenzofuryl)]propenoic acid (XV). One gram of 4-bromo-9-methoxypsoralene was dissolved in 50 ml. acetone. Dimethyl sulfate (7 ml.) was added, followed by 50 ml. of 20% potassium hydroxide. The solution was refluxed for 2 hr., then acidified and the acetone removed *in vacuo*. The product was collected and crystallized from dilute methanol; yield 0.75 g., m.p. 143–145°.

Anal. Calcd. for $C_{13}H_{11}O_5Br$: C, 47.7; H, 3.37. Found: C, 48.0; H, 3.55.

2-Bromo-5,6-dimethoxy-4-hydroxy-m-phthalaldehyde (XVI). Two grams of the foregoing unsaturated acid was dissolved in 100 ml. of chloroform and the solution was cooled in an ice bath. A stream of approximately 3% ozonized oxygen was bubbled through this solution for 3 hr. at the rate of about 50 ml. per minute. The solvent was then removed *in vacuo* and 50 ml. water was added. This mixture was kept at room temperature overnight and then placed on the steam bath for 15 min. The water was decanted and the residue recrystallized from dilute methanol to yield 0.40 g., m.p. 89–91°.

Anal. Calcd. for $C_{10}H_9O_5Br$: C, 41.7; H, 3.10. Found C, 42.0; H, 3.15.

2,3-Dihydro-9-methoxy-2,3,4-tribromopsoralene (XVII). One gram 9-methoxypsoralene (1 mole) was dissolved in 100 ml. chloroform and bromine (7.5 grams, 10 moles in 50 ml. of chloroform) was added. This solution was evaporated on the steam bath until 20–25 ml. of chloroform remained. The residue was then poured into 200 ml. of petroleum ether and cooled. The insoluble product was collected and crystallized from methanol. The yield was 1.5 g., m.p. 165–166°.

Anal. Calcd. for $C_{12}H_7O_4Br_3$: C, 31.7; H, 1.54. Found C, 31.5; H, 1.63.

x-Bromo-2,3-dihydro-9-methoxypsoralene. Two grams of 2,3-dihydro-9-methoxypsoralene was dissolved in a small volume of chloroform to which had been added a one molar excess of bromine. This solution was placed on the steam bath and allowed to evaporate to dryness. The residue was recrystallized from 95% ethanol; yield 2.60 g., m.p. 202–203°.

Anal. Calcd. for $C_{12}H_9O_4Br$: C, 48.5; H, 3.02. Found: C, 48.3; H, 2.96.

2,3-Dihydro-x-hydroxy-9-methoxypsoralene. One-half gram of *x*-bromo-2,3-dihydro-9-methoxypsoralene was refluxed for 30 min. in 25 ml. of 6*N* sodium hydroxide. This solution was then acidified with 6*N* sulfuric acid, and the product was filtered to yield 0.39 g. of material which melted at 264–268° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.6; H, 4.27. Found: C, 61.3; H, 4.21.

9-Methoxyfuro[3,2-g]thiocoumarin (XVIII). 9-Methoxypsoralene (1.75 g.) was mixed intimately with 3.5 g. phosphorus pentasulfide. This mixture was heated for 2 hr. in 75 ml. of xylene at the refluxing temperature. The mixture was then filtered and cooled. The product was collected and then recrystallized from glacial acetic acid; yield 1.85 g., m.p. 197–198°.

Anal. Calcd. for $C_{12}H_8O_3S$: C, 62.2; H, 3.44. Found: C, 62.2; H, 3.61.

4-Bromo-9-methoxyfuro[3,2-g]thiocoumarin (XIX). One gram of 4-bromo-9-methoxypsoralene and 2.5 g. of phosphorus pentasulfide were mixed intimately. The mixture was refluxed in 75 ml. xylene for 2 hr. The xylene solution was then filtered and cooled and the product was collected and recrystallized from ethanol; yield 0.80 g., m.p. 235–238°.

Anal. Calcd. for $C_{12}H_7O_3BrS$: C, 46.3; H, 2.25. Found: C, 46.2; H, 2.35.

9-Methoxy-4-nitrofuro[3,2-g]thiocoumarin (XX). One gram 9-methoxy-4-nitropsoralene and phosphorus pentasulfide (2.5 grams) were mixed intimately and then heated 3 hr. in 75 ml. of refluxing xylene. The xylene was decanted and cooled. The product was collected and crystallized from ethanol to yield 0.45 g., m.p. 205–206° (dec.).

Anal. Calcd. for $C_{12}H_7O_5NS$: C, 52.0; H, 2.53. Found C, 51.9; H, 2.52.

2,3-Dihydro-9-methoxyfuro[3,2-g]thiocoumarin (XXI). 2,3-Dihydro-9-methoxypsoralene (0.7 gram) was mixed intimately with phosphorus pentasulfide (1.75 gram) and heated 3 hr. in 75 ml. of refluxing xylene. The xylene was decanted and taken to dryness and the residue was crystallized from ethanol; yield 0.25 gram, m.p. 165–167°.

Anal. Calcd. for $C_{12}H_{10}O_3S$: C, 61.6; H, 4.27. Found C, 61.3; H, 4.47.

5-(3-Hydroxy-1-propenyl)-6-hydroxy-7-methoxybenzofuran (XXII). One gram of 9-methoxypsoralene and one gram of lithium aluminum hydride were refluxed in 300 ml. of dry ether for 8 hr. At the end of this time, water was added to destroy the excess reagent and the mixture was acidified with dilute sulfuric acid. Upon evaporation, the ether layer was found to contain 0.91 gram of a mixture which was shown to contain some inorganic material. This mixture was recrystallized from benzene yielding 300 mg. of a pure compound, m.p. 124–126°.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.6; H, 5.46. Found: C, 65.6; H, 5.49.

3-[5-(6-Hydroxy-7-methoxybenzofuryl)]propenoic hydrazide (XXIII). Two grams 9-methoxypsoralene (1 mole) and hydrazine hydrate (1.4 grams, 3 moles) were refluxed 24 hr. in 100 ml. of 95% ethanol. The solution was then diluted with water and cooled. The product was collected and recrystallized from ethanol, yield 1.7 grams, m.p. 183–185°.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.2; H, 4.84. Found: C, 58.3; H, 5.02.

6-(1,2-Diphenylethyl)-7,8-dihydroxycoumarin (XXIV). One gram of 9-methoxypsoralene was refluxed with 2 g. of aluminum chloride in 100 ml. benzene for 30 min. The benzene was decanted and evaporated to dryness. The residue was acidified and crystallized from dilute ethanol; yield 0.8 g. m.p. 240–244°.

Anal. Calcd. for $C_{23}H_{18}O_4$: C, 75.2; H, 4.90. Found: C, 74.7; H, 5.17.

The *diacetyl derivative* (XXV) was prepared by refluxing 200 mg. in acetic anhydride and pyridine for 2 hr. The solution was poured into water and the product was collected and recrystallized from dilute ethanol; yield 200 mg., m.p. 138–140°.

Anal. Calcd. for $C_{27}H_{22}O_6$: C, 73.5; H, 4.98. Found: C, 73.5; H, 4.95.

4-Bromo-6-(1,2-diphenylethyl)-7,8-dihydroxycoumarin (XXVI). One gram of 4-bromo-9-methoxypsoralene and 2.0 g. aluminum chloride were mixed intimately and then covered with 75 ml. benzene. This mixture was refluxed 20 min.; the benzene was then decanted and evaporated. The resulting residue was acidified with dilute hydrochloric acid, washed with water, and recrystallized twice from dilute ethanol and finally from dilute isopropyl alcohol; yield 0.46 g., m.p. 230–233°.

Anal. Calcd. for $C_{23}H_{17}O_4Br$: C, 63.3; H, 3.90. Found: C, 63.0; H, 4.07.

4-Bromo-7,8-dimethoxy-6-(1,2-diphenylethyl)coumarin (XXVII). 4-Bromo-7,8-dihydroxy-6-(1,2-diphenylethyl)coumarin (250 mg.) was dissolved in 20 ml. acetone. Two ml. dimethyl sulfate and one gram potassium carbonate were added and the solution was refluxed 17 hr. It was then poured into 100 ml. of water and cooled. The insoluble product was collected and recrystallized from dilute ethanol to yield 140 mg., m.p. 127–130°.

Anal. Calcd. for $C_{25}H_{21}O_4Br$: C, 64.5; H, 4.53. Found C, 64.3; H, 4.65.

3-[5-(2,3-Dihydro-6,7-dimethoxybenzofuryl)]propenoic acid (XXVIII). 2,3-Dihydro-9-methoxypsoralene (0.5 gram) was dissolved in 25 ml. acetone and 5.0 ml. of dimethyl sulfate was added. The solution was heated to reflux and 25 ml. of 20% potassium hydroxide was added slowly. Reflux was continued for 2 hr. after addition of the alkali. The solution was then cooled, acidified with dilute hydrochloric acid, and the acetone removed *in vacuo*. The insoluble product was collected and crystallized from dilute methanol to yield 0.3 g., m.p. 100–102°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.5; H, 5.61. Found: C, 62.4; H, 5.72.

Acknowledgment: The authors wish to thank the Paul B. Elder Co. of Bryan, Ohio, whose generous contribution of xanthotoxin made this investigation possible.

CORVALLIS, ORE.

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

The Functional Groups of Nomilin and Obacunone[1]

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In conjunction with evidence derived from infrared spectra and including intensity measurements in the carbonyl-stretching region, the chemical properties of nomilin and obacunone indicate that these compounds are ketonic dilactones with a furan ring and but one carbocyclic system. One lactone ring of nomilin carries a β-acetoxyl group whereas obacunone has the corresponding α,β-unsaturated lactone ring; this ring is readily opened by hydrolysis. The second lactone ring is opened by hydrogenolysis generating a carboxyl group which is remarkably acidic, properties that permit tentative conclusions to be drawn as to the relative positions of some of the functional groups.

Of the three optically active, lactonic, bitter principles of citrus fruits, limonin[3] has been more thoroughly studied than nomilin and obacunone, knowledge of which is chiefly due to Emerson,[4] who showed that both nomilin, $C_{28}H_{34}O_9$, and obacunone, $C_{26}H_{30}O_7$, gave obacunoic acid, $C_{26}H_{32}O_8$, on hydrolysis, the former yielding acetic acid at the same time. Further evidence indicated the presence of two lactone rings, one carrying a β-acetoxyl group, and one of a somewhat unreactive carbonyl group. The present investigation has confirmed and extended these results.

The absence of hydroxyl groups from obacunone was clear from the inertness of this compound to acetylation and from its transparency near 3μ in the infrared. Because the intense and ill-resolved absorption (Fig. 1) in the region 1700–1734 cm.$^{-1}$ due to the lactonic system and carbonyl group made it difficult to detect individual functions, attention was directed to the spectrum of obacunone oxime, which, in paraffin mulls, had two bands of more or less equal intensity at 1749 and 1677 cm.$^{-1}$ Whilst the latter band was correctly placed for the C=N stretching frequency of an oxime, its intensity was unexpectedly high compared with the data given by Cross and Rolfe,[5] who quote oximes having extinction coefficients approximately one tenth those of ketones. In an attempt to minimize inter-

TABLE I

ULTRAVIOLET END-ABSORPTIONS

		$\epsilon \times 10^{-3}$ 209 mμ		218 mμ
Nomilin		5.70		4.27
Obacunone		16.7		16.0
Methyl obacunoate		13.6		11.3
Obacunone oxime		15.4		13.1
α-Obacunol		18.3		14.4
Dihydroobacunone		10.0		6.4
Obacunone hydrochloride		5.5		4.0
Double bonds[10]				
(i) Disubstituted		~1		~0
(ii) Trisubstituted		3–4		~1.5
(iii) Tetrasubstituted		4.5–10		4–6
Furan	λ_{208}	5.6	λ_{216}	5.0
Marrubin[29]	λ_{210}	5.7		—

(1) This work formed part of a Technical Cooperation Project (1955) sponsored by the Foreign Operations Administration (U.S. Government).

(2) Department of Organic Chemistry, Liverpool University, Liverpool, England.

(3) O. H. Emerson, *J. Am. Chem. Soc.*, **74**, 688 (1952); B. V. Chandler and J. F. Kefford, *Australian J. Sci.*, **16**, 28 (1953); A. Fujita and Y. Hirose, *J. Pharm. Soc. Japan*, **76**, 129 (1956).

(4) O. H. Emerson, *J. Am. Chem. Soc.*, **70**, 545 (1948); **73**, 2621 (1951).

(5) L. H. Cross and A. C. Rolfe, *Trans. Faraday Soc.*, **47**, 354 (1951).

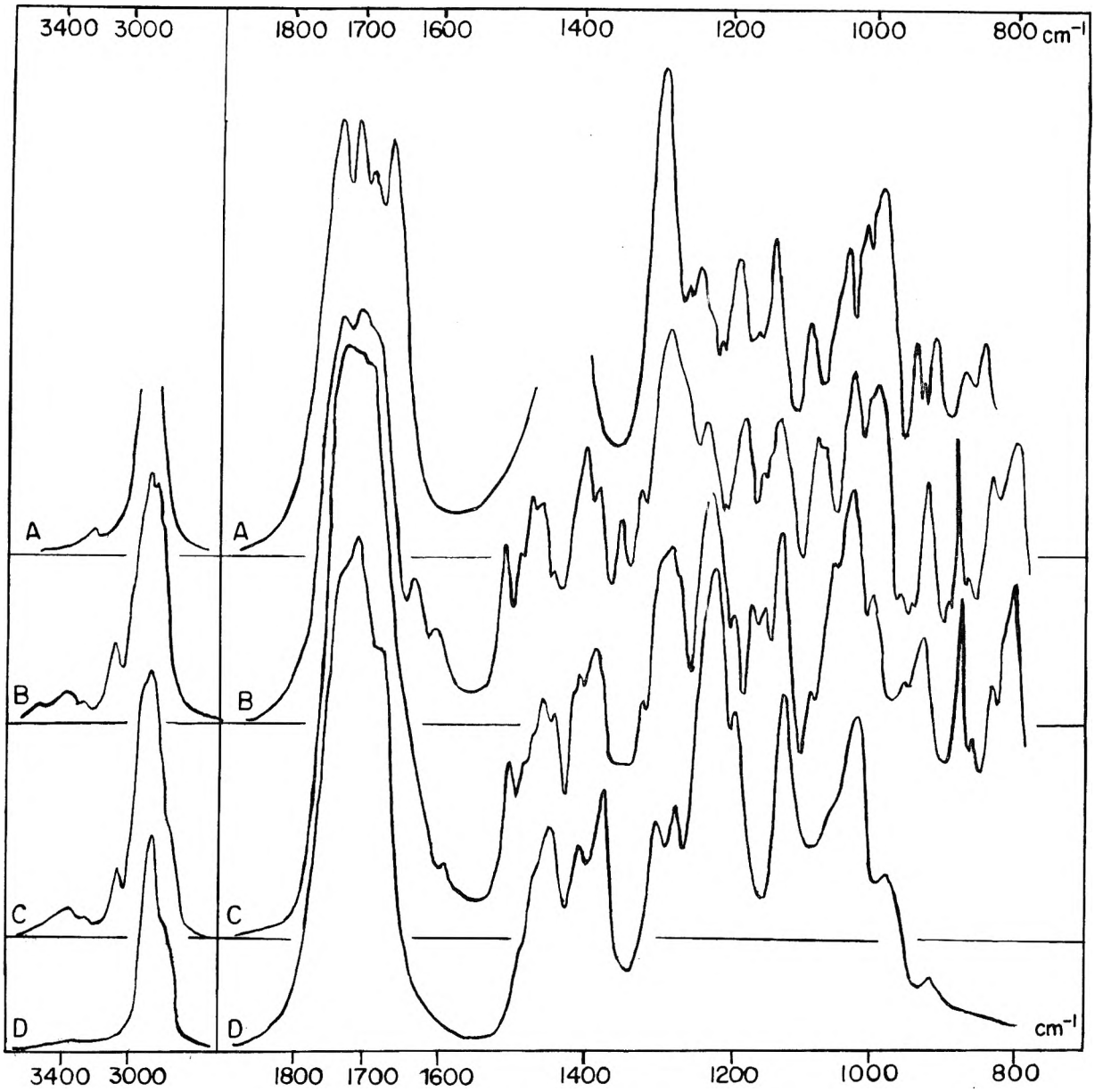


Fig. 1. A. Ozonolysis product of obacunone (in Nujol). B. Obacunone (film from $CHCl_3$). C. Nomilin (film from $CHCl_3$). D. Methyl hexahydronomilinate (film from $CHCl_3$)

ference from shifts of lactone bands induced by hydrogen-bonding, measurements were also made in chloroform, but in this solvent the oxime exhibited a complex band at 1694–1727 cm.$^{-1}$ and no marked absorption near 1670 cm.$^{-1}$ This type of behavior does not appear to have been reported for simple oximes, and we have confirmed that the spectrum of cyclohexanone oxime is essentially the same in mulls and in solution. Pyruvic acid oxime had bands at 1700 cm.$^{-1}$ and 1660 cm.$^{-1}$ of the expected positions and relative intensities, but in parallel work complex changes were encountered when the spectra of *syn*- and *anti*-monoximes of benzil and camphorquinone were examined in mulls and in solution. On the other hand, the spectra of obacunone oxime were not in accord with the results obtained by Mathis[6] for hydroxamic acids and indeed the substance gave no ferric reaction; but the possibility that hydroxylamine might have reacted with a lactone ring necessitated the acquisition of independent evidence for the presence of a carbonyl group.

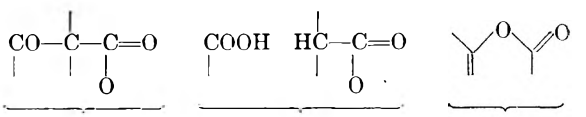
The slow reaction between 2,4-dinitrophenylhydrazine sulphate and obacunone gave only amorphous material, but the rapid reaction with sodium borohydride gave a mixture consisting of a α-obacunol, $C_{27}H_{32}O_7$, with some of the isomeride β-obacunol. The presence of a third product was indicated by the intense color reaction given with hydrobromic acid, but the substance responsible

(6) F. Mathis, *Compt. rend.*, 232, 505 (1951).

could not be isolated. Because borohydrides do not readily attack esters or lactones, α-obacunol was regarded as an alcohol derived from a ketone rather than a glycol from a lactone, a view confirmed by the formation of a monoacetate transparent at 3μ in the infrared. Attempts to reoxidize α-obacunol to obacunone failed: Oppenauer's method did not appreciably affect the substance (a result which may have been due to steric hindrance, as the ketone is not very reactive or to complex formation),[7] and chromic acid induced only ill-defined oxidation similar to that suffered by obacunone. Subsequently, the existence of a carbonyl group was clearly indicated by the spectra (discussed in the sequel) of related compounds having no ethylenic unsaturation but having well-resolved ester and lactone bands and also a band at 1711 cm.$^{-1}$ typical of acyclic ketones or of cyclic ketones with more than five members. Although obacunone gave a positive iodoform reaction, an acetyl group is probably not present because the Zimmerman reaction[8] was negative and because appropriate bands[9] were absent from the infrared spectra. β-Obacunol has not been closely studied, but it may be diastereoisomeric with α-obacunol: both compounds had selective absorption at 3500 cm.$^{-1}$ (OH), and at 1730 and 1690 cm.$^{-1}$ (lactonic absorption).

The elimination of acetic acid from nomilin by means of boiling pyridine and acetic anhydride as described by Emerson[4] gave erratic results not improved by omission of the acetic anhydride or by the addition of pyridine hydrochloride, but in α-picoline the reaction occurred regularly. Whilst this loss of acetoxyl could not be followed from frequencies in the carbonyl-stretching region, bands typical of acetates[9] and shown by nomilin at 1432, 1377, and 1225 cm.$^{-1}$ were absent from, or much weakened in, the spectrum of obacunone. In agreement with previous work, removal of acetoxyl resulted only in an increase in the ultraviolet end-absorption (Table I), which, taken with the fact that nomilin cannot contain a ketonic ring of less than six members, proved that obacunone was not an α,β-unsaturated ketone. This deduction was confirmed by the absence of marked bands near 1680 and 1640 cm.$^{-1}$ or near 1720 and 1600 cm.$^{-1}$ from the infrared spectrum. On the other hand, highly substituted double bonds[10] have absorption characteristics near 210 mμ closely similar to those of α,β-unsaturated esters[11] and lactones[12] so that the increase in this region could not be justifiably used to differentiate these systems, but a base-catalyzed as opposed to a thermal nature for the elimination was made probable not only by the stability of nomilin in xylene as opposed to γ-picoline but also by the ready loss of acetic acid accompanying the hydrolysis to obacunoic acid, and favored the formulation of obacunone as α,β-unsaturated lactone. Further, unconjugated double-bonds absorb near 1645 cm.$^{-1}$ whereas (in this region) obacunone but not nomilin had a weak band at 1620 cm.$^{-1}$ (Fig. 1), the position of which suggested conjugation: the corresponding bathochromic shift of a lactonic absorption was difficult to isolate from the complex band near 5.8μ.

As noted by Emerson, the ready hydrolysis of nomilin or of obacunone gave obacunoic acid, converted into the methyl ester by diazomethane. Acetylation of obacunoic acid gave Emerson only an amorphous solid of which the analysis seemed to differ little from that of the original substance; we have not been able to obtain an acetate of methyl obacunoate because in mild conditions no reaction took place, and in more vigorous conditions amorphous material resulted. In preliminary experiments, we were unable to confirm Emerson's comment (without experimental details) that methyl obacunoate possessed hydroxyl absorption near 3μ, so that when this ester was found not to react smoothly with hydroxylamine (in conditions under which obacunone formed an oxime comparatively readily) it became necessary to consider the possibility that the hydrolysis involved the fission of a (modified) β-ketoester system, as in (I) giving (II), rather than the fission of a lactone ring.



I II III

During attempts to obtain further information on this point, obacunoic acid and its methyl ester were subjected to sodium borohydride reduction, and α-obacunol was subjected to hydrolysis. In each case a rapid reaction ensued but the products were amorphous. In spite of its ill-defined nature, this evidence suggested that the carbonyl group was not involved in the hydrolysis and prompted a renewed search for hydroxyl absorption in the infrared spectrum of methyl obacunoate. When examined in paraffin mulls, in chloroform, or in carbon disulphide, this ester showed no absorption near 3μ sufficiently well-defined to be differentiated from overtones of the strong absorption near 6μ, but, surprisingly, solid films deposited from chloro-

(7) M. Ehrenstein, A. R. Johnson, P. C. Olmstead, V. I. Vivian, and M. A. Wagner, *J. Org. Chem.*, **15**, 264 (1950).

(8) W. Zimmerman, *Z. physiol. Chem.*, **233**, 257 (1935); I. E. Broadbent and W. Klyne, *Biochem. J.*, **56**, XXX (1954).

(9) A. R. H. Cole and D. W. Thornton, *J. Chem. Soc.*, 1007 (1956); R. N. Jones and A. R. H. Cole, *J. Am. Chem. Soc.*, **74**, 5648 (1952).

(10) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952)

(11) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, **73**, 1564 (1951).

(12) L. Dorfmann, *Chem. Revs.*, **53**, 47 (1953).

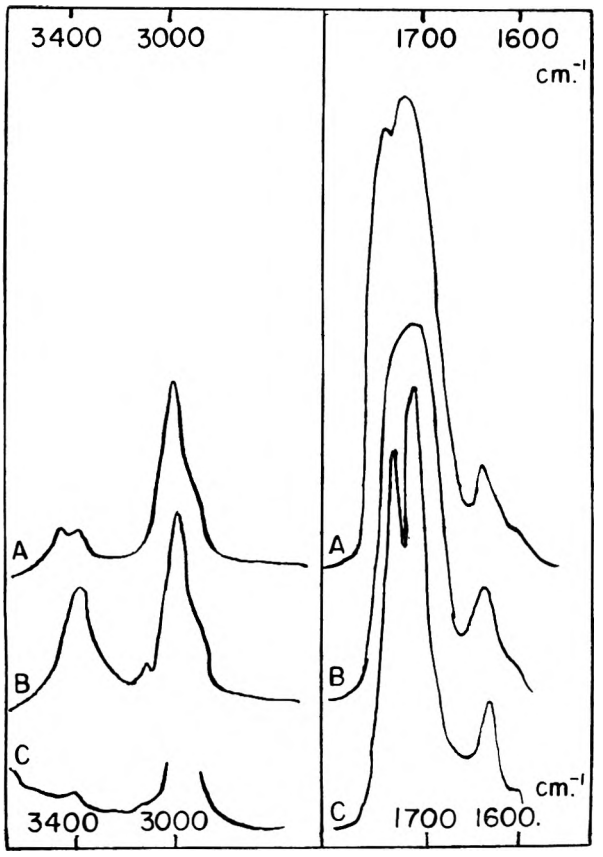


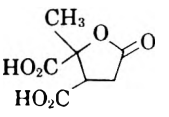
Fig. 2. Methyl obacunoate: A, in $CHCl_3$. B. Solid film. C, Nujol mull

form or acetone showed a marked hydroxyl band (Fig. 2) which persisted when care was taken to exclude moisture and alcohol and is, therefore, positive evidence for the existence of an unreactive hydroxyl group. No other compound examined in this work behaved thus, but a somewhat similar phenomenon has been observed with tetronic[13] acids in which the degree of enolization and consequently the existence of hydroxyl or carbonyl groups depended upon the physical state of the sample. This explanation was apparently not applicable because methyl obacunoate did not have the requisite properties in the ultraviolet region, was not acidic, could not be oximated readily, and gave no ferric reaction. Further, had nomilin contained a lactonic system of type (III), hydrolysis would have yielded a keto-acid rather than a hydroxy-acid, but the parent compound must have exhibited absorption at 1770–1790 cm.$^{-1}$ which was not apparent. Finally, lactones of type (III) react readily with aniline[14] whereas obacunone was recovered from treatment with this reagent.

Hydrogenation of nomilin was erratic unless large amounts of catalyst were employed, but in the best runs exactly four equivalents of hydrogen were absorbed. The product, hexahydronomilinic acid, $C_{28}H_{42}O_9$, was a monobasic acid of pK_a value 2.7, which appeared to have resulted from hydrogenolysis of a lactone ring not involved in hydrolysis since obacunoic acid had a pK_a value of 4.0. With diazomethane, the new acid gave a methyl ester spectroscopically devoid of hydroxyl groups but possessing a carbonyl group responsible for a shoulder at 1700 cm.$^{-1}$ on the ester band (Fig. 1). It was concluded that the four moles of hydrogen were used to open one lactone ring and saturate three double bonds since hexahydronomilinic acid could not be hydrogenated further and, unlike nomilin, gave no yellow color with tetranitromethane and had very little end-absorption at 210 mμ. It followed that nomilin contained but one carbocyclic system.

The absence of double bonds from hexahydronomilinic acid made it necessary to suppose that the high acidity was due to the inductive effect of substituents at the α-position. Pyruvic acid having[15] a pK_a value of 2.5, nomilin and its derivatives were first examined for α-ketoacid functions, but obacunone would not react with *o*-phenylenediamine under conditions in which pyruvates furnish quinoxalones. It has been reported[16] that pyruvates have only unresolved ester absorption at 1745 cm.$^{-1}$, whereas the carbonyl frequency is resolved in some compounds of the present series, and nomilinic acid was recovered from treatment of its salts with aqueous hydrogen peroxide.

The dissociation data given by Paul[17] for α-acetoxypropionic acid (pK_a 3.0) and by Walden[18] for the acid (IV) (pK_a 2.18) suggested that the acidity of hexahydronomilinic acid could have resulted from the groupings (V), found for example, in scilliroside,[19] or (VI) as in monocrotalic acid.[20]



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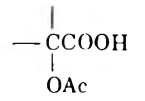
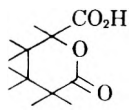
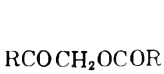


V

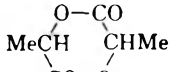


VI

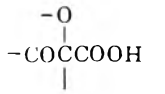


VII

VIII



IX



X

(13) L. A. Duncanson, *J. Chem. Soc.*, 1207 (1953).

(14) F. A. Kuehl, Jr., R. P. Linstead, and B. A. Orkin, *J. Chem. Soc.*, 2213 (1950).

(15) J. Boeseken, L. W. Hanson, and S. H. Bertram, *Rec. trav. chim.*, **35**, 309 (1915).

(16) References and a discussion of the spectra of coumarandiones are given by J. F. Grove, *J. Chem. Soc.*, 883 (1951).

(17) T. Paul, *Z. Elektrochem.*, **28**, 435 (1922).

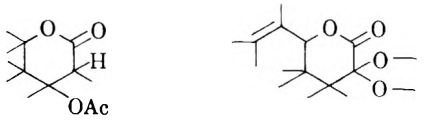
(18) P. Walden, *Zeit. phys. Chem.*, **10**, 563, 638 (1892).

(19) A. Stoll and J. Renz, *Helv. Chim. Acta*, **25**, 377 (1942).

(20) R. Adams and T. R. Govindachari, *J. Am. Chem. Soc.*, **72**, 158 (1950).

The complex hydrogenation of obacunone was accomplished by methanolysis and gave an acid now called methyl hydrogen octahydroobacunoninate since it was more easily obtainable by the comparatively smooth hydrogenation of methyl obacunoate in which nearly five moles of hydrogen were absorbed. The new acid had pK_a 2.9 for which neither system (V) nor system (VI) could be responsible. Systems (V) and (VI) are similar to α-acyloxyketones (VII) in which considerable shifts to shorter wave lengths of both carbonyl and ester frequencies occur,[21] but we found that the corresponding shift in ethyl α-acetoxypropionate (VIII) was relatively slight and similar to that in mesodilactide[22] (IX). This shift resulted in peaks at 1736 cm.$^{-1}$ in chloroform and 1767 cm.$^{-1}$ in carbon tetrachloride, but the appropriate derivatives of nomilin were hardly soluble in the latter solvent and so this shift could not be used as a criterion in the present example.

The possibility that the acidity of hexahydronomilinic acid was partly caused by a carbonyl group in the β-position was considered improbable because properties in keeping with β-ketoester and β-ketoacid systems were not apparent. For example, hexahydronomilinic acid did not readily lose carbon dioxide until decomposition set in at temperature greater than 220°. The presence of a malonic acid grouping was also discounted because this would have required the carboxyl groups of both hexahydronomilinic acid and obacunoic acid to have closely similar properties. Further, prominent shifts to shorter wavelengths are often shown by dilactones and related compounds with both carboxyl groups attached to the same carbon atom.[23] The composite system (X), in which combined inductive effects of carbonyl and of ether oxygen could have accounted satisfactorily for the acidity of the carboxyl group, was eliminated from further consideration because of the argument presented above and because these compounds had only very feeble reducing powers. Because methoxyacetic acid[24] has a pK_a value of 3.53 compared with 4.74 for acetic acid; two ether oxygen atoms would have an effect of the obscured magnitude, and it was confirmed that ethyl diethoxyacetate has a normal ester frequency at 1749 cm.$^{-1}$ Published data on the glycidic acid grouping are limited but it seemed unlikely that this system would survive prolonged hydrogenation, and consideration of data supplied by Kilpatrick and Morse,[25] by Wode,[26] and by Apichandari and Jatkar[27] suggested that incorporation of the α-oxygen atom in a three-membered ring would not have any marked effect on the acidity.[27a] Therefore the lactone rings of nomilin were provisionally written as in the diagram, which makes it clear that the lactone ring (called lactone 1) which becomes unsaturated in obacunone must also be that involved in the hydrolysis to obacunoic acid. The double bond attached to lactone 2 was required to account for the hydrogenolysis of this system.



Lactone 1 Lactone 2

Lactone Rings of Nomilin

A study of the intensities of carbonyl absorption in the 6μ region substantiated the conclusions reached above. As we were not aware of any published study of the intensities of lactonic absorption, we first made measurements on a few lactones typical of various types and collected the results into Table II; whereas Table III was adapted chiefly from values given by Jones, Ramsay, Kier, and Dobriner[28] for ketones and simple esters, except that the provisional nature of the present work made it unnecessary to include the minor variations detailed by these authors. Comparison of Tables II and III showed that those environmental changes which affect ketonic carbonyl affect ester carbonyl similarly. Thus the inclusion of either type of carbonyl group in a ring-system increased the intensity (the size of the ring being comparatively unimportant), and conjugation also increased the

TABLE II

INTENSITIES[a] OF LACTONE CARBONYL ABSORPTIONS

	1×10^{-4}	Mean
γ-Valerolactone	4.12	
Dihydrocoumarin	3.84	3.92
Δ^2-Angelicalactone	3.88	
Santonin (at 1775 cm.$^{-1}$)	3.82	
Δ^1-Angelicalactone	5.28	
Coumarin	5.42	5.35
Ethyl cinnamate	3.83	

[a] Determined in chloroform by method III, Ref. 28.

(21) R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, 72, 956 (1950); R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 2820 (1952); J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(22) H. H. Wasserman and H. E. Zimmerman, *J. Am. Chem. Soc.*, 72, 5787 (1950).

(23) References and examples are quoted by D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 142 (1956).

(24) M. H. Palomaa, *Ann. Acad. Sci. Fennicae*, A, 1, (1911); *Chem. Zent.*, II, 596 (1912).

(25) M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, 75, 1846, 1854 (1953).

(26) G. Wode, *Svensk. kem. Tidsk.*, 40, 221 (1928).

(27) C. T. Apichandari and S. K. K. Jatkar, *J. Indian Inst. Sci.*, 21a, 373 (1938).

(27a) Since glycidic acids (e.g. phenylglycidic acid) have now been found to have pK_a values near 3.6 in water and near 4.4 in aqueous acetone, these acids are less affected by solvent changes than benzoic acid. Consequently a glycidic acid system is still possible in the present series.

(28) R. N. Jones, D. A. Ramsay, D. S. Kier, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 80 (1952).

intensity to some extent. Much the greatest increase resulted, however, when the carbonyl groups were simultaneously part of a ring system and conjugated with a double bond, thus permitting the easy differentiation of these structural types from others with similar ultraviolet spectra.

TABLE III

INTENSITIES[a] OF CARBONYL ABSORPTION OF KETONES AND ESTERS

	1×10^{-4}
Acyclic ketones	1.8
Cyclic ketones	
(i) 7-, 11- or 12-ketosteroids	2.2
(ii) 3-, 16- or 17-ketosteroids	2.7
Cyclic $\Delta^{\alpha,\beta}$-ketones	3.7
Cyclic $\Delta^{\beta,\gamma}$-ketones	2.9
Alkyl acetates	3.2
Aryl acetates	2.8
Methyl esters	3.1
1-Acetylcyclohexene[b]	2.04

[a] Adapted from values given in Ref. 28. [b] Determined in present work.

had opened. Finally, the result for α-obacunol was compatible with the reduction of a carbonyl group but not with the reduction of a lactone group.

As mentioned earlier, the results of hydrogenation showed that nomilin contained three relatively unreactive double bonds but both ultraviolet and infrared spectra were incompatible with the presence of a benzene ring. The fourth double bond of obacunone was more reactive and limited hydrogenation produced dihydroobacunone which had no significant absorption at 1620 cm.$^{-1}$, had a much reduced absorption below 220 mμ (Table I), and a carbonyl intensity which agreed with saturation of the lactone ring. When conducted in methanol, a similar hydrogenation gave a product which retained the solvent strongly in addition to two extra hydrogen atoms and had hydroxylic absorption near 3 μ; this compound may be the corresponding methyl dihydroobacunoate. Saturation of the lactone ring of obacunone resulted in the expected hypsochromic shift of the corresponding band so that the two lactone rings of dihydro-

TABLE IV

INTENSITIES OF CARBONYL ABSORPTION OF COMPOUNDS RELATED TO NOMILIN

	Lactone	$\Delta^{\alpha,\beta}$-Lactone	Methyl Ester	Acetate	Ketone	Calc.	Found
Nomilin	2×3.9			3.2	2.2	13.2	13.1
Obacunone	3.9	5.4			2.2	11.5	11.3
Methyl obacunoate	3.9		3.8[a]		2.2	9.9	9.8
Methyl hexahydronomilinate	3.9		3.1	3.2	2.2	12.4	11.8
α-Obacunol	3.9	5.4				9.3	9.0
Dihydroobacunone	2×3.9				2.2	10.0	9.6

[a] α,β-Unsaturated ester: intensity estimated from data in Ref. 5.

The values in Tables II and III were then used to calculate intensities for the compounds discussed above, it being assumed that no serious interactions were affecting the contributions of the various groups. In the absence of information as to the environment of the carbonyl group, the intermediate value 2.2 was employed. The intensities calculated in this way agreed sufficiently well with the experimental values (Table III) to indicate that there were no further carbonyl groups to be detected, that is, that the two uncharacterized oxygen atoms of nomilin or obacunone formed ether links only. Again, had elimination of acetic acid from nomilin *not* introduced conjugated unsaturation, the calculated intensity for obacunone would have been 9.8, a much less satisfactory figure than that tabulated. The agreement between the calculated and observed figures for methyl obacunoate clearly opposed formulation of the hydrolysis as either the change of (I) into (II) (which requires the product to have an intensity greater than 11.3) or the opening of a lactone ring type (III) (which requires the product to have an intensity of at least 11.0): the observed intensity also indicated that an unsaturated rather than a saturated ring

obacunone now had (unresolved) absorption at 1735 cm.$^{-1}$, whereas a weaker, but sharp and distinctive, band at 1710 cm.$^{-1}$ could confidently be ascribed to the carbonyl group. The spectrum of dimethyl octahydroobacunoninate, a glassy ester obtained from methyl hydrogen octahydroobacunoninate by means of diazomethane, confirmed this and other conclusions, since it showed a carbonyl band at 1711 cm.$^{-1}$, two resolved ester bands at 1754 and 1733 cm.$^{-1}$, and a marked band near 3μ which can be attributed to the hydroxyl group difficult to detect in methyl obacunoate.

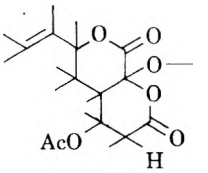
Obacunone added hydrogen chloride in conditions under which nomilin was inert; again the absence of a band at 1620 cm.$^{-1}$ and the reduced ultraviolet end-absorption showed that the lactonic double bond had been affected. With pyridine, obacunone hydrochloride readily regenerated obacunone. The results of perbenzoic acid titrations were curious, because nomilin could not be recovered in spite of the fact that no active oxygen had been destroyed. Obacunone did absorb one atom of active oxygen but failed to yield a crystalline product.

Comparisons between the infrared spectra of

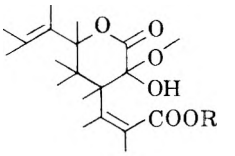
nomilin, methyl hexahydronomilinate, obacunone, and dimethyl octahydroobacunoninate showed that peaks at 3100, 1600, 1500 (all weak), 1050, 875, and 805 cm.$^{-1}$ (all strong) were absent from the spectra of the saturated compounds. This behaviour is similar to that of the terpenoid furans, marrubin[29] and columbin[30] and is therefore attributed to a furan ring, which also accounts for the red and violet colors developed by nomilin and its derivatives (except, of course, hexahydronomilinic acid and methyl hydrogen octahydroobacunoninate) with mineral acids, especially hydrobromic acid (compare cafestol[31]) and for the reaction with perbenzoic acid because with peracids furans often give products which are themselves peroxidic.[32] Although cyclopropanes[33] possess several of the infrared bands listed for furans, and, when suitably placed, can be hydrogenolyzed[34] without difficulty, they are not attacked by ozone whereas obacunone is.

Ozonolysis of obacunone was slow, and no volatile carbonyl compounds were formed, although some carbon dioxide resulted. The product, $C_{26}H_{32}O_8$, contained one methoxyl group derived from solvent methanol and had therefore been formed by loss of but one carbon atom from obacunone. Destruction of the furan ring was clear from the ultraviolet spectrum which lacked the end-absorption of nomilin, from the infrared spectrum which lacked all the characteristic peaks noted above, and from the negative color reaction with hydrobromic acid. The infrared spectrum of this ozonolysis product included peaks at 1725 and 1698 cm.$^{-1}$ and also new peaks at 1678 and 1646 cm.$^{-1}$ suggesting the presence of an α,β-unsaturated ketone: the corresponding ultraviolet absorption occurred at 244 mμ, and the compound gave a positive Zimmerman reaction. Although the new substance was neutral and gave no ferric reaction, it neutralized three equivalents of base upon hydrolysis indicating that a new (potential) acidic center had been generated. No crystalline material has been obtained from ozonolysis of nomilin.

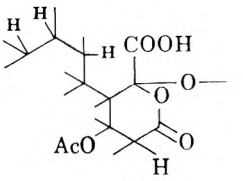
For the inclusion in the characteristic groups of nomilin of a furan ring and a carbonyl group in addition to the two proposed lactone rings, ten oxygen atoms were needed whereas nomilin contained but nine. Re-examination of the analytical data detailed by Emerson and obtained during the present study confirmed the formula proposed originally and ruled out molecules in the $C_{32}O_{10}$ and $C_{31}O_{10}$ ranges. The one way in which the functional groups of nomilin could be rewritten with economy of one oxygen atom gave a system type (XII).



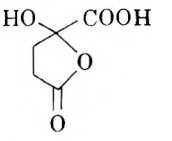
XII



XIII



XIV



XV

From the partial structure (XII) are derived (XIII; R = H) for obacunoic acid, and (XIV) for hexahydronomilinic acid. The double bond of (XII) may, of course, be part of the furan ring. The considerable similarity between limonin and nomilin suggests that the lactonic systems of the two compounds are closely related.

These lactol-type structures also seemed to offer grounds on which the curious behavior of the hydroxyl group of methyl obacunoate (XIV; R = Me) might be explained, because the surrounding oxygen atoms could interfere with the normal oxygen-hydrogen vibrations by bonding with the hydrogen atom. A few lactonic acids type (XV) are known:[35] the stability of the lactone ring and ease with which the hydroxyl group reacted, *e.g.*, in acetylation, depended closely upon the number and nature of the other substituents present. The other oxygen atom of (XIII) is presumably present in a five- or six-membered ring for reasons of stability.

The lactone rings are written as δ-lactones partly because obacunoic acid did not relactonize and partly because in this series lactonic absorption always occurred below 1750 cm.$^{-1}$ This last evidence was not conclusive because lactone frequencies vary considerably with the phase and solvent (an excellent example is given by Djerassi, Farkas, Lemin, Collins, and Walls[36]) and the solubility characteristics of these compounds prevented accurate measurements in carbon disulphide or carbon tetrachloride; however, the poorly defined peaks obtained in these solvents were also situated

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(36) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins, and F. W. Walls, *J. Am. Chem. Soc.*, **76**, 2969 (1954).

below 1750 cm.$^{-1}$ and so we have retained the δ-lactonic formulation.

EXPERIMENTAL

Separation of nomilin and obacunone. The mixture of lactones obtained from citrus seed oil by means of aqueous methanol was fractionated from methylene chloride essentially as described by Emerson[4] to remove limonin, but the procedure advocated by this author for the separation of nomilin and obacunone was less effective. These lactones were adsorbed too strongly on alumina to permit use of this material for chromatographic analysis, but silica gel appeared satisfactory. The crude mixture (5.00 g.) of nomilin and obacunone was chromatographed on a silica gel[37] column (1.6 × 54 cm.) from benzene saturated with water. A yellow band travelled rapidly down the column and was removed; thereafter, obacunone was present in the eluate, the next 650 ml. of which contained the whole of this lactone (2.9 g.). After a second similar purification followed by one crystallization from methanol obacunone formed prisms, m.p. 229–230°, indicating a purity otherwise attainable only by many recrystallizations.

Anal. Calcd. for $C_{26}H_{30}O_7$: C, 68.68; H, 6.66. Found: C, 68.86; H, 6.71.

Nomilin (0.9 g., m.p. 254°) was eluted from the column by the use of 10% ethyl acetate in benzene (400 ml.), and after several recrystallizations from the same solvent the best specimens had m.p. 270° (decomp.). For analysis a specimen was dried at 100° at 0.001 mm. for 4 hr.

Anal. Calcd. for $C_{28}H_{34}O_9$: C, 65.33; H, 6.67; equiv. wt. (3 acid functions) 171.3. Found: C, 65.39; H, 6.76; equiv. wt. (back titration) 173.

Gummy material (0.9 g.) remaining on the column could be eluted with acetone or alcohol but was not examined further.

Obacunone with Brady's reagent gave an amorphous yellow precipitate after several hours at room temperature. When heated to boiling, a solution of obacunone in acetic acid containing a few drops of constant-boiling hydrogen bromide soon developed a mauve color. No color appeared when anhydrous hydrogen bromide in acetic acid or hydriodic acid were used; hydrochloric acid gave unreliable results. Negative reactions resulted with Tollen's, Fehling's, and Légal's reagents.

Nomilin gave a purple color in the hydrogen bromide reaction, and did not react with Tollen's, Fehling's, or Légal's reagent.

Conversion of nomilin into obacunone. Nomilin (0.4 g.) in boiling pyridine (15 ml.) was unchanged after 6 hr. Addition of a drop of water, pyridine hydrochloride (0.1 g.), or acetic anhydride (0.5 m.) had no effect, but when the smallest possible volume of pyridine was employed the reaction occurred occasionally.

Nomilin (0.4 g.) in boiling γ-picoline (20 ml.) was converted after 1 hr. into obacunone (0.29 g.) which remained after removal of the solvent *in vacuo* and when purified from methanol formed prisms, m.p. 226–228°, not depressed by authentic material.

Nomilin (0.4 g.) was recovered intact from 6 hr. heating in boiling xylene (60 ml.) and then had m.p. and mixed m.p. 265° (decomp.).

Attempted condensation of obacunone with amines. Obacunone (150 mg.) was kept at 145–155° in aniline (1 ml.) for 30 min. The yellowish product was added to dilute hydrochloric acid and the precipitate, when purified from methanol, gave obacunone in prisms (100 mg.) m.p. and mixed m.p. 226°.

A similar experiment in which *o*-phenylenediamine hydrochloride (100 mg.) in pyridine (2 ml.) replaced aniline, and the time of reaction was 2 hr., gave a similar result.

Obacunoic acid. This acid was readily prepared by the method of Emerson[4] and crystallized from aqueous acetone in needles (0.34 g.), m.p. 213° with but little decomposition. The acid had no ferric reaction in alcohol and did not react with diazotized *p*-nitraniline. For analysis, the substance was dried to constant weight at 110°/0.001 mm.

Anal. Calcd. for $C_{26}H_{32}O_9$: C, 63.93; H, 7.23. Found: C, 63.77; H, 7.01.

Potentiometric titration at 23° in 50% acetone showed obacunoic acid to be monobasic with pK_a 5.26. In the same conditions, the pK_a value of benzoic acid was 1.29 units greater than in water, therefore pK_a (water) for obacunoic acid was taken as 3.97.

The methyl ester was prepared according to Emerson[4] and formed prisms, m.p. 172–173°, from methanol; α_D^{23} −95.9° (1 dm., 0.4663 g. per 10 ml. in acetone).

Anal. Calcd. for $C_{27}H_{34}O_9$: C, 66.67; H, 7.05. Found: C, 66.38; H, 7.08.

Attempted acetylation of methyl obacunoate. Methyl obacunoate (80 mg.), acetic anhydride (0.6 ml.), and pyridine (1 drop) were kept on the steam bath for 15 min. Addition of water (3 ml.) to the cold solution caused almost quantitative separation of methyl obacunoate m.p. and mixed m.p. 171°.

Methyl obacunoate (80 mg.) was kept in boiling acetic anhydride (1 ml.) containing sodium acetate (200 mg.) for 1 hr. Vacuum evaporation of acetic anhydride and dissolution of sodium acetate in water left a gum which did not yield to attempted crystallization or chromatographic separation on alumina.

Obacunone hydrochloride. Hydrogen chloride was slowly bubbled through a solution of obacunone (0.50 g.) in chloroform (5 ml.); after about 4 hr. the mixture solidified. The solvent was pumped off and replaced by fresh chloroform (5 ml.) which was then also pumped off. Crystallized from a mixture of Skellysolve B and ethyl acetate, the residue supplied obacunone hydrochloride in colorless leaflets (0.29 g.) which decomposed near 230°. This substance in 50% aqueous acetone containing dilute nitric acid gave no precipitate with silver nitrate: for analysis, it was dried at 100° at 0.01 mm. for 3 hr.

Anal. Calcd. for $C_{26}H_{31}ClO_7$: C, 63.61; H, 6.37; Cl, 7.23. Found: C, 63.90; H, 6.45; Cl, 7.47, 7.20.

In paraffin mulls, obacunone hydrochloride absorbed at 3100 (CH of olefin), 1725 (shoulder at 1740) (lactones), 1500 and 875 cm.$^{-1}$ (furan ring). There was no peak at 1620 cm.$^{-1}$

A solution of obacunone hydrochloride (0.20 g.) in pyridine (1.0 ml.) was kept at boiling point for 1 hr., after which the solvent was removed *in vacuo*. The residue was washed with a little cold methanol and then crystallized from the same solvent giving obacunone in prisms (0.12 g.) m.p. and mixed m.p. 229°. The methanol washings gave a positive reaction for chloride ions.

Nomilin (0.5 g.) in chloroform (10 ml.) was unaffected by hydrogen chloride during 3 hr. The recovered material had m.p. and mixed m.p. 275° (decomposition) and its infrared spectrum (mull) was identical with that of an authentic specimen.

α- and β-Obacunols. To obacunone (0.50 g.) in methanol (30 ml.) was added potassium borohydride (50 mg.) in a few drops of water. The crystalline precipitate which readily appeared (2–5 min.) was collected as soon as possible (since it began to redissolve when kept) and fractionally crystallized from ethyl acetate containing a little light petroleum (b.p. 60–80°). The earlier crops were purified from ethyl acetate giving α-obacunol in granules (0.18 g.) melting at 248° when slowly heated. This substance appeared to have a transition point at about 180°, at which temperature it melted when heated rapidly. The specimens for analysis were dried at 150°/0.01 mm. for 4 hr. The substance had $[\alpha]_D^{20}$ +84° (c, 0.3002 in acetone; 1 dm.).

(37) 200–300 Mesh; supplied by L. Light and Company, Ltd., Colnbrook, England.

Anal. Calcd. for $C_{26}H_{32}O_7$: C, 68.42; H, 7.08. Found: C, 68.25; H, 7.22.

The infrared spectrum of a solid film included peaks at 3500 (OH), 3100 (CH of olefin), 1730 and 1685 (lactonic absorption), 1625 (C=C), 1500 and 875 cm.$^{-1}$ (furan).

α-Obacunol (0.20 g.) dissolved in hot acetic anhydride (10 ml.) containing sodium acetate (0.50 g.) was kept on the steam bath for an hour. Removal of volatile material and addition of water to the residual glass gave an opaque semi-solid mass which was purified from aqueous methanol giving α-obacunyl acetate in prisms m.p. 216–217°. For analysis, a specimen was dried at 120°/10 mm. for 3 hr.

Anal. Calcd. for $C_{28}H_{34}O_8$: C, 67.46; H, 6.88. Found: C, 67.00; H, 7.02; MeO, negative.

In acid hydrolysis this acetate frothed excessively. After preliminary alkaline hydrolysis, this compound appeared to contain 13.79% acetyl, but α-obacunol under the same conditions gave an apparent acetyl value of 4.79; therefore the true value for the acetate was near 9.00 (calcd. for a nomoacetate, 8.62).

A solid film of this acetate possessed absorption maxima at 3100 (CH of olefin), 1738, 1704 + 1698 (double maxima), 1631 (C=C), 1510 and 875 cm.$^{-1}$ (furan), but no hydroxyl absorption.

From the mother liquors of α-obacunol, thin prisms (0.05 g.) of β-obacunol separated and when repeatedly purified from the same solvent and then from methanol had m.p. 242–244°, depressed to 218° by α-obacunol, and $[\alpha]_D^{20}$ +72° (c, 0.2211 in acetone; 1 dm.). For analysis, the substance was dried at 130°/0.01 mm. for 3 hr.

Anal. Calcd. for $C_{28}H_{34}O_8$: C, 68.42; H, 7.08. Found: C, 68.36; H, 7.25; MeO, negative.

In Nujol, β-obacunol had peaks at 3500 (OH), 3100 (CH of olefin), 1730 and 1692 (lactone rings), 1634 (C=C), 1515 and 877 cm.$^{-1}$ (furan). α- and β-Obacunols can most easily be differentiated in Nujol by the strong, single bands shown by α-obacunol at 1124, 1081, 827, and 812 cm.$^{-1}$; at these points β-obacunol has weaker bands at 1144 and 1116, 1068 and 1059, and 818 and 799 cm.$^{-1}$

Whereas α- and β-obacunols give only brownish colors in the hydrobromic acid test, the mother liquors gave an intense violet reaction developing rapidly even in the cold and therefore contained a third substance which has not yet been isolated. Acetylation of β-obacunol by the method successful with α-obacunol failed to give a characteristic product.

α-Obacunol (0.10 g.) in methanol (2.0 ml.) and pyridine (1.0 ml.) containing hydroxylamine hydrochloride (0.10 g.) was heated to boiling for 4 hr. Removal of volatile matter and crystallization of the product from methanol containing a drop of dilute hydrochloric acid supplied long thin prisms, which, when dried to constant weight at 110°/0.01 mm., melted over a range of about 210–240°.

Anal. Calcd. for $C_{23}H_{33}NO_8$: N, 2.97. Found: N, 1.28.

To α-obacunol (0.20 g.) in acetone (2 ml.), 0.5*N* sodium hydroxide (20 ml.) was added. When warmed, the precipitate rapidly dissolved and did not separate in the cold. Addition of dilute hydrochloric acid liberated a curdy solid which at first was soluble in aqueous sodium bicarbonate but gradually lost this property when kept. It could not be crystallized, and gave no crystalline fraction when attempts were made to purify it from ethyl acetate on a silicic acid column.

α-Obacunol (0.27 g.), in a mixture of toluene (25 ml.) and cyclohexanone (3.0 ml.) from which 10 ml. of distillate had been collected, was treated under reflux with aluminium *tert*-butoxide (0.30 g.) for 25 hr. after which the solvents were removed under vacuum and the yellowish residue was washed in chloroform with Rochelle salt in water. This treatment did not remove all the aluminum, therefore the chloroform was pumped off and the residue was precipitated from its solution in methanol by dilute hydrochloric acid. Traces of cyclohexanone were removed by precipitating the product from its solution in ethyl acetate with light petroleum. The product then crystallized from methanol giving long prisms (0.18 g.) m.p. 248° not depressed by authentic α-obacunol.

Borohydride reduction of methyl obacunoate. This ester (0.70 g.) in methanol (15 ml.) was treated with potassium borohydride (50 mg.) in water (1.0 ml.) for 3 min. No precipitate appeared; the mixture was diluted with water and the product was extracted with chloroform, dried (Na_2SO_4) and on evaporation of the solvent formed a faintly yellow gum which gave the prompt, intense violet hydrobromic acid color test characteristic of the crude reduction product of obacunone. This gum resisted crystallization and attempts to purify it on silica from chloroform (which eluted nothing) or chloroform containing up to 10% ethyl acetate (which eluted all the material as one band). For analysis, which showed at least that the methyl ester group was intact, the gum was dried at 150°/10 mm. for 1 hr.

Anal. Calcd. for $C_{27}H_{36}O_8$: C, 66.39; H, 7.44; MeO, 6.35. Found: C, 65.67; H, 7.58; MeO, 6.82.

A similar reduction was carried out with obacunoic acid. The product, an amorphous solid, also gave an intense purple color with hydrobromic acid in acetic acid, but could not be purified.

Dihydro-obacunone. Obacunone (484 mg.) dissolved in acetic acid (20 ml.), was shaken in an atmosphere of hydrogen (at 23°; 754 mm.) with 10% palladium-on-carbon (0.5 g.). Reaction was slow and a plot of uptake against time showed no clear break. Hydrogenation was interrupted when the absorption reached the theoretical value for one double bond (*ca.* 26 ml.): removal of the catalyst and solvent left a gum which solidified in contact with methanol and after several recrystallizations from this solvent gave dihydroobacunone in small granular prisms (40 mg.), m.p. 183°, with a brownish-purple color reaction in the hydrobromic acid test. For analysis a specimen was dried at 100°/0.001 mm. for 2 hr.

Anal. Calcd. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.06. Found: C, 68.68; H, 7.21.

In Nujol, this compound absorbed at 3100 (CH of olefin); 1735 with shoulder at 1750 (lactone rings), 1710 (C=O), 1500 and 875 cm.$^{-1}$ (furan).

Methyl dihydroobacunoate. Absorption of hydrogen by obacunone (484 mg.) in methanol (70 ml.) containing 10% palladium-on-charcoal (0.5 g.) was stopped at 30 ml. and the catalyst and solvent were removed leaving a gum which was dissolved in benzene and placed on a column of alumina (1 cm. × 15 cm.). Elution with 10% ethyl acetate in benzene removed no significant material, but ethyl acetate eluted a gum which crystallized from methanol in prisms (30 mg.), m.p. 145°. This substance, methyl dihydroobacunoate, was also obtained from the crude hydrogenation product by repeated extraction with Skellysolve B containing a little benzene followed by concentration of the extracts and crystallization of the residue from methanol. It gave a bluish-purple color in the hydrobromic acid test and had an ultraviolet spectrum almost identical with that of dihydroobacunone. The analytical specimen was dried to constant weight at 100° at 0.001 mm.

Anal. Calcd. for $C_{27}H_{36}O_8$: C, 66.38; H, 7.43; MeO, 6.35. Found: C, 66.68; H, 7.62; MeO, 6.12.

In Nujol, this ester had absorption bands at 3500 (OH), 1730 and 1712 (lactones and C=O), 1500 and 875 cm.$^{-1}$ (furan).

Methyl hydrogen octahydroobacunoninate. (*a*) Obacunone (0.5 g.) in acetic acid (15 ml.) containing 1% palladium-on-alumina (0.5 g.) was shaken under hydrogen until the maximum absorption (113 ml.) was observed (about 6 hrs.). The residue from the filtered and evaporated solution was partly soluble in aqueous sodium hydrogen carbonate. Regained by acidification of the solution with 2*N* sulphuric acid, methyl hydrogen octahydroobacunoninate crystallized from methanol in sheaves of needles (130 mg.) which melted at 175–177° with evolution of gas but no charring. For analysis, a specimen was dried at 120°/15 mm. for 3 hr.

Anal. Calcd. for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93; MeO, 6.25;

equiv. wt. (1 carboxyl), 496. Found: C, 65.15; H, 8.62; MeO, 6.23; equiv. wt. (titration with 0.01*N* NaOH), 464.

(*b*) In the presence of 1% palladium-on-alumina (1 g.), methyl obacunoate (0.50 g.) in acetic acid (15 ml.) absorbed 116 ml. of hydrogen (calcd. for 5 double bonds, 125 ml.) in 2 hr. The gum left after filtration and evaporation of the solvent was almost entirely soluble in sodium bicarbonate solutions and when purified from methanol had m.p. 175–177° (with gas evolution). Losses during recrystallization were considerable; the yield of pure material was approximately 290 mg. at best. The substance was identified as methyl hydrogen octahydroobacunoninate by infrared spectral comparison of dried material. It did not react easily with 2,4-dinitrophenylhydrazine sulfate and gave a weak red color in the hydrobromic acid test.

Potentiometric titration in 50% aqueous acetone showed one inflection only and gave pK_a 4.13. In the same circumstances, benzoic acid suffered a solvent shift of 1.24 units. Methyl hydrogen octahydroobacunoninic acid in water therefore has pK_a 2.89.

Dimethyl octahydroobacunoninate was obtained as a clear glass by interaction of the foregoing acid in ether with diazomethane. When a solution in ether was allowed to evaporate slowly, prisms losing solvent and melting near 80° resulted, and as no conventional crystallization procedure was successful, this operation was repeated several times to purify the substance. Further purification was effected from benzene on a silica column, when a little gum was removed. The main fraction, which appeared when 10% ethyl acetate in benzene was the eluent, was still uncrystallizable, and was therefore dried at 150°/15 mm. for 2 hr. for analysis. In acetone it had $[\alpha]_D^{24.5}$ +128 (c, 0.07336; 1/2 dm. tube).

Anal. Calcd. for $C_{26}H_{46}O_8$: C, 65.86; H, 9.08; MeO, 12.16. Found: C, 66.21; H, 9.30; MeO, 12.57.

The infrared spectrum of this ester had absorption maxima at 3500 (OH), 1754 and 1733 (lactones), and 1711 cm.$^{-1}$ (C=O). There were no peaks at 3100, 1500, or 875 cm.$^{-1}$.

Hexahydronomilinic acid. Shaken under hydrogen with 5% palladium-on-charcoal (1.0 g.), nomilin (0.50 g.) in acetic acid (15 ml.) absorbed 103 ml. in 3 hr. (theory for 4 double bonds, 105 ml.). Isolated in the usual way, hexahydronomilinic acid separated from methanol in thin rectangular plates (0.36 g.) melting at 223° with evolution of gas (carbon dioxide was indicated by a positive test with baryta) but without charring. This acid was readily soluble in aqueous sodium hydrogen carbonate, gave no color in the hydrobromic acid test, and no color with tetranitromethane. It retained methanol of crystallization strongly. For analysis a sample was dried at 110°/0.001 mm. for 3 hr.

Anal. Calcd. for $C_{28}H_{42}O_9 \cdot MeOH$: C, 62.80; H, 8.36; MeO, 5.60; equiv. wt. (one carboxyl) 554. Found: C, 63.00; H, 8.67; MeO, 5.69; equiv. wt. 546 (titration with 0.01*N* NaOH).

After being dried at 150°/0.01 mm. for 10 hr. this acid gave a negative result in the Zeisel determination but still had m.p. 223° and when recrystallized from methanol took up this solvent once more giving material indistinguishable from the analytical specimen.

In potentiometric titration in 50% acetone, hexahydronomilinic acid behaved as a monobasic acid pK_a 3.92. In the same conditions, the solvent correction for benzoic acid from 50% acetone to pure water was −1.30, therefore hexahydronomilinic acid had pK_a (water) 2.62.

A solution of hexahydronomilinic acid (327 mg.) in aqueous sodium hydrogen carbonate (10 ml.) was kept at 0°. Ten minutes after the addition of 2.8% hydrogen peroxide (1.5 ml.) the solution was acidified with 2*N* sulfuric acid and the precipitate, when crystallized from methanol, gave prisms (280 mg.) m.p. 205° (decomposition). A second crystallization gave pure hexahydronomilinic acid identified by its infrared spectrum and melting characteristics.

Methyl hexahydronomilinate. The rapid reaction between hexahydronomilinic acid in acetone and diazomethane in ether gave methyl hexahydronomilinate; isolated by evaporation of the solvents and purified from methanol, this ester formed plates melting at 222° without decomposition and having in acetone $[\alpha]_D^{23}$ +74° (c, 1.1868, 1/2 dm. tube). For analysis, a sample was dried at 110°/0.01 mm. for 3 hr.

Anal. Calcd. for $C_{29}H_{44}O_9$: C, 64.92; H, 8.29. Found: C, 65.14; H, 8.11.

As a solid film, this compound had peaks at 1725 with shoulder at 1740 (lactone rings and acetate), and 1700 cm.$^{-1}$ (ill-resolved) (C=O). There were no bands at 3500, 3100, 1500, or 875 cm.$^{-1}$

Ozonolysis of obacunone. Ozonized oxygen was passed into a solution of obacunone (2.0 g.) in ethyl acetate (100 ml.) at 20°. After 45 min. obacunone could no longer be detected in the solution and the solvent was removed *in vacuo* leaving a yellowish glass which was powdered under water and left for 12 hr. The mixture gave no reaction with the starch-iodide reagent. A current of air passed through the solution did not affect aqueous 2,4-dinitrophenylhydrazine sulphate but with baryta gave a precipitate which effervesced with dilute acids. The solid ozonolysis product was warmed with methanol but still failed to crystallize: it gave a red ferric reaction, reduced Fehling's solution slowly, and gave an orange (amorphous) precipitate with 2,4-dinitrophenylhydrazine sulphate in aqueous alcohol but no color with hydrogen bromide.

Purification of the crude product dissolved in chloroform was effected with a silica column (1 × 20 cm.). Fourteen fractions (each 200 ml.) were collected, but only the third, fourth, and fifth gave partially crystalline material. This formed colorless prisms m.p. 274° (decomp.) when crystallized from a mixture of methanol and acetone and then methanol. The pure material did not affect Fehling's solution or ferric chloride and was insoluble in cold 2*N* sodium hydroxide.

Anal. Calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83; MeO, 6.57; equiv. wt. (3 carboxyls) 157.2. Found: C, 66.18, 66.19; H, 6.75, 6.88; MeO, 6.87, 6.79; equiv. wt. (back titration), 157.

In ethanol, this compound has λ_{max} 244 mμ (ϵ, 16.1 × 10^3) with a shoulder at 220 mμ (ϵ, 10.4 × 10^3).

Spectra. The majority of the infrared spectra were determined by means of a Perkin-Elmer Spectrophotometer 21B. Intensity measurements were carried out in chloroform solution as in Method III of ref. 28 and with the approximations for polycarbonyl compounds used there. Ultraviolet spectra were determined in ethanol using a Cary recording spectrophotometer.

Analyses. Analyses were determined by Heather King of the University of California, Los Angeles, and by Adam Inglis of the University of Liverpool.

Los Angeles, Calif.

Notes

A department for short papers of immediate interest.

Isolation of Methyl Monohydroperoxido-9-octadecynoate from the Autoxidized Methyl 9-Octadecynoate[1]

N. A. Khan

Received March 23, 1956

Apart from the synthetic preparation of hydroperoxides of acetylenic hydrocarbons,[2] there has not been any record describing the isolation of hydroperoxides from the autoxidized acetylenic compounds. However, it is known that autoxidation of acetylenic compounds does form peroxides[3] whose structures have never been established.

We wish now to report the isolation of methyl hydroperoxide-9-octadecynoate as the sole product from autoxidized methyl stearolate (9-octadecynoate). The peroxide concentrate representing all autoxidized substances were proved to be methyl hydroperoxide-9-octadecynoate through peroxide values, formation of proper hydroxyl derivatives of methyl stearolate and stearate, and finally through polarographic and infrared analyses. The polarographic studies indicated that the peroxide concentrate consists of over 98% hydroperoxide. Fig. 1 shows the results from infrared analyses on the original methyl stearolate, the isolated peroxide concentrate, and the product from $SnCl_2$ reduction, for a range of more lengths: 2.0–6.0 μ. The hydroperoxide bond appeared at 2.95 μ, the hydroxyl band at 2.89 μ, and the band for triple bond at 4.42 μ. The increment in the absorption by the triple bond in the new products may be attributed to the dissymmetry[4] introduced by the hydroperoxide or by the hydroxyl group. Hence, the peroxide concentrate and its reduced product consist of a pure hydroperoxide and a hydroxy compound respectively.

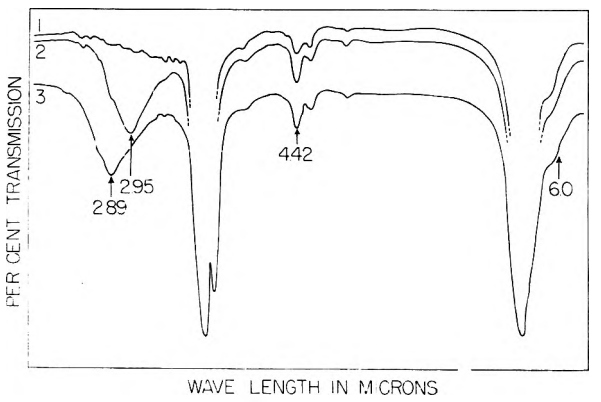

Fig. 1. Infrared absorption spectra: 1. methyl stearolate, 2. peroxide concentrate, 3. reduced peroxide concentrate

The physical and chemical properties of the reduced peroxide concentrate left no doubt as to its identity as methyl monohydroxy-9-octadecynoate.

From these evidences, it may be concluded that methyl stearolate reacts with oxygen and yields monohydroperoxide with the triple bond intact during the initial stages of autoxidation.

EXPERIMENTAL

Autoxidation of methyl 9-octadecynoate. Methyl stearolate (hydrogen absorption value, 1.98 moles/mole) prepared by the method of Khan, *et al.*[5] was autoxidized to 10% peroxide content by bubbling oxygen through a 30% *n*-heptane solution while irradiated by visible light from a 100-watt bulb. The reaction vessel (a three-necked flask fitted with a gas dispersion tube, stirrer, and an outlet connecting a guard tube of anhydrous calcium chloride), was maintained at a constant temperature of 16–17°. *n*-Heptane was freed from the unsaturated substances by the method of Cooper and Melville.[6]

Isolation of methyl monohydroperoxido-9-octadecynoate. The peroxides were quantitatively concentrated by countercurrent extraction,[7] using two immiscible solvents, 87% alcohol and *n*-heptane (each saturated by the other). The peroxide concentrate gave the peroxide value of 6030 m.e./kg. (theoretical value for methyl monohydroperoxido-9-octadecynoate, 6125 milliequivalents/kilogram) and added 2.94 moles H_2 to yield on saponification and subsequent hydrolysis, monohydroxystearic acids (m.p. 75–77.5°;[8] hydroxyl, 1.06 moles/mole). The polarographic studies were conducted by the method of Lewis, *et al.*[9] The infrared spectra were determined in carbon tetrachloride (10% solution), using a Perkin Elmer Model 21 instrument.

Preparation of methyl monohydroxy-9-octadecynoate. The peroxide concentrate was then reduced in alcohol solution (1.0 gm./100 ml.) by agitation with stannous chloride (5 moles $SnCl_2$/mole of peroxide) for 3 hr. with oxygen-free nitrogen. The resulting mixture was diluted with distilled water and then extracted with the peroxide-free ether; the

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(2) N. A. Miles and O. L. Mageli, *J. Am. Chem. Soc.*, **74**, 1471 (1952).

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(6) H. R. Cooper and H. W. Melville, *J. Chem. Soc.*, 1988 (1951).

(7) N. A. Khan, *Pakistan J. Sci. Ind. Research*, **1**, 12 (1957).

(8) S. Bergstrom, *Nature*, **156**, 717 (1945).

(9) W. R. Lewis, F. W. Quackenbush, and T. De Vries, *Anal. Chem.*, **21**, 762 (1949).

ether extract was washed twice with 3% HCl solution, then with distilled water until free of acid, and finally dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the reduced peroxide concentrate consisting of methyl monohydroxy-9-octadecynoate: hydrogen absorption value, 1.96 moles/mole; hydroxyl, 1.02 moles/mole.

Anal. Calcd. for $C_{19}H_{34}O_3$: C, 73.51; H, 10.97. Found: C, 73.42; H, 10.88.

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Reaction of 1,5-Dinitropentane with Methyl Vinyl Ketone

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Michael-type condensations of aliphatic mononitro and *gem*-dinitro compounds with compounds having an activated double bond have been studied by many investigators.[2-4] However, the literature is void of this reaction with α,ω-dinitro compounds.

This communication deals with the reaction of 1,5-dinitropentane and methyl vinyl ketone, in the presence of a sodium hydroxide catalyst. The reaction was carried out in different solvents and under a variety of conditions. In all runs, besides intractable oils, a solid was obtained which analyzed correctly for a di-addition product. The maximum refined yield of 25% resulted when the reaction was carried out in 90% ethanol at 50° for 20 hr.

Two di-addition products might arise from this reaction, the symmetrical adduct I and the unsymmetrical one (Ia).

$$O_2NCH_2(CH_2)_3CH_2NO_2 \xrightarrow[OH^-]{H_2C{=}CHCOCH_3} H_3CCO(CH_2)_2CH(NO_2)(CH_2)_3CH(NO_2)(CH_2)_2COCH_3$$

I

or

$$[H_3CCO(CH_2)_2]_2CNO_2(CH_2)_3CH_2NO_2$$

Ia

Proof that 5,9-dinitro-2,12-tridecanedione (I) had formed was obtained by (1) the Nef[5] reaction, (2) the red-white-and-blue test,[6] (3) infrared spectra, and (4) the bromination product.

The Nef reaction of the disodium salt of I gave in 28% yield a white nitrogen-free solid II, which was unstable to light and air at room temperature. The infrared spectrum of II showed a strong absorption peak at 5.93 μ, characteristic of the carbonyl group and no maxima for nitro groups. Since tertiary nitro groups are not affected in the Nef reaction, structure Ia is eliminated.

$$I \xrightarrow[2.\ H_2SO_4]{1.\ NaOH} CH_3CO(CH_2)_2CO(CH_2)_3CO(CH_2)_2COCH_3$$

II

When II was reacted with semicarbazide a new compound was obtained, the nitrogen analysis of which gave a low value for the expected tetrasemicarbazone and a high value for a disemicarbazone. It is possible that not all of the carbonyl groups in II had reacted, and it is believed that the product obtained constituted a mixture of semicarbazones. Attempts to form an oxime of II yielded only gummy materials. Treatment of II with 2,4-dinitrophenylhydrazine in sulfuric acid yielded the 2,4-dinitrophenylhydrazone of acetone (III) and some unreacted II. It is believed that III arose from the oxidation of II to acetoacetic acid, followed by decarboxylation.

The presence of secondary nitro groups in the addition product I was further confirmed by the blue color which resulted from the red-white-and-blue reaction. The presence of a primary nitro group would have been indicated by a red color, and a tertiary nitro group is not affected by this test.

The infrared spectrum of the di-addition product exhibited absorption maxima for the carbonyl group at 5.88 μ and the nitro group at 6.50 μ (asym. stretching) and 7.39 μ (sym stretching). These findings are also in agreement with structure I, because according to the studies of Brown,[7] a structure such as Ia should show splitting of the nitro bond in the asymmetric stretching vibration.

Additional evidence for I resulted from its bromination in the presence of two or less-than-two equivalents of base. A dibromo compound was obtained in 61% yield, the analysis and infrared spectrum of which agreed with the expected 5,9-dibromo-5,9-dinitro-2,12-tridecanedione (IV). As expected, IV was insoluble in base and gave a negative red-white-and-blue test.[8] Its infrared spectrum showed a maximum at 5.84 μ for the car-

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(5) J. U. Nef, *Ann.*, **280**, 263 (1894).

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(7) J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(8) A referee has suggested that besides structures I and Ia, the compounds $CH_3CO(CH_2)_3CO(CH_2)_2CH(NO_2)(CH_2)_3CH_2NO_2$ (V) and $CH_3COCH(CH_2CH_2COCH_3)CH_2CH(NO_2)(CH_2)_3CH_2NO_2$ (VI), derived from an abnormal Michael addition, should be considered. Although in addition reactions of nitro paraffins to methyl vinyl ketone such self-condensations of the ketone have never been reported in the literature, this possibility cannot be ruled out *a priori*. However, the insolubility of the dibromo derivative IV in base, together with the negative color test, is evidence that IV is not a derivative of V or VI.

bonyl group, and at 6.46 μ (asym. stretching) and 7.32 μ (sym. stretching) for the nitro group.

EXPERIMENTAL

5,9-Dinitro-2,12-tridecanedione. To 0.05 mole (8.10 g.) of 1,5-dinitropentane,[9] 50 ml. of 90% aqueous ethanol, eight drops of 13% methanolic sodium hydroxide, and 0.12 mole (9.90 g.) of 85% methyl vinyl ketone were added with stirring. The reaction mixture was gradually heated and kept at 50 ± 2°, with continuous stirring, for 20 hr., after which it was cooled and acidified to a *p*H of four with *N* hydrochloric acid. The acidified reaction mixture was chilled and the solid that separated out was collected by filtration. The crude product, m.p. 61–72°, weighed 5.15 g. Crude yield, 34%. Careful recrystallization from ethyl acetate gave pure *5,9-dinitro-2,12-tridecanedione*, m.p. 77.5–78.5°, representing 73% by weight of the crude taken for purification. Refined yield, 25%.

Anal. Calcd. for $C_{13}H_{22}N_2O_6$: C, 51.64; H, 7.34; N, 9.21. Found: C, 51.80, 51.88; H, 7.35, 7.50; N, 9.57, 9.63.

The *disemicarbazone* of the refined product was prepared. The derivative melted at 180.0–180.5° (dec.), after one recrystallization from aqueous tetrahydrofuran.

Anal. Calcd. for $C_{15}H_{28}N_8O_6$: C, 43.26; H, 6.78; N, 26.91. Found: C, 43.48, 43.30; H, 6.84, 7.03; N, 26.70, 26.79.

2,5,9,12-Tridecanetetrone (II). A solution of 2.7 g. (approximately 27 mmoles) of sulfuric acid in ten ml. of water was cooled down to 0–5° with an ice bath. The solution of the disodium salt, previously prepared by allowing a mixture of 0.9 g. (3 mmoles) of 5,9-dinitro-2,12-tridecanedione, 20 ml. of methanol, 10 ml. of water, and 9.0 ml. of 2*N* methanolic sodium hydroxide (approximately 18 mmoles of sodium hydroxide) to stand 1.5 hr., was added to the acid solution, with stirring, over a 15-min. period. The mixture was chilled and filtered to give the first crop of solid, which was 0.6 g. of sodium sulfate. The liquor was evaporated, rechilled, and filtered to yield a second crop of solid, which was the crude product weighing 0.2 g. (28%). Recrystallization from aqueous ethanol gave *2,5,9,12-tridecanetetrone*, m.p. 106–107° (dec.). The compound was unstable to light and air at room temperature.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.95, 65.02; H, 8.43, 8.46.

Reaction of II *with semicarbazide.* By following the procedure of Shriner, Fuson, and Curtin[10] and employing 0.5 g. of II, 0.1 g. of a solid was obtained which after several recrystallizations from aq. ethanol melted at 211–214° (dec.).

Anal. Calcd. for $C_{17}H_{32}N_{12}O_4$ (tetrasemicarbazone): N, 35.88; for $C_{15}H_{26}N_6O_4$ (disemicarbazone): N, 23.71. Found: N, 26.50, 26.71.

Reaction of II *with 2,4-dinitrophenylhydrazine.* The procedure of Shriner, Fuson, and Curtin[10] was followed. The reaction mixture was filtered and the solid, after several recrystallizations from aq. ethanol melted at 125.5–126.5°. It was identified as the semicarbazone of acetone. A mixed melting point determination with an authentic sample gave no depression.

The above filtrate deposited on cooling a solid which was unreacted II.

5,9-Dibromo-5,9-dinitro-2,12-tridecanedione. A solution consisting of 1.8 g. (6 mmoles) of 5,9-dinitro-2,12-tridecanedione, 60 ml. of methanol, 10 ml. of water, and 6.0 ml. of 2*N* methanolic sodium hydroxide (approximately 12 mmoles of sodium hydroxide) was cooled to 3° with an ice bath. Then 9.0 g. of bromine was added with stirring, and the mixture was removed from the ice bath and allowed to stand for 5 min. The excess bromine and some solvent were stripped off and the mixture was chilled and filtered to give 1.7 g. (61%) of *5,9-dibromo-5,9-dinitro-2,12-tridecanedione*, m.p. 65.5–66.5°. Recrystallization from carbon tetrachloride gave a refined product, m.p. 65.5–66.0°.

Anal. Calcd. for $C_{13}H_{20}Br_2N_2O_6$: C, 33.93; H, 4.38; N, 6.09; Br, 34.74. Found: C, 33.81, 33.72; H, 4.18, 4.25; N, 6.00, 6.26; Br, 34.51, 34.69.

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(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, New York, 1956, p. 218.

Alkali-Resistant Hemicellulose in Luffa Cellulose[1]

CHEN-CHUAN TU[2]

Received June 12, 1957

This work was undertaken to investigate the relationship of the alkali-resistant hemicellulose and cellulose in the skeletal substance of the dishcloth gourd (*Luffa cylindrica*). In 1927[3] its constituents were reported to be cellulose, lignin, hemicellulose, and small amounts of mannan and galactan. An analysis of its constituents is shown in Table I.

TABLE I

ANALYSIS OF LUFFA CONSTITUENTS

alpha-Cellulose	62.8%
Pentosan	19.5%
Lignin	12.1%
Uronic anhydride	6.7%

Table II indicates that alcohol extraction, delignification with chlorine dioxide (sodium chlorite in acid solution), and alkali extraction were found to be a proper sequence of procedures for cellulose evaluation. The skeletal structure of the gourd was completely disintegrated by using the above sequence. The completion of disintegration was observed by the changes in the physical state of the gourd upon chemical treatment. When the other sequences in Table II were used, disintegration was incomplete. If the disintegration is incomplete, some hemicellulose originally trapped in the cellulose would not be separated. There appears to be some alcohol-soluble compound serving as a cementing agent to bind cellulose and hemicellulose together to a certain extent. It is possible that the alcohol-soluble constituent might be affected by the chemical treatments, particularly chlorine dioxide or alkali, so as to become less soluble in alcohol, rendering

(1) Presented before the Division of Carbohydrate Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Tex., April 8 to 13, 1956.

(2) Present address: Experiment Station, Hawaiian Sugar Planters' Association, Honolulu 14, T. H., U.S.A.

(3) S. Masuda, *Cellulose Industry*, **3**, 321 (1927).

the disintegration incomplete. Likewise, if delignification is incomplete, disintegration would also be incomplete.

TABLE II

METHODS OF CELLULOSE PREPARATION

Sequence of Treatment	
1. Alcohol, ClO_2, KOH (10%)	Skeletal structure completely disintegrated
2. Alcohol, KOH, ClO_2	Skeletal structure collapsed or deformed, but not completely disintegrated
3. KOH, alcohol, ClO_2	
4. KOH, ClO_2, alcohol	
5. ClO_2, alcohol, KOH	
6. ClO_2, KOH, alcohol	

The cellulose, prepared as described above, still contained a small amount of alkali-resistant hemicellulose. The alkali-soluble hemicellulose was identified as xylan by paper chromatography after it was hydrolyzed with acid in the usual manner.

A small amount of alkali-resistant xylan in cellulose may be explained as a result of similar solubility in alkali of some higher degree of polymerization (D.P.) alkali-resistant xylan and of the lower D.P. fractions of cellulose. If this assumption is correct, it may be possible to remove the region of overlapping D.P. by a proper choice of solvent. Cupriethylenediamine was selected. Table III indicates that when about 30% of the material had been dissolved in a proper concentration of cupriethylenediamine solution, no detectable amount of xylan remained. Also, in Figure 1a[4] based on the summative and integral viscosity curves of Figure 1, the area under the curve to the right of the dotted line indicates the region of xylan-free cellulose. In consequence, this work provides evidence that the presence of xylan hemicellulose in cellulose can be defined as a result of an overlapping of molecular

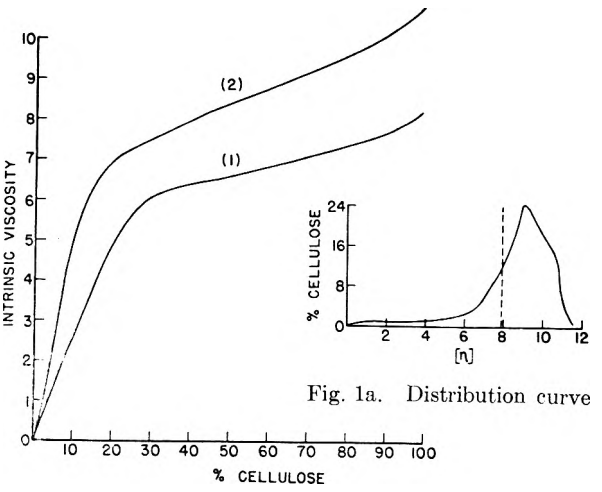

Fig. 1a. Distribution curve

Fig. 1. Summative (1) and integral (2) curves

weights and consequent similar solubilities in alkali. It is unlikely that the alkali-resistant hemicellulose is chemically bound. This finding may be useful, in general, to support the view that the alkali-resistant hemicellulose in wood and other plant celluloses can also be explained by the overlapping of its D.P. with that of cellulose in the lower D.P. region.

EXPERIMENTAL

Preparation of cellulose and hemicellulose. Twenty grams of the gourd was exhaustively extracted with 95% alcohol in a large Soxhlet extractor. After drying, the residue weighed 18.4 g. The alcohol-extracted gourd was delignified with sodium chlorite at *p*H 4 and 75° in the usual manner. The delignified gourd was deformed but its structure still remained. The yield of holocellulose, *i.e.*, the weight of the delignified gourd, was 16.2 g. The holocellulose was extracted with 10% KOH under nitrogen overnight. At the beginning of the extraction, the gourd underwent disintegration. After the extraction was complete, the cellulose was separated and washed with 1% dilute acetic acid and water. The yield was 10.0 g. The solution was neutralized with 50% acetic acid and precipitation occurred. Alcohol was slowly added to the suspension until the alcohol concentration reached

TABLE III

FRACTIONATION DATA

No.	$Cu(en)_2$ Soln. M	Efflux Time (sec.) Solv. t.	Efflux Time (sec.) Soln. t_1	Cellulose Dissolved, g./100 ml. (0.1 g. used)	Sugars Present after Hydrolysis: Residue Glucose	Residue Xylose	Regenerated Glucose	Regenerated Xylose	$[\eta]$
1	0.09	103.7	128.0	0.0220	99.50	0.50	—	—	5.7
2	0.15	111.0	136.2	0.0300	—	—	—	—	—
3	0.17	114.0	133.0	0.0275	*Ca.* 100.00	Undetectable	96.00	4.00	6.0
4	0.20	114.7	145.0	0.0397	*Ca.* 100.00	Undetectable	96.50	3.50	6.2
5	0.22	116.0	170.0	0.0594	*Ca.* 100.00	Undetectable	97.70	2.30	6.8
6	0.23	117.0	216.0	0.0900	—	—	—	—	7.9
7	0.24	117.5	224.0	0.0930	—	—	—	—	7.9
8	0.26	119.0	240.0	0.1052	—	—	—	—	8.2
9	Cellulose not treated with cupriethylenediamine solution				98.50	1.50	—	—	—

(4) Wm. A. Mueller and L. N. Rogers, *Ind. Eng. Chem.*, **45**, 2522 (1953).

20%. On standing, the precipitated hemicellulose flocculated and was separated by centrifuging. The separated hemicellulose was treated with 95% alcohol, acetone, and ether in the usual manner. Two and five-tenths grams of dry, white hemicellulose, identified by hydrolysis and chromatography as 95% xylan, was obtained. The use of other sequences of reagents for the preparation of cellulose was not so successful as the one described above. The sequences of treatment and results are shown in Table II.

Fractionation and characterization. One-tenth gram of the cellulose obtained above was transferred into a 100-ml. centrifuge bottle to which 10 glass beads and a selected amount of water was added. The bottle was then stoppered with a serum-bottle rubber stopper.

The stopper was pierced with a syringe needle, to which, in addition to a cupriethylenediamine reservoir, nitrogen and vacuum lines with appropriate stopcocks were also connected. The air in the bottle was first evacuated and then replaced with purified nitrogen. The bottle was again evacuated and filled with cupriethylenediamine to make up 100 ml. and finally filled with nitrogen. The bottle was then shaken for 2 hr. and centrifuged. Ten milliliters of the supernatant solution was withdrawn with a syringe and transferred into an Ubbelohde viscometer in which the viscosity was determined. The transferring and the measurement of viscosity were conducted under nitrogen. The viscosities of the samples obtained with varied concentrations of cupriethylenediamine solution are shown in Table III. The residue was separated and washed with 1% acetic acid and water. Fifty milliliters of the supernatant solution was neutralized with 50% acetic acid. Precipitation occurred. The precipitate was centrifuged, separated, washed, and weighed. Thirty milligrams each of the residue and of the regenerated cellulose were hydrolyzed with sulfuric acid, chromatographed and analyzed for glucose and xylose.[5] The results are shown in Table III.

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(5) J. F. Saeman, W. E. Moore, R. L. Mitchell, and M. A. Millett, *Tappi*, **37**, 336 (1956); J. Pridham, *Anal. Chem.*, **28**, 1967 (1956).

Structure of 2,1,3-Benzoselenadiazole and Its Derivatives. III.[1] Preparation and Absorption Spectra of 5-Styryl-4-nitro-2,1,3-benzoselenadiazoles[2]

EUGENE SAWICKI[3] AND ALBERT CARR[4]

Received June 25, 1957

The nitration of 2,1,3-benzothiadiazole[5] and 2,1,3-benzoselenadiazole[1] (I) has been shown to take place in the 4-position. The attack at this position is believed to be due to the greater electron density at the 4- and 7-positions of the dicationic salt of I as compared to the 5- and 6-positions.[1] Because of the ortho-para directing effect of the methyl group, the nitration of 5-methyl-2,1,3-benzoselenadiazole (II) could be expected in the 4-position. The following facts bear this out. The nitration of II gave a nitro derivative (III) whose

TABLE I

ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA OF SOME 2,1,3-BENZOSELENADIAZOLE DERIVATIVES

Substituted 2,1,3-Benzoselenadiazole	λ_{max} (log ϵ)			Solvent[a]
5-Nitro-	230 (3.71)	274 (4.02)	342 (4.21)	E
	224 (3.86)	274 (4.03)	348 (4.22)	A
			400[b] (3.2)	
4-Nitro-		271 (3.57)	339 (4.19)	E
			370 (3.8)[c]	
		275 (3.73)	340 (4.16)	A
			380 (3.7)	
4-Nitro-5-methyl-			338 (4.27)	E
			370 (3.3)[c]	
		279 (3.61)	351 (4.22)	A
			380 (3.7)	
4-Nitro-5,7-dimethyl-			336 (4.26)	E
			370 (3.56)[c]	
	245 (3.56)	302 (3.81)	352 (4.31)	A
			390 (3.67)	
5-Amino-	236 (4.25)	324 (3.94)	426 (3.80)	E
	265 (3.65)			
	236 (3.97)	333 (4.10)	459 (3.74)	Ac
4-Amino-	242 (4.14)	*322* (4.00)	462 (3.28)	E
		329 (4.08)		
		336 (4.07)		
	231 (3.70)	333 (4.23)	*370* (3.1)[c]	Ac
4-Amino-5-(and 7)-methyl-	238 (4.11)	323 (4.00)	466 (3.23)	E
		329 (4.04)		
		336 (4.05)		
	232 (3.75)	330 (4.18)	*370* (3.4)[c]	Ac
5-Methyl-	*232* (3.70)	333 (4.24)	*370* (3.3)[c]	E
4-Nitro-5-styryl-		292 (4.33)	388 (4.32)	Ed
4-Nitro-5-(4′-methylstyryl)-		300 (4.26)	400 (4.23)	Ed
4-Nitro-5-(4′-chlorostyryl)-		295 (4.30)	382 (4.10)	Ed
4-Nitro-5-(3′,4′-dimethoxystyryl)-	240 (4.22)	335 (4.22)	408 (3.79)	Ed
4-Nitro-5-(4′-dimethylaminostyryl)-		340 (4.38)	489 (4.32)	Ed

[a] E = 95% ethanol; A = 95% sulfuric acid; Ac = 50% alcoholic 1.2*N* HCl; Ed = 95% ethanol containing 0.2% dioxane. [b] Underlined values are shoulders. [c] Weak inflection.

(1) Paper II: E. Sawicki and A. Carr, *J. Org. Chem.*, **22**, 507 (1957).

(2) This investigation was supported by research grants C-1066 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service and CH-14 from the American Cancer Society.

(3) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(4) Taken in part from the dissertation to be submitted by Albert Carr in partial fulfillment of the requirements for the Doctor of Philosophy Degree at the University of Florida.

(5) L. Efros and R. Levit, *Zhur. Obshcheĭ Khim.*, **23**, 1552 (1953); *Chem. Abstr.*, **48**, 12091 (1954).

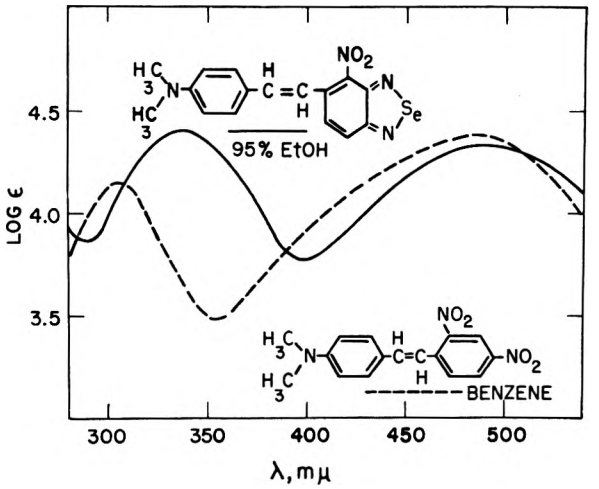
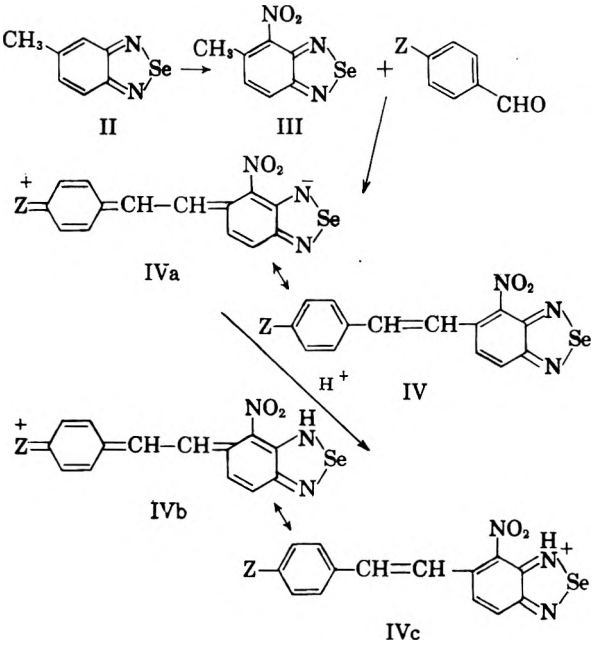


Fig. 1. Absorption spectra: 5-(4′-Dimethylaminostyryl)-4-nitro-2,1,3-benzoselenadiazole in 95% ethanol (———); 4-Dimethylamino-2′,4′-dinitrostilbene in benzene (- - - -)

spectra in alcoholic and sulfuric acid solutions more closely resembled the spectra of 4-nitro-2,1,3-benzoselenadiazole in these same solvents than the spectra of the 5-nitro isomer, Table I. For the same reasons the nitration of 4,6-dimethyl-2,1,3-benzoselenadiazole is believed to take place in the 7-position, Table I. Reduction of III to the triamine followed by reaction with selenium dioxide gave a mixture of amino-5-methyl-2,1,3-benzoselenadiazoles that was difficult to separate. The mixture of amino-5-methyl-2,1,3-benzoselenadiazoles was found to be closely similar spectrally in alcoholic and acidic solution to 4-amino-2,1,3-benzoselenadiazole in the same solvents and entirely different spectrally from 5-amino-2,1,3-benzoselenadiazole, Table I. As III undergoes condensation with aldehydes (and II does not under identical conditions), the nitro group must be ortho to the methyl. This means that nitration of II takes place in the 4-position.

Examination of the absorption spectra of the stilbene derivatives (IV) in alcohol discloses that the long wave length band shifts toward the visible in the order Z = H = 4′-Cl < 4′-Me < 3′,4′-$(OMe)_2$ ≪ 4′-NMe_2, Table I. It would seem that in this series the long wave-length band is associated with a zwitterionic resonance structure which contributes mainly to the excited state and decreases in energy with the increasing electron donor strength of Z in IV. This would involve a closing up of the electronic levels of the ground and excited states with the increasing electron donor strength of Z.

4-Dimethylamino-2′,4′-dinitrostilbene and IV, Z = 4′-$N(CH_3)_2$, have closely similar visible absorption spectra, Fig. 1. This is not surprising, for it has been shown that a nitro group and a N_2Se group are both strong electron-attracting groupings. The compound IV, Z = 4′-$N(CH_3)_2$, absorbs in the following solvents at the indicated wave length maximum in millimicrons: acetone, 335, 480; dimethylformamide, 340, 487; dimethylaniline, 340, 498; dimethyl sulfoxide, 349, 501; chloroform, 337, 501; pyridine, 347, 502; anisaldehyde, 505; 50% aqueous acetone, 349, 513; 50% aqueous dimethylformamide, 347, 513; and 50% aqueous pyridine, 350, 520. In the pure solvents the long wave-length band was slightly more intense than the shorter wave-length band; in the aqueous solutions the long wave-length band was relatively less intense and shifted further into the visible. Apparently the water molecules arrange themselves so as to stabilize dipolar structures, such as IVa, to a somewhat greater extent in the excited state. This "closing up" of the energy levels is reflected in the red shift.



Two protons add to the heterocyclic nitrogens of I in sulfuric acid[1] while only one proton adds to III in the same solvent. In the styryl derivatives there must be an increase in the basicity for two protons can add to the molecule in sulfuric acid, Table II. The spectra of the bases, monocationic and dicationic salts of the styryl derivative (IV) are given in Table II. In the dimethylamino derivative the first proton adds to the amino nitrogen to give the salt absorbing at λ 374 mμ; in trifluoroacetic a second proton adds to the ring 1-nitrogen to form a dicationic salt, λ_{max} 441 mμ. Addition of the third proton (even in concentrated sulfuric acid) is not complete. A shoulder at 575 mμ is believed to be due to the tricationic salt.

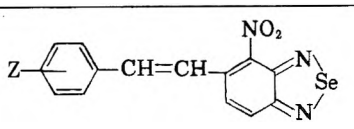
EXPERIMENTAL[6]

4-Nitro-5-methyl-2,1,3-benzoselenadiazole (III). A stirred solution of 2.0 g. (0.01 mole) of 5-methyl-2,1,3-benzo-

(6) Melting points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Fla.

TABLE II

COLOR AND LONG WAVE-LENGTH MAXIMA OF 4-NITRO-5-STYRYL-2,1,3-BENZOSELENADIAZOLE DERIVATIVES

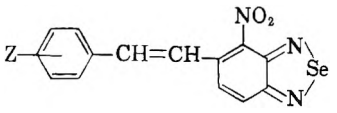


Z	Color (λ_{max}, mμ) Base[a]	Mono-cation[b]	Di-cation[c]
H	Yellow (392)	Orange-red (505)	Blue (673)
4′-Cl	Yellow (382)	Red (515)	Blue (685)
4′-CH_3	Yellow (400)	Violet (548)	Blue (723)
3′,4′-$(OCH_3)_2$	Yellow (408)	Blue (595)	Blue —
3′,4′-(O_2CH_2)	Yellow —	Blue —	Blue —
4′-$N(CH_3)_2$	Orange (489)	Light yellow (374)	Yellow (441)

[a] In 95% ethanol. [b] In trifluoroacetic acid except Z = 4′-$N(CH_3)_2$ which is in 50% alcoholic 1.2*N* HCl. [c] In concentrated sulfuric acid except Z = 4′-$N(CH_3)_2$ which is in trifluoroacetic acid. This latter compound is orange in concentrated sulfuric acid with λ_{max} 476 mμ due to the dication and a shoulder at 575 mμ due to the trication.

TABLE III

5-SUBSTITUTED 4-NITRO-2,1,3-BENZOSELENADIAZOLES



Z	M.P., °C.	Yield, %	Formula Wt.	Analyses Theory N	Found N
H	232–234	61	$C_{14}H_9N_3O_2Se$	12.7	12.4
4′-Cl	240–241	61	$C_{14}H_8ClN_3O_2Se$	11.5	11.2
4′-Me	252–253	76	$C_{15}H_{11}N_3O_2Se$	12.2	12.0
4′-NMe_2	246–247	47	$C_{16}H_{14}N_4O_2Se$	15.0	14.7
3′,4′-$(OMe)_2$	249–251	51	$C_{16}H_{13}N_3O_4Se$	10.8	10.8
3′,4′-(O_2CH_2)	254–255	60	$C_{15}H_9N_3O_4Se$	11.2	11.0
2′,3′-$(CH)_4$	255–256	45	$C_{18}H_{11}N_3O_2Se$	11.0	10.8

selenadiazole[1] in 4 ml. of concentrated sulfuric acid was treated with a mixture of 1 ml. of nitric acid (d. 1.4) and 2 ml. of sulfuric acid at 0–10°. The mixture was allowed to stand 30 min. at room temperature, then was poured on ice and filtered. Two crystallizations from xylene gave 1.5 g. (62%) of light yellow crystals, m.p. 192–194°.

Anal. Calcd. for $C_7H_5N_3O_2Se$: N, 17.4. Found: N, 17.2.

4-Amino-5-methyl-2,1,3-benzoselenadiazole and 4-amino-7-methyl-2,1,3-benzoselenadiazole. To a suspension of 2.42 g. of 4-nitro-5-methyl-2,1,3-benzoselenadiazole in 70 ml. of hot water and 20 ml. of concentrated hydrochloric acid was added 8 g. of zinc dust. The mixture was vigorously refluxed for 30 min. and filtered hot. To the cold filtrate was added an equal volume of concentrated hydrochloric acid. The mixture was cooled to 0° and filtered. The residue was washed with 20 ml. of cold 25% hydrochloric acid dissolved in a minimum amount of water and neutralized with potassium acetate. A solution of 1 g. of selenium dioxide in 2 ml. of water was added at 0–5°. Quick filtration gave 1.4 g. of crude product, m.p. 135–139°. Several crystallizations from heptane gave yellow crystals, m.p. 138–142°.

Anal. Calcd. for $C_7H_7N_3Se$: N, 19.5. Found: N, 19.9.

4,6-Dimethyl-2,1,3-benzoselenadiazole. To a solution of 98 g. of 2-nitro-4,6-dimethylacetanilide[7] in 200 ml. of hot Methyl Cellosolve was added 100 ml. of concentrated hydrochloric acid. Following 90-min. reflux, excess water was added. The crude 2-nitro-4,6-dimethylaniline (85 g.) was dissolved in 50 ml. of concentrated hydrochloric acid. A solution of 450 g. of stannous chloride in 400 ml. of hydrochloric was cautiously added. The mixture was boiled to one half volume, cooled and filtered. The residue was treated with cold aqueous sodium hydroxide solution until the mixture was definitely alkaline. The residue was extracted with alcohol, the extract treated with a concentrated aqueous solution containing 65 g. of selenium dioxide, cooled and filtered. Two crystallizations from heptane gave 44 g. of colorless crystals, m.p. 154–155°.

Anal. Calcd. for $C_8H_8N_2Se$: N, 13.3. Found: N, 13.2.

4-Nitro-5,7-dimethylbenzoselenadiazole. To a stirred solution of 2.11 g. (0.01 mole) of 4,6-dimethyl-2,1,3-benzoselenadiazole in 4 ml. of concentrated sulfuric acid at 0–10° was added a mixture of 1 ml. nitric acid (dec. 1.4) and 2 ml. of sulfuric acid. The mixture was allowed to stand at room temperature for 30 min., poured on ice, and filtered. Crystallization from Methyl Cellosolve followed by heptane gave 1.8 g. (71%) of light yellow crystals, m.p. 164–165°.

Anal. Calcd. for $C_8H_7N_3O_2Se$: N, 16.4. Found: N, 16.0.

4-Nitro-5-styryl-2,1,3-benzoselenadiazole (IV, Z = H). A mixture of 0.24 g. (0.001 mole) of 4-nitro-5-methyl-2,1,3-benzoselenadiazole and 0.9 ml. (0.009 mole) of benzaldehyde was heated in an oil bath at 150° until homogeneous. Two drops of piperidine were added and the mixture was heated at 150° for 30 min. Two ml. of methanol was added to the cold mixture. The residue obtained from the mixture was washed well with methanol. Crystallization from Methyl Cellosolve (β-methoxyethanol) gave glistening yellow crystals, m.p. 232–234°.

This general procedure was followed for all the styryl derivatives, Table III.

Anal. Calcd. for $C_{14}H_9N_3O_2Se$: N, 12.7. Found: N, 12.4.

Ultraviolet-visible absorption spectra. A Beckman Model DU quartz spectrophotometer with 1-cm. silica cells was used by the procedure described in previous publications.

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(7) Eastman Kodak Co., White Label product.

Basicity of Some Nitrilated Amines

SAUL SOLOWAY AND ABRAHAM LIPSCHITZ[1]

Received July 22, 1957

In the course of estimating the basicity of some amines with the Davidson Indicators[2] it was found that β-dimethylaminopropionitrile and β,β′-dicyanodiethylamine were in the pK_b range of 7 to 12. Since the common aliphatic amines have pK_b values between 3 and 4, these semiquantitative observations indicated the presence of a large inductive effect in nitrilated amines. In order to ascertain the magnitude of this effect a few compounds were prepared, and the pK_a values of their conjugate acids were measured.

The pK_a values of cyanamide, diethylcyanamide, alpha and beta substituted nitrilated amines at 29° are given in Table I. The magnitude of the inductive effect between the parent amine and a nitrilated derivative may be judged from the difference in their pK_a values. On the average the substitution of a cyano group for an N-hydrogen increases the pK_a value 9.0 units, for an alpha hydrogen 5.6 units, and for a β-hydrogen 3.2 units.

By the application of thermodynamic theory alone Langmuir[4] showed that the interaction of an electronegative group with a carboxyl group on a chain should fall off exponentially with distance. This follows from the standard free energy equation (1).

$$F = -RT \ln K_a \qquad (1)$$

Applying this equation to the ionization of acids it follows that the difference (λ) in the standard free energies of ionization of two acids is the difference in the work per mole of removing their ionizable protons. For the case of an unsubstituted acid and a derivative we obtain Equation 2.

$$\lambda = \Delta F^\circ \text{ (parent)} - \Delta F^\circ \text{ (derivative)} = \frac{RT \ln K \text{ (derivative)}}{K \text{ (parent)}} \qquad (2)$$

Equation 2 may be tested by investigating the constancy of the ratios of any two isomers which differ in having the constituent groups separated by a single carbon atom on a chain. In order to so utilize equation 2 for the direct calculation of λ ratios from pK values, it has been modified as given in Equation 3.

TABLE I

DISSOCIATION CONSTANTS (pK_a) OF SOME NITRILATED AMINES

Compound	Boiling Point,[a] °C. (Found)	Boiling Point,[a] °C. (Literature)	pK_a 29°C. (Found)	pK_a (Literature)
Cyanamide	45[b]	43[b,c]	1.1	
Diethyl cyanamide	186	186[d]	1.2	
Aminoacetonitrile	60/21 mm.	58[e]/15 mm.	5.3	
Dimethylaminoacetonitrile	136	137[f]	4.2	
Diethylaminoacetonitrile	84/30 mm.	71/24[g] mm.	4.5	
α-Aminoisobutyronitrile				
2-Amino-2-cyanopropane	58/18 mm.	52/15[h] mm.	5.3	
β-Aminopropionitrile	89/23 mm.	89/23[i] mm.	7.7	
β-Isopropylaminopropionitrile	87/17 mm.	87/17[i] mm.	8.0	
β-Dimethylaminopropionitrile	172	172[j]	7.0	6.86 (30°)
β-Diethylaminopropionitrile	108/30 mm.	87/20[i] mm.	7.6	
β,β′-Dicyanodiethylamine	179/14 mm.	173/10[j] mm.	5.2	5.3 (25°)

[a] Boiling points are at atmospheric pressure unless otherwise indicated. [b] Melting point. [c] A. Franssen, *Bull. soc. chim. France*, (4), **43**, 185 (1928). [d] Cyanamide New Product Bulletin, **Coll. Vol. I**, American Cyanamid Co., New York, N. Y., 1949. [e] A. Klages, *J. prakt. Chem.* (2), **65**, 189 (1902). [f] J. Von Braun, *Ber.*, **40**, 3937 (1907). [g] A. Klages, *J. prakt. Chem.* (2), **65**, 193 (1902). [h] A. P. Snessarew, *J. Prakt. Chem.* (2), **89**, 364 (1914). [i] A. N. Kost, *Vestnik Moskov Univ., No. 2*, 141 (1947); *Chem. Abstr.* **42**, 3722 (1948). [j] Cyanamide New Product Bulletin, **Coll. Vol. II**, American Cyanamid Co., New York, N. Y., 1950.

The various attempts to combine thermodynamic and electrostatic theory toward a basic understanding of inductive effects is amply reviewed by Wheland.[3] These treatments, however, require assumptions of some predominant molecular conformation of the solute and its effect on the dielectric constant of the solvent.

$$\frac{\lambda_1}{\lambda_2} = \frac{2.303RT \log \frac{K \text{ (derivative 1)}}{K \text{ (parent)}}}{2.303RT \log \frac{K \text{ (derivative 2)}}{K \text{ (parent)}}} = \frac{pK \text{ (parent)} - pK \text{ (derivative 1)}}{pK \text{ (parent)} - pK \text{ (derivative 2)}} \qquad (3)$$

The λ ratios calculated from the data in Table I are given in Table II. In the later table the parent amines and their nitrilated derivatives are shown in horizontal apposition. Several assumptions were

(1) North American Aviation Corp., Los Angeles, Calif.

(2) D. Davidson, *J. Chem. Educ.*, **19**, 221 (1942).

(3) G. W. Wheland, *Advanced Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1949, Chapter XI.

(4) I. Langmuir, *Chem. Revs.*, **6**, 467 (1929).

TABLE II

λ VALUES OF SOME NITRILATED AMINES[a]

Parent Amine	*N*-Nitrilated Amine	α-Carbon Nitrilated Amine	$\frac{\lambda(N-C\equiv N)}{\lambda(\alpha C-C\equiv N)}$	β-Carbon Nitrilated Amine	$\frac{\lambda(\alpha C-C\equiv N)}{\lambda(\beta C-C\equiv N)}$
Methylamine 10.7	Methyl cyanamide[b] 1.2	Aminoaceto-nitrile 5.3	1.8		
Dimethylamine 10.7	Dimethyl cyanamide[b] 1.2				
Trimethylamine 9.9		Dimethylamino-acetonitrile 4.2	1.7		
Ethylamine 10.7	Ethyl cyanamide[b] 1.2				
				β-Aminopropioni-trile 7.7	1.8
Isopropylamine 10.7		2-Amino-2-cyano propane 5.3	1.8		
Diethylamine 11.1	Diethylcyanamide 1.2				
Triethylamine 10.8				β-Diethylamino-propionitrile 7.6	1.8
Methyldiethylamine 10.4		Diethylamino-acetonitrile 4.5	1.7		

[a] pK_a values are given below the name of the compound. Values other than those given in Table I were obtained from the Handbook of Chemistry and Physics, 31st ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1952–53, p. 1450. [b] These assumed values are discussed in the text.

made in calculating these ratios because of a lack of data. These were the following:

(1) The monoalkylcyanamides have the same pK_a values as diethylcyanamide. Literature values are unavailable, and we found these derivatives to be difficult to prepare in a pure state because of rapid polymerization to the corresponding *N*-alkylmelamines. However, in view of the fact that cyanamide and diethylcyanamide differ by only 0.1 pK_a unit, this assumption is reasonable.

(2) Branched chain compounds have the same pK_a values as straight chain ones if the number of carbon atoms is unequal by one or two. This assumption is borne out by the fact that ethyl and isopropyl amines have about the same pK_a values as do aminoacetronitrile and α-aminoisobutyronitrile.

(3) The pK_a values of several parent amines were needed in making calculations on nitrilated tertiary amines. A secondary amine was necessary to obtain the pK_a difference between it and the corresponding cyanamide derivative, whereas a tertiary amine was required to calculate the pK_a difference between it and the alpha and beta substituted derivatives.

Despite the handicap of insufficient data, the λ ratios are constant at 1.8. It should be noted that the constancy of these ratios is independent of whether the nitrile group is on a nitrogen or carbon atom of the chain. Hence, one may conclude that the transmission of electrostatic effects in these compounds is a property of single bonds. Using the ionization constants of chlorinated propionic and butyric acids, Langmuir showed the λ ratios for any two isomers with chlorine on adjacent carbon atoms to be constant and equal to 2.7. Langmuir assumed this value to be independent of the nature of the interacting groups, but a property of the chain only. It may well be that he was considering the interaction of uncharged groups, *i.e.*, dipole-dipole effects, whereas in the nitrilated ammonium ions the interaction is charge-dipole. There should be a considerable difference in these interactions because the electrostatic field around a charge decreases as the first power of the distance whereas it falls off as the square of the distance around a dipole.

The difference in pK_a between triethylamine and diethylaminopropionitrile is 3.2 units, whereas the difference between diethylamine and β,β′-dicyanodiethylamine is 5.9 units. This result indicates that independent inductive effects in these compounds are approximately additive.

EXPERIMENTAL

The compounds used in this study were either redistilled commercial samples or were prepared by the reaction of glyconitrile, acetone cyanohydrin, and acrylonitrile with amines. Two examples are given as typical of the rest of the preparations. All compounds were distilled a few days

before the pK_a measurements were made. The fractions collected for pK_a measurements boiled over less than a 1° range.

Dimethylaminoacetonitrile. A commercial sample of glycolonitrile was cooled to 0° in a heavy walled flask and saturated with dimethylamine. The latter was generated by dropping a concentrated aqueous solution of the hydrochloride onto pellets of sodium hydroxide. After the flask was tightly stoppered, it was removed from the ice bath and allowed to warm up to room temperature. On standing for 4 to 6 hr. the reaction mixture was fractionally distilled. The product boiled at 135–136° at atmospheric pressure.

β-Aminopropionitrile. Four hundred milliliters of an ice cold 28% aqueous solution of ammonia and 100 ml. of ice cold acrylonitrile were mixed in a heavy walled liter flask. After the flask was securely stoppered, it was allowed to warm up and remain at room temperature for several days. It was then fractionally distilled under reduced pressure. The product boiled at 89°/23 mm. Aminoacetonitrile polymerizes quite rapidly so that it was titrated immediately after preparation.

Measurements of pK_a values. The amine solutions titrated were between 0.05 and 0.10 molar. Hydrochloric acid (0.183*M*) was used as the titrant. The equivalence point was taken at the maximum $\frac{d(pH)}{d(ml)}$ from the titration curves. Activity coefficients were taken at unity so that the pK_a = pH at half neutralization. The pH measurements were made with a Beckmann pH meter, industrial model, using glass and saturated calomel electrodes at 29 ± 1°. A conservative estimate of the total error involved in these measurements is 0.1 pK_a unit in the cases of cyanamide and diethylcyanamide. For the other compounds it is closer to 0.05 pK_a unit.

Acknowledgment. We are indebted to the American Cyanamid Co., New York, N. Y., for gifts of the following chemicals: cyanamide, diethylcyanamide, β-isopropylaminopropionitrile, β-dimethylaminopropionitrile, and β,β′-dicyanodiethylamine.

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Chlorination of 1,1-Difluoro-2,2-dichloroethane

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Received July 25, 1957

Henne and Ladd[1] reported that photochemical chlorination of 1,1-dichloro-2,2-difluoroethane (I) at room temperature yields, as the only monochlorination product, 1,1-difluoro-2,2,2-trichloroethane (II). Since the other possible monochlorination product, 1,1-difluoro-1,2,2-trichloroethane (III), and II should have nearly identical boiling points, Henne and Ladd[1] characterized their product by dehalogenation with zinc, wherefrom only 1-fluoro-2,2-dichloroethylene (IV) (b.p. 35°) was isolated.

$$\underset{\text{I}}{CHF_2CHCl_2} + Cl_2 \xrightarrow{h\nu} \underset{\text{II}}{CHF_2CCl_3}$$

$$\underset{\text{II}}{CHF_2CCl_3} + Zn \longrightarrow \underset{\text{IV}}{CHF{=}CCl_2}$$

The photochemical chlorination of spectroscopically pure I, prepared by the method of Swarts,[2] was recently carried out in this laboratory using a procedure similar to that of Henne and Ladd.[1] The chlorination apparatus described by Muskat and Northrup[3] was used wherein the reaction mixture was heated under reflux (60–70°) and the chlorine was introduced into the vapor between the reflux condenser and the reflux boiler. A General Electric Photoflood No. RFL2 was used as the light source.

The monochlorination product (b.p. 72°) was separated by distillation and subjected to mass spectrometric and infrared analyses. The mass spectrum of pure III, prepared after Henne and Ladd[1] by fluorination of pentachloroethane with antimony trifluoride, was available. Henne and Ladd established the structure of III by zinc dehalogenation, which gave 2-chloro-1,1-difluoroethylene (V) (b.p. −17°). A quantitative comparison of the spectrum of pure III with that of the monochlorination product of I revealed that the latter contained 56 mole % III.[4] The remainder was assumed to be II, as there was no evidence for the presence of I or 1,1-difluoro-1,2,2,2-tetrachloroethane (VI). Thus, approximately equivalent amounts of the two isomers were produced and the reactivities of the two hydrogens of I were approximately equal at the reaction temperature (60–70°). These results will necessitate a slight modification of the theory advanced by Hauptschein and Bigelow.[6]

$$\underset{}{CCl_3CHCl_2} \xrightarrow{SbF_3} \underset{\text{III}}{CF_2ClCHCl_2}$$

$$\underset{\text{III}}{CF_2ClCHCl_2} + Zn \longrightarrow \underset{\text{V}}{CF_2{=}CHCl}$$

The mass spectrometric analysis was carried out at a high potential so that considerable bond rupture occurred. Table I gives a comparison of the major peaks in the mass spectra of pure I, III, and VI with the monochlorination product of I. The strong peaks of the mixture at m/e = 83, 85, and 87 are due to III, whereas those at m/e = 51, 117, 119, 133, and 135 are due to II. The peaks at m/e

(1) A. L. Henne and E. C. Ladd, *J. Am. Chem. Soc.*, **58**, 402 (1936).

(2) F. Swarts, *Chem. Zent.*, **I**, 13 (1903).

(3) I. E. Muskat and H. E. Northrup, *J. Am. Chem. Soc.*, **52**, 4043 (1930).

(4) A discussion of the factors involved and the methods of quantitative analysis by mass spectrometer has been given by Barnard.[5]

(5) G. P. Barnard, *Modern Mass Spectrometry*, The Institute of Physics, London, 1953, chapter 7.

(6) M. Hauptschein and L. A. Bigelow, *J. Am. Chem. Soc.*, **73**, 5591 (1951).

TABLE I

COMPARISON OF MASS SPECTRA

m/e	CF_2HCHCl_2[a] I	$CF_2ClCHCl_2$[a] III	CF_2ClCCl_3[b] VI	Mixture	Ion	Expected for[c] CHF_2CCl_3
51	16.3	0.6	0.09	10.2	CHF_2^+	l
82	1.6	2.0	27.6	6.0	CCl_2^+	s
83	100.0	100.0	0.4	100.0	$CHCl_2^+$	—
84	1.7	2.4	17.7	4.9	CCl_2^+	s
85	64.3	77.4	43.4	74.9	$CHCl_2^+$ CF_2Cl^+	—
87	10.5	14.4	13.8	13.7	$CHCl_2^+$ CF_2Cl^+	—
117	1.6	0.41	100.0	26.1	CCl_3^+	l
119	0.3	0.25	94.9	24.2	CCl_3^+	l
121	—	0.08	30.5	7.6	CCl_3^+	l
132	0.1	0.6	14.6	1.1	$C_2F_2Cl^+$	s
133	2.7	19.2	0.36	46.7	$C_2F_2HCl_2^+$	l
134	21.5	0.75	9.4	3.9	$C_2H_2F_2Cl_2^+$ $C_2F_2Cl_2^+$	s
135	2.1	12.1	0.19	29.6	$C_2HF_2Cl_2^+$	l
136	13.6	0.3	1.5	2.0	$C_2F_2HCl_2^+$ $C_2F_2Cl_2^+$	s
167	—	0.02	97.9	4.0	$C_2F_2Cl_3^+$	s
169	—	0.06	93.6	4.0	$C_2F_2Cl_3^+$	s
171	—	0.04	29.8	1.3	$C_2F_2Cl_3^+$	s

[a] Peak strength relative to m/e at 83 = 100. [b] Peak strength relative to m/e at 117 = 100. [c] "l" indicates a major peak predicted, "s" a minor peak predicted.

= 133 and 135 particularly indicate the presence of II.

The infrared spectrum of the mixture confirmed the presence of III and indicated the presence of another compound which was neither I nor VI. The weak peaks at m/e = 134, 136, 167, 169, and 171 in the mass spectrum of the mixture could be due to small amounts of I and VI in the mixture. However, as is indicated in Table I, all of the fragments could be derived from II so there is no reason to assume, by necessity, that I or VI are present. Conversely, there is no reason to assume that I and VI are entirely absent either.

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Synthesis and Configuration of *cis*-8-Methylhydrindane

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Received August 1, 1957

In connection with the determination of the skeletal structure of picrotoxinin we have described a synthesis of DL-*cis*-5-isopropyl-8-methylhydrin-4,6-diene (picrotoxadiene);[3] we now wish to detail the observations made in a repetition of part of this synthesis with optically active materials. Although an extension of this work will make possible the assignment of absolute configuration in the picrotoxin series the results herein are sufficient to allow such assignment for an important reference compound, *cis*-8-methylhydrindane, as well as some of its ketonic derivatives.

Cis-2-methyl-2-carboxycyclopentane-1-acetic acid (I),[4] prepared *via* 2-methyl-2-carbethoxycyclopentylidenecyanoacetic ester,[3,5] was resolved with the aid of its brucine salt; after twenty-one recrystallizations of this salt from water the rotation ($[\alpha]_D^{21}$ +37°) of the regenerated acid showed no further increase. Partially resolved (−) acid was obtained from the mother liquors. The remaining transformations (to IX) indicated in the diagram were carried out in a manner similar to that described previously for the corresponding racemic series; the compounds were characterized by their infrared spectra, in all cases identical with those of the racemic series. The optically active bicyclic hydrocarbon (X) was prepared from IX by the Huang-Minlon modification of the Wolff-Kishner reduction.

The assignment of the *cis* configuration in this series has rested on the obtention by Errington and

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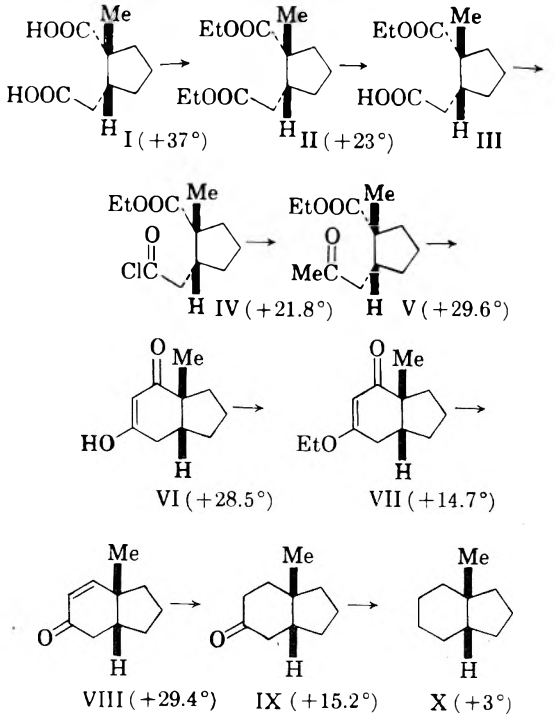
(3) H. Conroy, *J. Am. Chem. Soc.*, **73**, 1889 (1951); **74**, 491 (1952); **74**, 3046 (1952).

(4) K. D. Errington and R. P. Linstead, *J. Chem. Soc.*, 666 (1938).

(5) P. Bagchi and D. K. Banerjee, *J. Ind. Chem. Soc.*, **24**, 12 (1947).



Figures in parentheses are $[\alpha]_D$.

Linstead[4] of the diacid (I) from a bicyclo[3.3.0]-octanone derivative believed for good reason to contain the *cis* ring junction. Nevertheless the evidence may not be entirely convincing, and apparently has been the subject of recent doubt.[6] The infrared spectrum of our hydrocarbon (X) was identical in all respects with that of the cis-8-methylhydrindane (3a-methyl-*cis*-hexahydroindan) reported recently by Kronenthal and Becker[7] and different from that of their *trans* modification. Their synthesis was based upon a Diels-Alder addition and is stereochemically unequivocal.

We owe the assignment of absolute configurations depicted in the diagram for the dextrorotatory materials to the powerful method of rotatory dispersion as elaborated by Djerassi *et al.* (*Cf.* ref. 6, etc.). A comparison of the curves for (+) *cis*-8-methylhydrindan-5-one (IX) and coprostanone-3 (A/B *cis*) leaves no doubt that the immediate steric environments of the respective carbonyl groupings are similar in the absolute sense.

EXPERIMENTAL

Resolution of cis-2-methyl-2-carboxycyclopentane-1-acetic acid (I). The racemic acid[3] (m.p. 110–111°) (459.5 g.; 2.46 moles) was dissolved in a minimum amount of hot water and 1948 g. (2.46 moles) of brucine was added with enough hot water to dissolve it. The brucine salt separated when the solution was cooled; twenty-one such recrystallizations of the salt were carried out before the diacid regenerated by treatment of the salt with 10% hydrochloric acid and extraction with ether gave a constant rotation. The resolved diacid (70.5 g.) had the m.p. 114° and $[\alpha]_D^{21}$° +37° (4% in chloroform). Racemic acid (186 g.) recovered from the mother liquor and put through a similar treatment with extensive recrystallization of the brucine salt gave an additional 18.5 g. of resolved acid, making a total of 89 g. Partially resolved (−) acid (109 g.) $[\alpha]_D^{25}$° −6.4° was also obtained from the mother liquor.

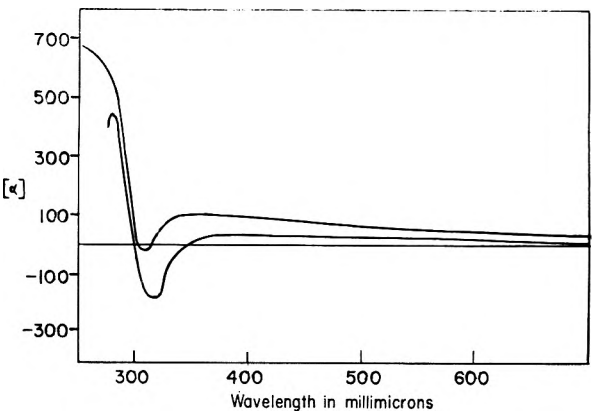


Fig. 1. Rotatory dispersion curves for coprostanone-3 (in methanol; upper curve) and (+)*cis*-8-methylhydrindan-5-one (in dioxane; lower curve)

(+) *Ethyl cis-2-methyl-2-carbethoxycyclopentane-1-acetate* (II). The diester (70 g.; 68% yield) was obtained from 89 g. of the diacid (I) with ethanol and sulfuric acid after a long reflux period. It distilled at 87–89° (0.5 mm.) $[\alpha]_D^{25}$° +23° (7% in chloroform).

(+)*cis-2-Methyl-2-carbethoxycyclopentane-1-acetyl chloride* (IV). The oily half-ester (III) obtained by partial hydrolysis of 70 g. of II with 11.5 g. of sodium hydroxide in aqueous ethanol was dried by distillation with 150 ml. of benzene and then refluxed together with 41.8 g. of thionyl chloride until the gas evolution ceased. After distillation, 59 g. (88.6%) of acid chloride, b.p. 75–78° (0.35 mm.), n_D^{27}° 1.4635 and $[\alpha]_D^{27}$° +2..8° (7% in chloroform) was obtained.

(+)*cis-2-Methyl-2-carbethoxycyclopentane-1-acetone* (V). The preparation was conducted as described previously.[3] From 58 g. of acid chloride (IV) and the sodium salt from 101 g. of diethyl malonate and 15 g. of sodium hydride in benzene there was obtained after hydrolysis-decarboxylation 30 g. of V, b.p. 77–85° (0.4–0.8 mm.), n_D^{27} 1.4505, $[\alpha]_D^{27}$° +29.6° (4% in chloroform). The 2,4-dinitrophenylhydrazone, recrystallized from ethanol, melted at 72°.

(+)*cis-8-Methylhydrindan-5,7-dione* (VI). The preparation was conducted as described previously. From 36.3 g. of the acetonyl derivative (V), 8.3 g. of sodium hydride in 30 ml. of benzene there was obtained 20.5 g. (70%) of VI, m.p. 151–152° with $[\alpha]_D^{26}$° +28.5° (3% in chloroform).

(+)*cis-5-Ethoxy-8-methylhydrind-5-ene-7-one* (VII). A mixture of the diketone (VI), 100 ml. of benzene, 40 ml. of absolute ethanol, and 0.5 g. of *p*-toluenesulfonic acid was distilled slowly through a column packed with helices. The vapor temperature rose to 67° at the completion of the reaction when water was no longer formed. The solvents were removed on the steam bath, finally *in vacuo*, and the product was distilled. The yield of material, b.p. 83–84° (0.2 mm.), was 20.2 g. (84%); n_D^{25}° 1.5085, $[\alpha]_D^{26}$° +14.7° (chloroform).

(+)*cis-8-Methylhydrind-6-ene-5-one* (VIII). Lithium aluminum hydride reduction of VII (20.1 g.) followed by mild acid hydrolysis, as previously described, gave 13.1 g. (84.5%) of the unsaturated ketone with b.p. 57–59° (0.8 mm.), n_D^{25}° 1.4995 and $[\alpha]_D^{25}$° +29.4° (4% in chloroform).

(+)*cis-8-Methylhydrindan-5-one* (IX). Four grams of the unsaturated ketone (VIII) in 40 ml. of methanol with 200 mg. of platinum oxide was hydrogenated at atmospheric

(6) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956), footnote 15.

(7) R. L. Kronenthal and E. I. Becker, *J. Am. Chem. Soc.*, **79**, 1095 (1957).

pressure; gas absorption was complete in 2.5 hr. The catalyst was removed by filtration and the solvent evaporated on the steam bath. The residue had $n_D^{25°}$ 1.4790 and $[\alpha]_D^{25°}$ +15.2°. The dibenzylidene derivative had the m.p. 124–125°.

(+)*cis-8-Methylhydrindane* (X). The ketone (IX) (3.5 g.) was refluxed for two hr. at 135° with 4.0 g. of potassium hydroxide, 80 ml. of diethyleneglycol, and 7.0 g. of 85% hydrazine hydrate. The water was distilled off and then the temperature was raised to 200° for 4 hr. The mixture was cooled, taken up in water, extracted with pentane, and the pentane layer washed with concentrated sulfuric acid until the acid no longer became colored. The pentane solution was washed with water, dried over magnesium sulfate, and the pentane removed, leaving two grams of an oil whose infrared spectrum showed no carbonyl band and was identical with that given in ref. 7. The oil crystallized on cooling, m.p. 5°, $[\alpha]_D^{26°}$ +3° (6% in chloroform).

Acknowledgment. We wish to thank Prof. Gilbert Stork for his help and interest in this work and as well, Prof. Carl Djerassi for the rotatory dispersion curves.

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A New Synthesis of *cis*-1,2-Cyclohexanediol

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cis-1,2-Cyclohexanediol (I) has found considerable use as a model compound for synthetic and mechanistic studies. In discussing methods of preparing I, Criegee and Stanger[2] have recommended a four-step method starting with cyclohexene. As pointed out by Winstein, Hess, and Buckles,[3] however, its success is dependent on the reaction conditions of the replacement reaction.

We have developed a much simpler two-step synthesis of I from cyclohexene which requires about a day's time and which is amenable to large scale work. The method employed is that developed[4] for *cis*-hydroxylation in the synthetic steroid series. It involves the interaction of an olefin with iodine, silver acetate, and wet acetic acid to give, by way of a neighboring group replacement reaction,[3] *cis*-hydroxy acetate in one operation. Subsequent hydrolysis yields the free diol.

Using this technique, we have obtained after one recrystallization quite pure I in 66% yield. Considerable variation of the reaction conditions did not improve the yield. The use of iodine monochloride in place of iodine decreased the yield of I to 32%.

(1) Thanks are due the Du Pont Co. for a Summer Faculty Fellowship.

(2) R. Criegee and H. Stanger, *Ber.*, 69B, 2753 (1936).

(3) S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am. Chem. Soc.*, 64, 2796 (1942); S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, 64, 2787 (1942).

(4) R. B. Woodward and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, 80, 209 (1958).

EXPERIMENTAL[5]

cis-1,2-Cyclohexanediol (I). To a slurry of 16 g. (0.096 mole) of silver acetate in 150 ml. of glacial acetic acid in a three-neck flask equipped with a condenser, thermometer, and stirrer was added 3.42 g. (0.0416 mole) of freshly distilled cyclohexene, b.p. 83–85°. Accompanied by vigorous stirring, 11.7 g. (0.046 mole) of powdered iodine was added over a 30-min. period at room temperature. Finally, 0.67 g. (0.042 mole) of water was added and the reaction mixture was heated with vigorous stirring for 3 hr. at 90–95°. After the reaction mixture was cooled, filtered, and the silver iodide precipitate washed well with hot benzene and ethyl acetate, the combined filtrates were evaporated at the water pump to give a yellow viscous oil which was taken up in methanol and filtered. The filtrate was neutralized with a few ml. of alcoholic potassium hydroxide, treated with 3.5 g. of potassium hydroxide in 20 ml. of methanol and hydrolyzed by refluxing for 1.5 hr. (darkening occurred). After evaporation of the methanol at the water pump, the residue was taken up in 500 ml. of warm diethyl ether and filtered. The filtrate was evaporated yielding 3.92 g. (81%) of crude glycol. Recrystallization from carbon tetrachloride yielded 3.2 g. (66%) of white *cis*-1,2-cyclohexanediol, m.p. 97–98°, lit.[2] m.p. 96–98°.

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(5) All melting points are uncorrected.

Some 4-Substituted Thiourazoles[1]

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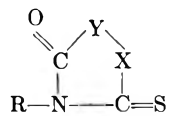
Received August 12, 1957

It was shown that 3-substituted rhodanines (I) possess pronounced antimicrobial activity.[3–5] The present work deals with the synthesis of some related 4-substituted thiourazoles (II). The thioura-



I, X = S, Y = CH_2
II, X = Y = NH

III

(1) This work was supported in part by a research grant [E-695(c)] from the National Microbiological Institute of the National Institutes of Health, Public Health Service. Abstracted from a thesis submitted by Sidney T. Webster in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Duke University, 1957.

(2) Monsanto Chemical Co. Fellow 1956–1957.

(3) G. J. Van der Kerk, H. C. Van Os, G. deVries, and A. K. Sijpestein, *Mededel. Landbouwhogeschool en Opzoekingsstas. Staat Gent*, 18, 402 (1953).

(4) F. C. Brown, C. K. Bradsher, S. M. Bond, and R. J. Grantham, *Ind. Eng. Chem.*, 46, 1508 (1954).

(5) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, Jr., *J. Am. Chem. Soc.*, 78, 384 (1956).

TABLE I

1-SUBSTITUTED-2-THIOBIUREAS AND 4-SUBSTITUTED THIOURAZOLES

R	Yield,[a] %	M.P.,[b] °C.	Formula	C Calcd.	C Obsd.	H Calcd.	H Obsd.	N Calcd.	N Obsd.
			Thiobiureas (III)						
CH_3	97	210–211	(Lit.[c] 212°)						
C_2H_5	94	200.5	$C_4H_{10}N_4OS$	29.62	29.65	6.21	6.30	34.55	34.46
C_3H_7	84	201–201.5	$C_5H_{12}N_4OS$	34.07	34.13	6.88	6.83	31.79	31.80
C_4H_9	92	204	$C_6H_{14}N_4OS$	37.87	37.66	7.42	7.36	29.45	29.32
C_5H_{11}	96	206	$C_7H_{16}N_4OS$	41.15	41.02	7.90	7.89	27.43	27.29
C_6H_{13}	87	205.5–206	$C_8H_{18}N_4OS$	44.01	43.88	8.31	8.49	25.67	25.74
C_7H_{15}	74	206	$C_9H_{20}N_4OS$	46.52	46.97	8.68	8.68	24.12	24.28
$(CH_3)_2CH$	95	194.5–195	$C_5H_{12}N_4OS$	34.07	34.31	6.88	6.62	31.79	31.80
$C_6H_5(CH_2)_2$	68	215–215.5	$C_{10}H_{14}N_4OS$	50.40	50.61	5.92	5.98	23.51	23.54
$C_6H_5CH_2$	100	193–194	$C_9H_{12}N_4OS$	48.19	48.12	5.40	5.47	24.98	25.15
C_6H_5	98	196.5–197.5	(Lit. 198°, Ref. 6)						
			Thiourazoles (II)						
CH_3	67	210–212	(Lit.[d] 212°)						
C_2H_5	69	184–184.5[e]	$C_4H_7N_3OS$	33.09	32.96	4.86	4.90	28.94	28.83
C_3H_7	75 (56)	175–176[f]	$C_5H_9N_3OS$	37.72	37.57	5.70	5.71	26.39	26.35
C_4H_9	74	154.5–155.5[g]	$C_6H_{11}N_3OS$	41.60	41.75	6.40	6.35	24.26	24.30
C_5H_{11}	77	151–151.5[h]	$C_7H_{13}N_3OS$	44.90	45.02	7.00	7.03	22.44	22.46
C_6H_{13}	91	146.5–147.5[i]	$C_8H_{15}N_3OS$	47.73	47.83	7.51	7.50	20.88	20.88
C_7H_{15}	88	145.5–146.5[i]	$C_9H_{17}N_3OS$	50.20	50.23	7.96	7.64	19.52	19.83
$(CH_3)_2CH$	51 (36)	174–175[f]	$C_5H_9N_3OS$	37.72	37.89	5.70	5.43	26.39	26.63
$C_6H_5(CH_2)_2$	93	171.5–172.5[j]	$C_{10}H_{11}N_3OS$	54.28	54.42	5.01	5.02	18.99	18.97
$C_6H_5CH_2$	83	216.5–217.5[k]	$C_9H_9N_3OS$	52.16	52.30	4.38	4.24	20.29	20.36
C_6H_5	83 (35)	193.5–195.5	(Lit. 196°, Ref. 6)						

[a] All yields are for products melting within 3° of the analytical sample. In a few cases yields have been based upon starting material actually consumed. In such cases the smaller number in brackets is the per cent of the starting material converted. [b] All melting points are for pure samples. [c] S. Janniah and P. Guha, *J. Indian Inst. Sci.*, **16A**, 25 (1933). [d] L. Loewe and M. Türgen, *Rev. fac. sci. univ. Istanbul*, **14A**, 227 (1949). [e] Previous sintering at 150–160°. [f] Sintering above 155°. [g] Sintering at 147–151°. [h] Previous sintering at 139–146°. [i] Sintering above 139°. [j] Sintering above 162°. [k] Sintering above 195°.

zoles were obtained by cyclizing 1-substituted-2-thiobiureas[6] (III) which had been obtained by the action of isothiocyanates on semicarbazide. Eleven 4-substituted thiourazoles were prepared and tested for activity against *A. niger*, *B. subtilis*, and *E. coli*. The intermediate thiobiureas were likewise tested. It is interesting that although none of the compounds showed useful activity toward the microorganisms used, several of the 1-substituted thiobiureas significantly *accelerated* the rate of growth of *A. niger* at 250 p.p.m.

EXPERIMENTAL[7]

Isothiocyanates. The alkyl and aralkyl isothiocyanates were prepared by the action of ethyl chlorocarbonate on the appropriate *N*-alkyl dithiocarbamate essentially as described earlier.[8]

1-Substituted-2-thiobiureas (III). To a solution containing 11.2 g. of semicarbazide hydrochloride and 5.4 g. of anhydrous sodium carbonate in about 30 ml. of hot water, 0.1006 mole of the alkyl (aryl) isothiocyanate was added in 50 ml. of ethanol. The solution was boiled gently on a hot plate for 2–4 min. and the solution was then cooled in an ice bath for about an hour. The product was collected and dried in a vacuum oven at 80°. The analytical sample was prepared by recrystallization from ethanol.

4-Substituted thiourazoles (II). Eight grams of the 1-substituted-2-thiobiurea was dissolved in 30–40 ml. of 2*N* sodium hydroxide by shaking, and the resulting mixture heated on the steam bath for thirty to fifty minutes (evolution of ammonia). The alkaline solution was acidified with hydrochloric acid and the resulting precipitate collected. The crude product was purified by shaking it in 20 ml. of 10% ammonium hydroxide solution which dissolved the 4-alkylthiourazole, but not the 1-alkyl-2-thiobiurea present. The unchanged starting material was recovered by filtration, and the desired thiourazole (II) was obtained by acidification of the filtrate with hydrochloric acid. The product usually separated as colorless needles which were collected and dried *in vacuo* at 100°. The analytical sample was prepared by recrystallization from hot water.

Antimicrobial testing. The testing methods were the same as those described earlier.[5,9]

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(6) F. Arndt, E. Milde, and F. Tschenscher, *Ber.*, **55**, 341 (1922).

(7) All melting points were taken on the Fisher-Johns melting point block and are corrected. All analyses were by Galbraith Laboratories.

(8) M. L. Moore and F. S. Crossley, *Org. Synthesis*, **Coll. Vol. III**, 599 (1955).

(9) We are indebted to Mrs. Dorcas Clarke for carrying out these tests.

Synthesis and Optical and Crystallographic Properties of Methyl [Methyl 4-*O*-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate

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Studies of enzyme specificity required crystalline compounds of known structure as substrates. Amorphous methyl α- and β-D-dimethyl esters of digalacturonic acid have been reported[1] but not crystallized.

The following method of synthesis starting with 4-*O*-α-D-galactopyranosyluronic acid-α-L-galactopyranuronic acid permits a yield of crystalline material to be obtained.

EXPERIMENTAL

Methyl [methyl 4-O-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate. A sample of 0.090 g. (0.00023 mole) of crystalline methyl 4-*O*-α-D-galactopyranosyluronic acid-α-D-galactopyranosiduronic acid[1] was dissolved in 20 ml. of methanol and cooled in an ice-water bath. An ethereal solution of diazomethane prepared from 0.5 g. of *N*-nitrosomethylurea was added at 0° with stirring until a yellow color persisted for 30 min. During the evaporation of excess diazomethane at room temperature, needle-like crystals appeared. The product was recrystallized from ethyl acetate, m.p. 120–121°, 0.071 g. (73%).

Methyl [methyl 4-O-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate. Four grams of brucine 4-*O*-(brucine α-D-galactopyranosyluronate)-α-D-galactopyranuronate monohydrate[2] was refluxed with 150 ml. of 0.2*N* dry hydrochloric acid in methanol for 3 hr. Crystals of brucine hydrochloride formed when the reaction mixture was allowed to stand at 5° overnight. The brucine salt was removed by filtration, washed with dry methanol, and the filtrate diluted with an equal volume of water. Residual brucine was removed from the filtrate with a strongly acidic cation exchange resin (Dowex 50) and the chloride ion removed with a basic anion exchange resin (Permutit S). The solution was evaporated at room temperature to a sirup and then dissolved in methanol. Ethyl acetate was added until the solution was turbid. Seed crystals of methyl [methyl 4-*O*-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate were introduced and, upon evaporation, needle-like crystals were isolated by filtration. A yield of 0.485 (34.6%) of crystalline material, m.p. 118–120°, was obtained. The needle-like crystals were recrystallized from a mixture of methanol and ethyl acetate, and had the following properties; melting point, 120–122°, $[\alpha]_D^{25}$ +162.6 (C = 1, H_2O).[3]

Anal. Calcd. for $C_{15}H_{24}O_{13}$: C, 43.67; H, 5.87. Found: C, 43.5; H, 5.78.

Crystals dissolved in water and chromatographed on Whatman No. 1 filter paper with butanol-ethanol-water solvent (40:11:19)[4] revealed no reducing sugar spot with aniline–trichloroacetic acid indicator and only one ester spot appeared with the hydroxamic acid–ferric ion test.[5] The structural formula is presented in Fig. 1.

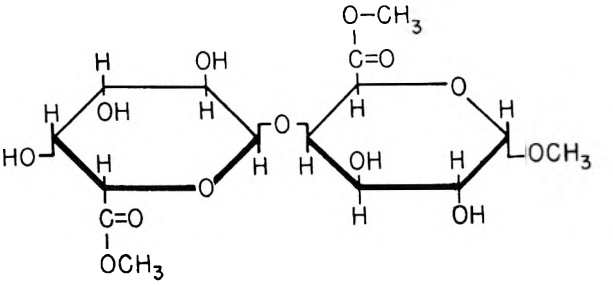

Fig. 1. Structural formula of methyl [methyl 4-*O*-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate

Evaporation of the mother liquor resulted in 0.455 g. of a glassy hygroscopic residue which upon similar chromatographic examination revealed the presence of a moderate amount of methyl [methyl 4-*O*-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate as well as four other esters. One of the esters had the same R_{GA} as methyl (methyl α-D-galactopyranosid)uronate. The other esters were present in small amounts and were not chromatographically identified.

Optical and crystallographic properties. The crystals obtained from methanol–ethyl acetate grew in loose radiating clusters of obliquely terminated prismatic needles. The individual crystals were hollow, being open on the free end, with the cavity tapering toward the base. Crystals suitable for the measurement of silhouettes were grown from a drop of aqueous solution on a slide. The solution must be seeded; otherwise, it will evaporate to a viscous sirup. However, when crystal fragments are crushed in the saturated droplet which is then quickly covered with a cover glass, good

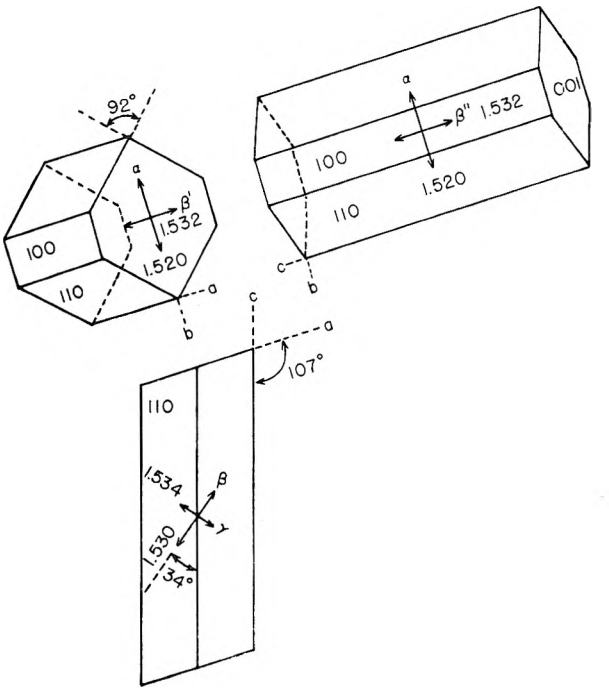

Fig. 2. Orthographic projection of the crystals of methyl [methyl 4-*O*-(methyl α-D-galactopyranosyluronate)]-α-D-galactopyranosiduronate

(1) R. M. McCready and C. G. Seegmiller, *Arch. Biochem. Biophys.*, **50**, 440 (1954).

(2) R. M. McCready, E. A. McComb, and D. R. Black, *J. Am. Chem. Soc.*, **76**, 3035 (1954).

(3) Rotations were made with a Rudolph Polarimeter with a 0.5 decimeter polarimeter tube.

(4) J. K. N. Jones and W. W. Reid, *J. Chem. Soc.*, 1361 (1954).

(5) M. Abdel-Akher and F. Smith, *J. Am. Chem. Soc.*, **73**, 5859 (1951).

crystals will grow as the solvent evaporates. Fragments of cover glass or of seed crystals should be present under the cover glass in order to obtain crystals thick enough to give distinct interference figures. The immersion oils used for refractive index measurements were removed by flooding repeatedly with petroleum ether or isooctane.

The angular measurements shown in Fig. 2 were made on crystals grown from aqueous solution. Refractive indices were measured on crystals from both sources. The fact that this compound is optically active requires that the crystals be hemimorphic although no forms (that would require this classification) were seen.

Crystal System: Monoclinic, Beta Angle = 107°.

Optical Properties: Refractive Indices (5893A; 27°) α = 1.520, β = 1.530, $\alpha\gamma$ = 1.534, β' and β'' = 1.532 (Fig. 2).

Optic Axial Angle (5893A; 27°) 2E = 65°.

Dispersion: Not noticeable.

Optical Character: Negative.

Acute Bisectrix: α = b.

Extinction: Views having b vertical show oblique extinction with the vibration direction β making an angle of 34° with the length direction (Fig. 2). Such views are rare. They show a hazy acute bisectrix interference figure. The most common view is that of a crystal lying on one of its main faces (110). Such a view which exhibits sweeping extinction, does not show any principal optical direction but exhibits a refractive index for nearly lengthwise vibrations of 1.532. The interference figure for this view shows one optic axis near the edge of the aperture (N.A. = 0.95). Crystals that have the greatest retardation and sharp parallel or symmetrical extinction lie on either (100) or (001). Such views show α crosswise and β'' or β', respectively. The interference figure is symmetrical but centered between the obtuse bisectrix and the optic normal.

Fusion Data: Crystals melt without noticeable decomposition but no crystals grow in the viscous melt which cools to a glass.

Acknowledgment. The authors wish to thank L. M. White and Geraldine Secor for the carbon and hydrogen analyses and N. Floy Bracelin for the drawings.

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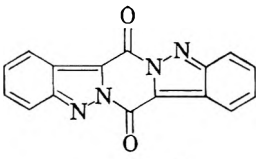
Diindazolo[2,3-*a*, 2′,3′-*d*]pyrazine-7,14-dione

RICHARD F. SMITH AND FRED. K. KIRCHNER

Received August 20, 1957

In the course of preparing some 3-indazolecarboxylic acid derivatives we attempted the preparation of 3-indazolecarbonyl chloride by the action of thionyl chloride on 3-indazolecarboxylic acid. The acid chloride had been reported but not characterized by previous workers.[1] Isolation of the "acid chloride" gave an orange-red compound containing no chlorine. Elemental analyses and saponification equivalent led to the consideration of I as the most likely structure.



I

A search of the literature revealed that von Auwers and Cauer[2] indicated the preparation of I but gave no physical constants or analytical data. However in a later paper von Auwers and Wolter[3] reported the preparation of the 1,2,3,4,8,9,10,11-octahydro derivative of I from the corresponding tetrahydroindazolecarboxylic acid and gave a structure analogous to I.

In common with other workers[4] using diketopiperazine derivatives derived from various 3-pyrazolecarboxylic acids, I was found to be an active acylating agent. On treatment with aqueous dimethylamine, an 85% yield of *N,N*-dimethyl-3-indazolecarboxylic acid amide[1] was obtained.

The formation of a polycyclic compound in the benzimidazole group has been reported.[5] The action of thionyl chloride on benzimidazole-2-acetic acid gave a compound whose structure is similar to I and which also readily acylates amines.

EXPERIMENTAL[6]

Diindazolo[2,3-a, 2′,3′-d]pyrazine-7,14-dione (I). A slurry of 53 g. of 3-indazolecarboxylic acid[1] and 100 cc. of thionyl chloride was heated under reflux for 2 hr. A large volume of benzene was added and the product filtered. The reddish-orange solid was suspended in Skelly E and heated on the steam bath to expel thionyl chloride. The product was filtered, washed with pentane, and dried. The yield was 30.0 g. (64%), m.p. >350°. The product was found to be insoluble in common organic solvents and was purified by extraction with boiling acetone for 3 hr. The insoluble orange solid gave the following results.

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 66.66; H, 2.80; N, 19.44; sapon. equiv. 144. Found: C, 66.49; H, 3.24; N, 19.45; sapon. equiv. 144.

N,N-Dimethyl-3-indazolecarboxylic Acid Amide. The diamide I (30 g.) was treated with 200 cc. of 25% aqueous dimethylamine. A mild exothermic reaction resulted and the reaction mixture was allowed to stand overnight at room temperature. The product was isolated by heating on the steam bath to drive off dimethylamine, followed by cooling and filtration. The dried white solid weighed 33.4 g. (85%), m.p. 191–193° (uncorr.). Recrystallization from nitromethane did not alter the melting point. (The reported[1] m.p. is 187–189°).

Anal. Calcd. for $C_{10}H_{11}N_3O$: N, 22.21. Found: N, 21.97.

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RENSSELAER, N. Y.

(1) H. R. Snyder, C. B. Thompson, and R. L. Hinman, *J. Am. Chem. Soc.*, **74**, 2009 (1952).

(2) K. von Auwers and E. Cauer, *Ber.*, **61**, 2402 (1928).

(3) K. von Auwers and E. Wolter, *Ber.*, **63**, 479 (1930).

(4) C. Musante and P. Pino, *Gazz. chim. ital.*, **77**, 199 (1947).

(5) R. A. B. Copeland and A. R. Day, *J. Am. Chem. Soc.*, **65**, 1072 (1943).

(6) Analyses are by Messrs. M. E. Auerbach, K. D. Fleischer, and their staffs.

Studies in Steroid Total Synthesis. VI. Exploration of an Alternate Route to *anti-trans* - 2,3,4,4a,4b,5,8,8a - Octahydro - 8a-methyl-2-oxophenanthrene-1-propionic Acid

QUENTIN E. THOMPSON

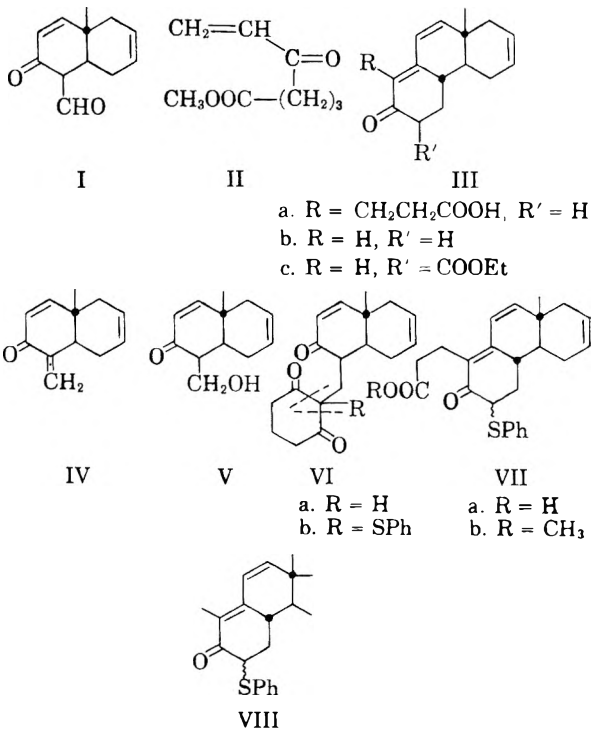
Received August 22, 1957

The tricyclic keto acid (−) *anti-trans*-2,3,4,4a,-4b,5,8,8a - octahydro - 8a - methyl - 2 - oxophenanthrene-1-propionic acid (IIIa), prepared in two steps from I and methyl 5-oxo-6-heptenoate (II), proved to be a key intermediate in a stereoselective ring A synthesis recently reported from this laboratory.[1] Early preparations of the vinyl ketone II were characterized by low yields and poor quality which complicated the synthesis of IIIa in quantity. These difficulties were eventually overcome, but the exploration of an alternative route to IIIa seemed advisable at the time. Some results of this investigation are reported herein. A good route to the unsubstituted tricyclic ketone IIIb was found, but the desired alternative synthesis of IIIa was realized only in a formal sense.

Treatment of I with aqueous alkali and formaldehyde gave a good yield of a mixture of bicyclic methylene (IV) and methylol (V) ketones. Condensation of IV with dihydroresorcinol using potassium *tert*-butoxide as catalyst gave a 63% yield of the adduct VIa. Hydrolytic cleavage of VIa at one of the indicated points followed by cyclization of the resulting open chain keto acid would be expected to yield IIIa directly. Unfortunately, in agreement with the observations of Wilds *et. al.*,[2] 2-monosubstituted 1,3-cyclohexanediones are quite enolic, and thus, are resistant to hydrolytic cleavage. In our case, only prolonged alkaline hydrolysis was sufficient to cleave VIa. The maximum yield from VIa to IIIa was roughly 35%. Isolation of IIIa was complicated by its poor crystallizing properties. A major side reaction to ring opening appeared to be a reverse Michael reaction[3] resulting in a large oily neutral fraction presumably derived from IV by a self-condensation. That the resistance of the 1,3-cyclohexanedione moiety of IVa to hydrolytic cleavage was due solely to its enol character was shown by the fact that conversion to VIb gave a product cleaved readily by dilute alkali.

The material resulting from this 1,3-diketone cleavage and subsequent cyclization was an impure, somewhat unstable noncrystalline keto acid whose gross structure appeared to be VIIa. Conversion to the methyl ester and purification on alumina gave an oily ester (λ_{max}^{alc} 292 mμ,ϵ 17,000) in excellent agreement with the ultraviolet spectrum (λ_{max}^{alc} 292 mμ, ϵ 19,800) for the thiophenyl substituted dienone chromophore VIII previously observed in connection with another study.[4] Several attempts to desulfurize VIIa to IIIa were attended by considerable reduction of the dienone system, and eventually this approach was abandoned.

In contrast to the difficulties in the preparation of IIIa, the unsubstituted tricyclic ketone (−) *anti - trans* - 4,4a,4b,5,8,8a - hexahydro - 8a-methyl-2(3*H*) phenanthrone (IIIb) was obtained smoothly and in good yield by condensation of IV with ethyl acetoacetate under the influence of a catalytic amount of potassium *tert*-butoxide. Ring closure and loss of water occurred immediately subsequent to addition of the keto ester to IV. The intermediate 3-carbethoxy ketone IIIc was hydrolyzed and decarboxylated to IIIb without isolation. Presumably ketones similar to IIIb where R = alkyl could also be prepared using β-keto esters more complex than acetoacetic ester.



EXPERIMENTAL

(−) *trans-4a,5,8,8a-Tetrahydro-4a-methyl-1-methylene-2(1H) naphthalenone* (IV) *and* (−) *trans-4a,5,8,8a-tetrahydro-4a-methyl-1-methylol-2(1H) naphthalenone* (V). To 19

(1) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).

(2) A. L. Wilds, J. Ralls, W. D. Wildman and K. E. McCaleb, *J. Am. Chem. Soc.*, **72**, 5794 (1950). See also Wilds, *et al.*, U. S. Patent **2,674,627**.

(3) For a discussion of the inverse Michael reaction see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y., 1953; p. 695. *Cf.* also C. A. Grobe and W. Bauman, *Helv. Chim. Acta*, **38**, 595 (1955); S. A. Julia, A. Eschenmoser, H. Heusser, and N. Tarkoy, *Helv. Chim. Acta*, **36**, 1885 (1953); M. N. Tilichenko, *J. Gen. Chem. U.S.S.R.*, **25**, 2503 (1955) for other recent examples.

(4) W. S. Knowles and Q. E. Thompson, *J. Am. Chem. Soc.*, **79**, 3212 (1957).

g. of the formyl ketone[5] I in 110 ml. of water plus 40 ml. of 36% aqueous formaldehyde at 5° was added over 2 hr. a solution of 4.5 g. of sodium hydroxide in 40 ml. of water. Vigorous agitation was maintained through the reaction period and for an additional 2 hr. Ether (150 ml.) was then added and the layers were separated. The aqueous layer was extracted once with 80 ml. of ether and discarded. The ether layers were combined, washed once with 50 ml. of water, and dried with "Drierite." Removal of solvent gave 16.5 g. of a clear, pale yellow oil which was subjected to vacuum distillation. Two fractions of distillate were collected 5.9 g., b.p. 119–123° (4 mm.) and 3.3 g., b.p. 124–145° (4 mm.). About 300 mg., the center portion of the first cut, was collected for analytical purposes. This material was good quality methylene compound IV, λ_{max}^{alc} 238 mμ, ε 8,500; $[\alpha]_D^{25}$ −287° (2% chloroform), as a clear mobile liquid when freshly distilled. Standing for several days, even at 0°, caused appreciable polymerization.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.73; H, 8.10. Found: C, 82.06; H, 7.83.

The pot residue crystallized on cooling. The crude brown material was dissolved in 200 ml. of ether and decolorized by filtering through a column of activated carbon (5 g.). The clear liquor resulting was concentrated to about 20 ml., cooled, and seeded. The first crop of crystalline methylol compound V amounted to 3.5 g., m.p. 76–77°. Recrystallization once from ether–petroleum ether gave pure material, m.p. 77–78°, $[\alpha]_D^{25}$ −272° (2% chloroform).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39. Found: C, 74.71; H, 8.57.

(−) *trans-1(2,6-Dioxocyclohexylmethyl)-4a,5,8,8a-tetrahydro-4a-methyl-2(1H)naphthalenone* (VIa). To a solution of 5.93 g. of IV in 50 ml. of *tert*-butyl alcohol was added 4.0 g. of dihydroresorcinol[6] and 3.5 ml. of 1 molar potassium *tert*-butoxide solution. The mixture was held at 55° for 16 hr. under nitrogen. The excess alcohol was removed *in vacuo* and the residue treated with 80 ml. of 0.5 molar sodium hydroxide solution. The alkaline solution was extracted once with 100 ml. of ether and the ether extract discarded. After acidifying with concentrated hydrochloric acid, the oil liberated was taken up in two 100-ml. portions of ether. The ether extracts were washed once with water, dried with "Drierite," and the solvent removed. The residual oil (8.0 g.) crystallized almost completely on cooling and trituration with ether. The first crop of crystals collected amounted to 5.0 g., m.p. 113–115°, with a second crop of 1.12 g., m.p. 100–108°, total yield of crystalline material, 63%. Recrystallization of first crop material twice from hexane gave pure VIa, m.p. 115–116°; $[\alpha]_D^{25}$ −20.6°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.75. Found: C, 75.90; H, 7.75.

This adduct was also prepared though in somewhat lower yield (40–50%) using the purified methylol compound V or crude mixtures of IV and V. In these cases, the amount of potassium *tert*-butoxide was increased to a slight excess over the molecular equivalents of methylol present.

(−) *Anti-trans-2,3,4,4a,4b,5,8,8a-octahydro-8a-methyl-2-oxophenanthrene-1-propionic acid* (IIIa). Approximately 286 mg. of adduct VIa was refluxed under nitrogen for 24 hr. with 10 ml. of 0.5 molar sodium hydroxide solution. The reaction mixture was then cooled, 10 ml. of water was added, and the solution extracted once with 30 ml. of ether. The ether extract was set aside and the aqueous phase acidified with concentrated hydrochloric acid. The oily keto acid liberated was taken up by extraction with two 30-ml. portions of ether which were combined, washed with water, and dried. Removal of solvent left 162 mg. of oily keto acid IIIa, as evidenced by its infrared spectrum. The crude oil showed an ultraviolet absorption maximum of λ_{max}^{alc} 289 mμ, ε 17,000 as compared to the known maximum of λ_{max}^{alc} 289 mμ, ε 24,900 for pure IIIa. On the basis of this assay, the over-all yield of IIIa was 38%.

Isolation of pure crystalline IIIa from this crude product was accomplished by chromatography on alumina deactivated with water (15%). About 75 mg. of crystalline acid, m.p. 98–101°, was obtained by elution of the column with wet benzene and ether. Infrared and ultraviolet absorption spectra of this material indicated its identity with IIIa prepared by our alternate route.[1] In addition, a mixed melting point of 98–101° further established this fact.

trans-1(1-Phenylthio-2,6-dioxocyclohexylmethyl)-4a,5,8,8a-tetrahydro-4a-methyl-2(1H) naphthalenone (VIb). A suspension of 4.0 milliequivalents of potassium *tert*-butoxide in anhydrous toluene was prepared by distilling out excess *tert*-butyl alcohol from a mixture of 4.3 ml. of 0.95 molar potassium *tert*-butoxide solution and about 100 ml. of boiling anhydrous toluene. To this hot suspension was added 1.0 g. of the adduct VIa which was immediately converted to its insoluble potassium salt. Distillation was then continued until all of the alcohol had been removed. The yellow suspension was cooled to 10° and treated with 580 mg. of benzenesulfenyl chloride.[7] Reaction occurred almost immediately, and the heavy precipitate was replaced by a fine precipitate of potassium chloride. After stirring at room temperature for an hour, dilute hydrochloric acid and a little benzene were added. The water layer was separated, extracted with benzene, and discarded. The organic layer was washed once with water and the solvent was removed. The residual light brown oil amounting to 1.64 g. crystallized readily on trituration with ether. The first crop amounted to 520 mg., m.p. 161–164°, and chromatography of the residues on alumina gave another 100 mg. of product of similar quality. Several recrystallizations from benzene and ether gave pure material, m.p. 168–169°; λ_{max}^{alc} 231 mμ, ε 19,300.

Anal. Calcd. for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.63; S, 8.13. Found: C, 72.80; H, 6.80; S, 8.50.

Alkaline cleavage of VIb. A mixture of 400 mg. of VIb and 200 mg. of sodium acetate in 5 ml. of water and 10 ml. of methanol was treated at reflux with 2 ml. of 0.50 molar sodium hydroxide solution. The solid (VIb) began to dissolve slowly. After 4 hr., the yellow solution was cooled, water (50 ml.) and a little more base was added. The aqueous layer was extracted once with chloroform and the extract discarded. The acidic material in the aqueous phase was liberated by acidification with concentrated hydrochloric acid. A yellow oily acid separated. This was taken up in ether and washed. The solution was dried with "Drierite" and the solvent removed leaving 248 mg. of yellow glass. The acid was converted immediately to its methyl ester with diazomethane and the latter cleaned up by passing over a short column of alumina. The clear yellow oily ester showed absorption in the ultraviolet at λ_{max}^{alc} 292 mμ, ε 17,000. Although the infrared spectrum of the purified ester or the free acid derived from it by hydrolysis was that expected for VIIb and VIIa, respectively; no crystalline material could be obtained.

(−) *Anti-trans-4,4a,4b,5,8,8a-hexahydro-8a-methyl-2(3H)-phenanthrone* (IIIb). To a solution of 1.087 g. of freshly distilled methylene ketone IV in 20 ml. of *tert*-butyl alcohol was added 1.04 g. of ethyl acetoacetate and 2 ml. of 1 molar potassium *tert*-butoxide solution. The pale yellow solution was allowed to stand at room temperature under nitrogen for 48 hr. About 20 ml. of water was then added and most of the alcohol and water were slowly distilled out. Ethanol (20 ml.) and 20 ml. of 0.5 molar sodium hydroxide were added and alcohol and water again distilled out until the volume was reduced to about 15 ml. This residue was treated with 4 ml. of 6 molar hydrochloric acid and refluxed for 30 min. The mixture was cooled and treated with 20 ml. of water and 50 ml. ether. After separating the layers,

(5) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5014 (1954).

(6) R. B. Thompson, *Org. Syntheses*, **27**, 21 (1947).

(7) H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

the water phase was extracted once with ether and discarded. The ether layers were combined, washed with a little water, and dried with "Drierite." The solvent was removed leaving 1.20 g. (90%) of a clear, yellow oil which solidified completely when touched with a spatula, m.p. 97–98°. The crude material was recrystallized twice from hexane to obtain the analytical sample, m.p. 102.5–103.5°; λ_{max}^{alc} 281 mμ, ε 25,000; $[\alpha]_D^{25}$ −480° (2% chloroform). The infrared spectrum of this optically active ketone was identical with that of the racemic material first prepared by Woodward, *et al.*[8]

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.46. Found: C, 84.24; H, 8.74.

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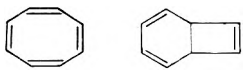
(8) See footnote number 25 of the paper by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

Ozonization of Cyclooctatetraene

Nicholas A. Milas, John T. Nolan, Jr.,[1] and Petrus Ph. H. L. Otto

Received August 27, 1957

Previous ozonizations of cyclooctatetraene in non-hydroxylic solvents led to the conclusion that it reacts with ozone through the fused ring structure II.[2] Although no physical evidence indicated the presence of this structure in equilibrium with cyclooctatetraene I, studies in bromination of I



I II

have demonstrated that certain cationic additions may proceed through this form.[3–5] Furthermore, rearrangement reactions[6] of cyclooctatetraene have been considered as typical homoallylic rearrangements[7] and for this reason ozonization reactions of this cycloölefin, under certain conditions, may be expected to proceed abnormally. It is therefore possible that the extremely low yields (1 to 2%) of the ozonization products reported by Wibaut and Sixma may have been due to abnormal rearrangements and the conclusions drawn may not be entirely valid.

Since we have already shown that abnormal ozonizations of allylic compounds proceed normally in hydroxylic solvents[8] to give high yields of normal products, we felt that the ozonization of cyclooctatetraene in these solvents may give results in accordance with its normal structure.

Accordingly, therefore, freshly purified cyclooctatetraene[9] was ozonized in methanol under various conditions and the peroxide intermediate formed in each case reduced with sodium bisulfite and immediately the 2,4-dinitrophenylhydrazone precipitated. The results of three independent experiments are recorded in Table I.

TABLE I

Ozonization of Cyclooctatetraene

Temp., °C.	C.O.T., Mmoles	O_3 Added, Mmoles	O_2 Absorbed, Mmoles	Active (O), M Atoms	Glyoxal, Mmoles
−16.5	10.03	42.7	40.6	25.6	15.0
−20	10.00	80.0	—	49.0	22.0
−78	5.22	44.1	23.7	17.9	20.0

The rate with which cyclooctatetraene absorbed the first three moles of ozone was fairly constant, then the rate decreased and much of the ozone passed through unabsorbed during the addition of the last mole. Consequently the solution in the last two cases was overozonized purposely in order to insure complete reaction.

At the end of each experiment and after the dissolved ozone was removed by passing through the mixture dry nitrogen, the peroxide content of the solution was determined and the total active oxygen recorded in Table I, column five. At −20° the peroxide found was much more than the amount expected and the excess was attributed to methyl hydroperoxide and other peroxides[10] which form from methanol after the olefin is completely consumed. At −20° methanol absorbs ozone at the rate of 7.8 mmoles per hr. while at −78° the rate is negligible. However, the formation of peroxides from methanol does not affect our results since reduction of the pure ozonized methanol with aqueous sodium bisulfite gave no carbonyl compounds.

Finally, the results shown in Table I indicate that, under the conditions of our experiments, cyclooctatetraene ozonizes in accordance with structure I rather than II as previously proposed.

EXPERIMENTAL

In 80 cc. of methanol was dissolved 1.042 g. (0.01 mole) of freshly distilled cyclooctatetraene and the solution cooled to −20°. Ozone was then passed through the solution for two hr. at the rate of 0.04 mole per hr. Dry nitrogen was

(1) From the Ph.D. Thesis of John T. Nolan, Jr., Massachusetts Institute of Technology, May, 1955.

(2) J. P. Wibaut and F. L. J. Sixma, *Rec. trav. chim.*, **73**, 797 (1954).

(3) S. L. Friess and V. Boekelheide, *J. Am. Chem. Soc.*, **71**, 4145 (1949).

(4) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948).

(5) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(6) A. C. Cope, N. A. Nelson, and D. S. Smith, *J. Am. Chem. Soc.*, **76**, 1100 (1954).

(7) E. Vogel, Habilitationshrift, Karlsruhe, 1957.

(8) N. A. Milas and J. T. Nolan, Jr., Paper presented before the International Ozone Conference, Chicago, November 1956.

(9) We are indebted to Prof. A. C. Cope for the cyclooctatetraene used in this work.

(10) The structure of these peroxides is being investigated.

then allowed to pass through the solution until the exit gases gave no test for ozone. The peroxide content of the solution was then determined and found to consist of 40 mmoles of active oxygen.

For the determination of glyoxal the following procedure was used. To 1 cc. of the ozonized cyclooctatetraene solution (measured at room temp.) was added 10 cc. of water containing 1 g. of sodium bisulfite and the mixture was treated with excess 2,4-dinitrophenylhydrazine reagent and heated on the water bath for 0.5 hr. From this was obtained 0.1142 g. of glyoxal bis-2,4-dinitrophenylhydrazone, m.p. 316° (from pyridine) alone and when mixed with an authentic sample. Jacobs and Witcher[11] report m.p. 311–312° for this derivative. No other carbonyl products were isolated. Therefore the total yield of glyoxal from this experiment corresponds to 2.2 mmoles of glyoxal per mmole of cyclooctatetraene ozonized.

Acknowledgment. We are indebted to Lucidol Division of Wallace and Tiernan, Inc., for financial support of this investigation and to Miss Rachel H. Keto for the determination of the rate of ozone absorption by pure methanol at −20°.

CONTRIBUTION FROM THE DEPARTMENT
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(11) T. L. Jacobs and W. J. Witcher, *J. Am. Chem. Soc.*, **64**, 2635 (1942).

Polymethylol[1]

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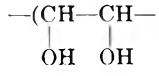
Received September 6, 1957

The preparation of vinylene carbonate has been described as well as its polymerization product.[2] This same reference describes a hydrolysis product of the polymer as being water-soluble, and the statement is made that it is "undoubtedly —(CHOH)$_n$—".[3]

This solubility behavior is inconsistent with the behavior of other polymeric materials having a regularly repeating sequence of hydroxyl functions along a long carbon chain. Pure poly(vinyl alcohol) of reasonably high molecular weight, for instance, is not soluble in cold water but is soluble in hot water. The solution on cooling is metastable, tending to gel on prolonged standing.

We have hydrolyzed poly(vinylene carbonate) under alkaline conditions to give a product whose solubility behavior is in line with that predicted for a polymer having the structure given.



The carbonate was prepared by the method of Newman and Addor.[2] The monomer was polymerized in a sealed tube at 75°, with 0.5% of benzoyl peroxide as catalyst. The hard, clear polymer was dissolved in dimethylformamide and the solution poured into a large volume of distilled water. The white precipitate was washed with distilled water and dried at 50°. The inherent viscosity determined in dimethylformamide was 0.31. The poly(vinylene carbonate) was suspended in 1*N* sodium hydroxide solution at room temperature, the polymer soon going into solution, and the hydrolyzed product precipitating out as a white powder about a minute later. This was filtered off, washed well with water, and dried.

Anal. Calcd. for CH_2O:C, 40.0; H, 6.7. Found: C, 39.2; H, 7.2.

The filtrate obtained after hydrolysis on acidification generated carbon dioxide.

Polymethylol is insoluble in water up to 140° and in most organic solvents, swells in boiling dimethylformamide, and is soluble in hot dimethyl sulfoxide, precipitating from this hot solution on cooling. A number of derivatives could be prepared by reaction in hot dimethyl sulfoxide, including the acetate, cinnamate, and phenyl urethane.

A possible explanation for the inconsistence regarding solubility may be found in the fact that partially esterified poly(vinyl alcohol) and cellulose are water-soluble (or at least more hydrophilic), whereas the parent alcohols are insoluble in cold water. By analogy, it could be argued that the hydrolysis product obtained by Newman and Addor might have been an incompletely hydrolyzed poly(vinylene carbonate).

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(1) Communication No. 1916 from the Kodak Research Laboratories.

(2) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **75**, 1263 (1953).

(3) Since the manuscript was submitted, a paper on the hydrolysis of polyvinylene carbonate, by K. Hayashi and G. Smets, has appeared in *J. Polymer Sci.*, **27**, 281 (1958).

A Convenient Synthesis of Glutaconic Ester

HOWARD J. SCHAEFFER AND B. R. BAKER[1]

Received September 11, 1957

Glutaconic ester has frequently been prepared[2–4] by procedures which employ acetonedicarboxylic ester, a compound which is cumbersome to prepare but which has recently become commercially available.[5] In the most recent procedure,[3] a good yield (67%) of glutaconic ester was reported. However, the yields were variable since the required high pressure catalytic hydrogenation of acetonedicarboxylic ester was difficult to reproduce; the hydrogenation was sensitive to the age of the catalyst and to its method of preparation.

(1) Present address: Stanford Research Institute, Menlo Park, Calif.

(2) H. v. Peckmann and K. Jenisch, *Ber.*, **24**, 3250 (1891).

(3) H. L. Lochte and P. L. Pickard, *J. Am. Chem. Soc.*, **68**, 721 (1946).

(4) C. Grundmann and H. Paul, *Chem. Ber.*, **86**, 186 (1953).

(5) Available from Chas. Pfizer Co., Brooklyn, N. Y.

We have now developed a convenient three-step synthesis of glutaconic ester with an over-all yield of 63–75% by the following procedure. The commercially available diethyl ethoxymethylenemalonate[6] was condensed with malonic ester. The resulting tetraester was hydrolyzed and decarboxylated with dilute hydrochloric acid, and the crude glutaconic acid which resulted was esterified by the usual procedure.

EXPERIMENTAL

Diethyl glutaconate. To a solution of 23.0 g. (1.00 mole) of sodium in 300 ml. of absolute ethanol was added 160 g. (1.00 mole) of diethyl malonate, followed by 216 g. (1.00 mole) of diethyl ethoxymethylenemalonate.[6] After the mildly exothermic reaction[7a] was complete, the reaction mixture was allowed to stand at room temperature for 24 hr. during which time the red solution solidified. A mixture of acetic acid (150 ml.), concentrated hydrochloric acid (100 ml.), and water (1 l.) was added, and the solution was extracted with benzene. The benzene was removed from the extract *in vacuo*,[7b] and the liquid residue was refluxed with dilute (1:2) hydrochloric acid (300 ml.) for 24 hours. The water and other volatile materials were removed *in vacuo*;[7b] the residue was dissolved in absolute ethanol, dried with magnesium sulfate, filtered, and again concentrated *in vacuo*.[7b] The residue was dissolved in absolute ethanol (300 ml.); 6 ml. of concentrated sulfuric acid was added, and the solution was refluxed overnight. The reaction mixture was processed in the usual manner and gave 117 g. (63.0%) of diethyl glutaconate[3]; b.p., 84–87°/0.5 mm., n_D^{20} 1.4448, The diester was hydrolyzed to give glutaconic acid,[8,9] m.p. 136–137°; neut. equiv., 65.0 (calcd. 65.1).

From a second preparation a 75% yield of diethyl glutaconate was obtained.

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(6) Available from Kay-Fries Chemicals, Inc., New York, N. Y.

(7) (a) L. Claisen, *Ann.*, **297**, 1 (1897). (b) The pressure was not measured but it was obtained with the aid of a water pump.

(8) E. Buchner, *Ber.*, **27**, 881 (1894).

(9) B. M. Iselin and K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 3220 (1954).

(10) This work was supported by funds from Mead Johnson and Co., Evansville, Ind.

Stereochemistry of the Cyclopentadiene-Itaconic Anhydride Adduct

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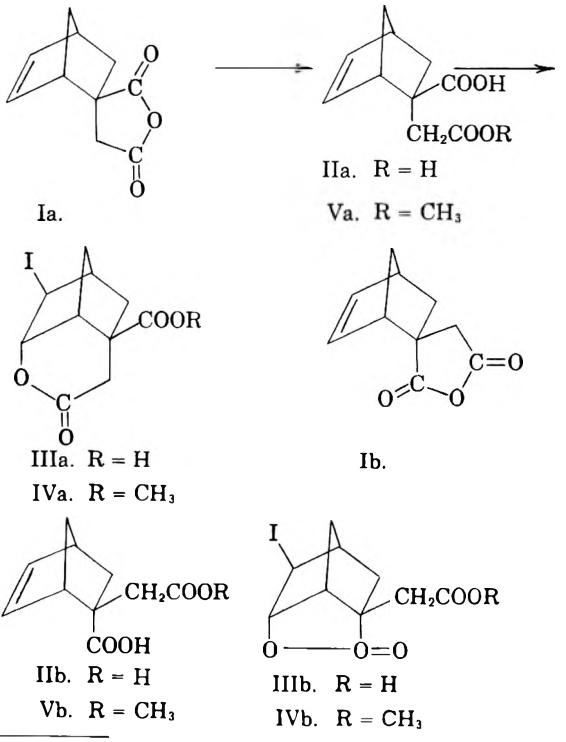
Received September 20, 1957

It has recently been reported[2] that the Diels-Alder addition of methacrylic acid to cyclopentadiene yields a mixture of isomeric products, in which the aduct with the *exo*-carboxyl predominates in violation of the rule[3] of maximum overlap of unsaturation. We wish to report that an even more striking violation of this principle occurs in the addition of cyclopentadiene to itaconic anhydride. After this work was complete, we learned[4] that Drs. B. E. Tate and A. Bavley, of Chas. Pfizer and Co., had carried out a thorough investigation of the cyclopentadiene–itaconic acid addition,[5] so we are presenting here a brief summary of our findings.

The adduct (I) of cyclopentadiene and itaconic anhydride was one of the first prepared by Diels and Alder[6] in their study of the diene addition. It was hydrolyzed to a diacid, but no evidence was presented to permit a decision between the alternative configurations IIa and IIb.

It has now been found that treatment of the diacid with iodine-bicarbonate solution[7] results in the formation of an iodo-lactone. A clear decision between the formulas IIIa and IIIb can be made on the basis of the infrared spectrum, which shows two peaks in the carbonyl region, at 5.80μ and 5.92μ (Nujol). The latter is assigned to the carboxyl group, while the former can be due only to a six-membered lactone, since γ-lactones of this series have been shown[8,9] to absorb at 5.61–5.69μ. The methyl ester (IV) of the iodo-lactone also shows two



Ia.
IIa. R = H
Va. R = CH_3
IIIa. R = H
IVa. R = CH_3
Ib.
IIb. R = H
Vb. R = CH_3
IIIb. R = H
IVb. R = CH_3

(1) Taken from a thesis presented by T.V.A. to the Department of Chemistry, Princeton University, 1957, in partial fulfillment of the requirements for the B.A. degree.

(2) J. S. Meek and W. B. Trapp, *J. Am. Chem. Soc.*, **79**, 3909 (1957).

(3) K. Alder and G. Stein, *Ann.*, **514**, 1, 197 (1934).

(4) Private communication from Dr. B. E. Tate.

(5) B. E. Tate and A. Bavley, Abstracts of Papers, 132nd Meeting of the American Chemical Society, New York, September, 1957, 40P; *J. Am. Chem. Soc.*, **79**, 6519 (1957).

(6) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

(7) A method first used in the bicyclic series by C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 3583, 4878 (1955).

(8) J. A. Berson, *J. Am. Chem. Soc.*, **76**, 4975 (1954).

peaks, at 5.77μ and 5.82μ (CS_2), neither of which is consistent with the γ-lactone structure IIIb. The iodolactone is thus IIIa, and the aduct Ia, the result of *exo*-addition of the conjugated carboxyl.

Added support for this conclusion is the following: a monomethyl ester can be formed by methanolysis of the anhydride, which must have the structure Va or Vb resulting from attack of methanol at the less hindered carbonyl.[10] This monoester does *not* form an iodo-lactone under the conditions used for the diacid. This can mean only that the ester is Va, in which lactone formation is sterically prohibited, and the adduct is consequently Ia.

EXPERIMENTAL

Iodolactone (IIIa). Diacid IIa[6] (1.0 g.) was dissolved with warming in a solution of 1.3 g. of sodium bicarbonate in 30 ml. of water. After cooling to room temperature, a solution of 2.5 g. iodine and 5.0 g. potassium iodide in 15 ml. of water was added, and the mixture kept in the dark for 24 hr. It was then filtered, the filtrate acidified with dilute hydrochloric acid, and treated with stannous chloride until the iodine color disappeared. The solution, on standing, deposited 1.5 g. of the iodo-lactone which, after two recrystallizations from ethanol, melted at 212.5–214°.

Anal. Calcd. for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.45; I, 39.39; Mol. wt. 322.1. Found: C, 37.23; H, 3.48; I, 39.23; Mol. wt. 318.7 (conductometric titration).

The *iodo-lactone methyl ester* (IVa) was formed with ethereal diazomethane, and recrystallized twice from ether, m.p. 97–99°.

Anal. Calcd. for $C_{11}H_{13}O_4I$: C, 39.30; H, 3.89. Found: C, 39.42; H, 4.00.

Monomethyl ester (Va). Five grams of the anhydride (Ia) was dissolved in 50 ml. of methanol and allowed to stand at room temperature for several days. Evaporation of the methanol left a clear sirup, which slowly crystallized on standing. After three recrystallizations from ether, it melted at 58–61°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.80; H, 6.76.

Acknowledgment. We are grateful to Dr. B. E. Tate for forwarding his results to us before publication, and acknowledge also helpful discussions with Dr. Paul Schleyer.

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

(10) M. S. Newman, *Steric Effects in Organic Chemistry*, Wiley, New York, 1956, p. 228.

Platinum-Catalyzed Addition of Triethylsilane to Methyl Methacrylate

JAMES W. CURRY AND GEORGE W. HARRISON, JR.

Received September 27, 1957

The addition of an Si—H compound to a terminally unsaturated organic compound generally proceeds with attachment of the silicon atom to the end carbon.[1–7] However, Goodman and his collaborators[8,9] found that in the presence of a platinum-on-carbon catalyst methyldichlorosilane adds to methyl acrylate in the reverse sense to yield methyl α-(methyldichlorosilyl)propionate. Other reports of "reverse" Si—H addition have appeared in the recent chemical literature.[10–15]

Goodman's initial communication[8] prompted us to examine the effect of an α-methyl group in the α,β-unsaturated ester. Accordingly, triethylsilane and methyl methacrylate were caused to react in the presence of platinum-on-carbon. There was obtained in 30.6% yield a 1:1 adduct. By means of nuclear magnetic resonance spectral analysis the structure of the new compound was established as methyl α-methyl-β-(triethylsilyl)-propionate (I).

$$(CH_3CH_2)_3SiCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2CH_3$$

I

In the NMR spectrum there was found a six-line pattern which was attributed to a single proton, spin-spin coupled to five particles of spin $^1/_2$. The attached methyl group was deemed responsible for three of these particles, and the other two were considered to arise from the methylene group joined to silicon. Moreover, the absence of a resonance peak assignable to two equivalent methyl groups on a

(1) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 188 (1947).

(2) E. W. Pietrusza, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 484 (1948).

(3) A. J. Barry, L. DePree, J. W. Gilkey, and D. E. Hook, *J. Am. Chem. Soc.*, **69**, 2916 (1947).

(4) A. J. Barry, L. DePree, and D. E. Hook (to Dow Chemical Co.), U. S. Patent **2,626,268**, January 20, 1953.

(5) C. A. Burkhard and R. H. Krieble, *J. Am. Chem. Soc.*, **69**, 2687 (1947).

(6) G. H. Wagner and C. O. Strother (to Union Carbide and Carbon Corp.), U. S. Patent **2,632,013**, March 17, 1953.

(7) G. H. Wagner (to Union Carbide and Carbon Corp.), U. S. Patent **2,637,738**, May 5, 1953.

(8) L. Goodman, Stanford Research Institute, Menlo Park, Calif., private communication, June 21, 1956.

(9) L. Goodman, R. M. Silverstein, and J. N. Shoolery, *J. Am. Chem. Soc.*, **78**, 4493 (1956).

(10) L. Goodman, R. M. Silverstein, and A. Benitez, *J. Am. Chem. Soc.*, **79**, 3073 (1957).

(11) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, **79**, 974 (1957). These investigators reported that the platinum-catalyzed addition of methyldichlorosilane to methyl acrylate gives *both* of the possible adducts. (However, in their more recent paper, Goodman *et al.* indicated that they might also have obtained some of the "normal" addition product. See reference 10.)

(12) L. H. Sommer, F. P. MacKay, O. W. Steward, and P. G. Campbell, *J. Am. Chem. Soc.*, **79**, 2764 (1957).

(13) S. Nozakura and S. Konotsune, *Bull. Chem. Soc. Japan*, **29**, 326 (1956). These workers also found that by modifying their reaction conditions they could cause terminal attachment of silicon. See reference 14.

(14) S. Nozakura and S. Konotsune, *Bull. Chem. Soc. Japan*, **29**, 322 (1956).

(15) S. Nozakura, *Bull. Chem. Soc. Japan*, **29**, 784 (1956).

carbon joined at once to a silicon atom and a carbonyl group provided added support for I by precluding the isomeric structure, methyl α-methyl-α-(triethylsilyl)propionate.

The α-methyl group thus influences the reaction in the direction of "normal" addition. It is interesting to note that both Speier *et al.*,[11] and Sommer *et al.*[12] obtained similar results with methyldichlorosilane and certain methacrylate esters.

EXPERIMENTAL[16-18]

Addition of triethylsilane to methyl methacrylate. A mixture of 20.0 g. (0.172 mole) of triethylsilane, 17.2 g. (0.172 mole) of methyl methacrylate, and 0.17 g. of a 0.06% platinum-on-carbon catalyst[17] was heated under reflux for a period of 115.5 hr., during which time the temperature rose from 97 to 150°. The reaction mixture was allowed to cool to room temperature, ether was added, and the catalyst was removed by filtration. (There remained in the reaction vessel 10.8 g. of a polymeric substance which was not further investigated.) The combined filtrate and ether washings were dried over anhydrous sodium sulfate, and the solvent was removed by distillation. Repeated fractionation of the liquid residue gave, ultimately, methyl α-methyl-β-(triethylsilyl)-propionate, b.p. 117–120° (23 mm.), n_D^{25} 1.4413–1.4421, yield 11.4 g. (30.6%). An analytical sample exhibited the following properties: b.p. 119.5–120° (23 mm.), n_D^{25} 1.4421, d_4^{25} 0.8905.

Anal. Calcd. for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18; mol. wt., 216; MR_D, 64.48. Found: C, 60.90; H, 11.14; mol. wt. (Rast), 192; MR_D, 64.31.

The proton magnetic resonance spectrum was determined using the Varian Associates High Resolution Spectrometer (V-4300B), operated at 40 mc. and 9394.7 Gauss.

Acknowledgment. The authors are grateful to the Dow Corning Corporation for financial support of this work and to Mr. Robert C. Jones of Varian Associates, Palo Alto, Calif., for running and interpreting the NMR spectrum discussed in this paper.

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(16) Boiling points are uncorrected.

(17) The microanalysis was performed by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

(18) The calculated molar refractivity was computed from bond refractivity values listed in the following references: A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *Chem. & Ind. (London)*, **1950**, 358; A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954).

Some *N*-Arylated Heterocycles as Liquid Scintillator Solutes

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Received September 23, 1957

In order to gain some insight into the effect of the point of attachment of polyaryls on their efficiency as liquid scintillator solutes, a number of *N*-aryl heterocycles and related amines have been screened for this purpose (Table I). Although some of the values are out of line with closely related compounds, a few structural relationships are beginning to emerge.

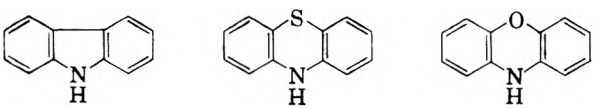
TABLE I

PRIMARY-SOLUTE RELATIVE PULSE HEIGHTS

No.	Compound	Relative Pulse Heights
1.	4-Biphenylyldiphenylamine	0.39[a]
2.	Bis-4-biphenylylamine	0.95[a]
3.	Bis-4-biphenylylphenylamine	0.61[a]
4.	Tris-4-biphenylylamine	0.58[a]
5.	9-Phenylcarbazole	0.24[b]
6.	9-(4-Biphenylyl)carbazole	0.35[b]
7.	*p*-Bis(9-carbazolyl)benzene	0.27[b]
8.	4,4′-Bis(9-carbazolyl)biphenyl	0.93[b]
9.	Phenoxazine	<0.10[c]
10.	10-Phenylphenoxazine	<0.10[c]
11.	10-Benzylphenoxazine	0.10[c]
12.	10-(2-Bromophenyl)phenoxazine	<0.10[c]
13.	10-(4-Bromophenyl)phenoxazine	<0.10[c]
14.	10-(4-Biphenylyl)phenoxazine	<0.10[c]
15.	*p*-Bis-(10-phenoxazyl)benzene	<0.10[c]
16.	4,4′-Bis(10-phenoxazyl)biphenyl	<0.10[c]
17.	10-Allylphenothiazine	<0.10[d]
18.	10-Phenylphenothiazine	<0.10[e]
19.	10-Phenylphenothiazine-5-oxide	<0.10[d]
20.	10-Phenylphenothiazine-5,5-dioxide	<0.10[f]
21.	10-(*o*-Tolyl)phenothiazine	<0.10[g]
22.	10-(4-Biphenylyl)phenothiazine	<0.10[h]
23.	*p*-Bis-(10-phenothiazinyl)benzene	<0.10[h]

[a] J. Piccard, *Helv. Chim. Acta*, **7**, 789 (1924). [b] H. Gilman and J. B. Honeycutt, *J. Org. Chem.*, **22**, 226 (1957). [c] H. Gilman and L. O. Moore, *J. Am. Chem. Soc.*, **79**, 3485 (1957). [d] H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944). [e] H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944). [f] C. Finzi, *Gazz. chim. ital.*, **62**, 175 (1932). [g] H. Gilman, R. D. Nelson, and J. F. Champaigne, Jr., *J. Am. Chem. Soc.*, **74**, 4205 (1952). [h] See Experimental.

The three heterocycles under consideration, carbazole (I), phenothiazine (II) and phenoxazine (III), differ only in the manner of bridging two benzene rings bonded to the same nitrogen atom. Derivatives of the sulfur heterocycle, II, were expected to have poor values on the basis of a previous



I II III

investigation,[1] and, in fact, gave no values at all; the corresponding oxidized derivatives (Compounds 19 and 20) also fail to respond. The phenoxazine derivatives give no measurable pulse height, but this may be a side effect attributable to the persistent color of these derivatives, which probably

(1) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

results in some self-quenching.[2] It has been previously noted in the case of dibenzofuran and dibenzo-*p*-dioxin[3] that the direct union of two benzene rings in a heterocycle, provides a more efficient scintillator nucleus than the corresponding heterocycle with an oxygen bridge. This is clearly confirmed in the comparison of derivatives of I and II. The 9-aryl carbazoles give values ranging from 0.24 to 0.93 (Compounds 5 through 9) while exactly analogous phenoxazine derivatives (Compounds 10, 14, 15, and 16) all fail to respond within the sensitivity of the instrument. The amine related to Compounds 5 and 9, triphenylamine, has been reported[4] to have a very low value (about 0.06 on our scale), markedly lower than that of 9-phenylcarbazole. 4-Biphenylyldiphenylamine (Compound 1) on the other hand has a slightly higher value than the corresponding carbazole derivative (Compound 6).

The synthetic methods employed in the preparation of these compounds are listed in the footnotes to Table I and appear to be completely general. An extension of these methods may prove rewarding in view of the fact that Compound 8 with six benzene rings is soluble to the extent of about 5 g./l. in toluene. A number of promising scintillator solutes, notably 1,4-di[2-(5-phenyloxazolyl)]benzene and 2,5-di(4-biphenylyl)oxazole,[5] have been relegated to use as secondary solutes because of poor solubility in toluene.

The values reported in Table I were measured in the pulse height analyzer previously described,[1] and all were measured at a concentration of 3 g./l. in toluene except compound 16, which, due to limited solubility, was measured as a saturated solution. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

EXPERIMENTAL[6]

10-(4-Biphenylyl)phenothiazine. Twenty grams (0.10 mole) of phenothiazine, 35 g. (0.15 mole) of 4-bromobiphenyl, 12 g. (0.11 mole) of anhydrous sodium carbonate, and 1 g. of copper powder were stirred at 150–160° for 16 hr. After this period the temperature was raised to 200° where it was maintained for an additional 4 hr. Steam distillation of the mixture afforded 15 g. (43%) of unreacted 4-bromobiphenyl. The undistilled residue was extracted with benzene, and this solution was chromatographed on alumina and eluted with more benzene. Evaporation of the eluate left 29 g. of hard resinous solid, melting at 140–170°. Two crystallizations from an acetone-water pair afforded 20 g. (57.5%) of pale yellow powder, melting at 174–178°.

Anal. Calcd. for $C_{24}H_{17}NS$: S, 9.12. Found: S, 9.24, 9.37.

p-Bis(10-phenothiazinyl)benzene. Twenty-four grams (0.12 mole) of phenothiazine, 16.5 g. (0.05 mole) of *p*-diiodobenzene, 12 g. (0.11 mole) of anhydrous sodium carbonate, and 1 g. of copper powder were stirred at 200° for 12 hr. During this period it was necessary to scrape the sublimed *p*-diiodobenzene from the sides of the reaction vessel in order to return it to the reacting mass. After cooling to room temperature the solid was crushed and extracted with five 200-ml. portions of benzene. The benzene was removed and the residue was extracted with three 20-ml. portions of absolute ethanol to remove unreacted *p*-diiodobenzene and phenothiazine. The remaining material was chromatographed on alumina using benzene as solvent and eluant. Removal of the solvent from the eluate left 18 g. of material melting at 248–250°. Recrystallization from benzene gave 16.5 g. (70%), m.p. 253–255°.

Anal. Calcd. for $C_{30}H_{20}N_2S_2$: S, 13.57. Found: S, 13.70, 13.70.

Acknowledgment. This work was supported by the U. S. Atomic Energy Commission under Contract No. AT(11-1)-59. The authors are indebted to Drs. Wright H. Langham and Donald G. Ott of the Los Alamos Scientific Laboratory for their interest and helpful suggestions, to Vernon N. Kerr and Elizabeth Hansbury, also of the Los Alamos Scientific Laboratory, for technical assistance and to Drs. Julian B. Honeycutt and Leonard O. Moore of Iowa State College for samples of many of the compounds tested.

AMES, IOWA

(2) For discussion of this phenomenon see (a) V. N. Kerr, F. N. Hayes, and D. G. Ott, *Intern. J. Appl. Radiation and Isotopes*, **1**, 284 (1957); (b) D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Am. Chem. Soc.*, **79**, 5448 (1957).

(3) H. Gilman, E. A. Weipert, J. J. Dietrich, and F. N. Hayes, *J. Org. Chem.*, in press.

(4) H. Kallman and M. Furst, *Nucleonics*, **8**, No. 3, 32 (1951).

(5) F. N. Hayes, D. G. Ott, and V. N. Kerr, *Nucleonics*, **14**, No. 1, 42 (1956).

(6) Melting points are uncorrected.

Rearrangement in the Reactions of *p*-Halotoluenes with Potassium Anilide[1]

FRANCO SCARDIGLIA AND JOHN D. ROBERTS

Received September 24, 1957

In recent years it has been shown that alkali amides in liquid ammonia[2-4] and refluxing piperidine[5,6] and organolithium compounds[7,8] react with non-activated aryl halides by the way of benzyne (I) intermediates. Strong bases and nucleophiles in liquid ammonia react with aryl halides in liquid

(1) (a) Taken in part from the Ph.D. thesis of Franco Scardiglia, California Institute of Technology, 1957; (b) 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 said fund.

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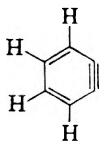


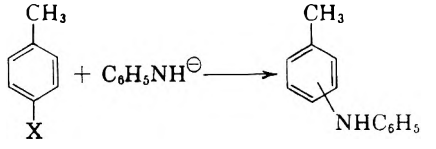
I

ammonia only in the presence of alkali amides.[9–13] Sodium and potassium hydroxides react with aryl halides only at very elevated temperatures[14–17] and when the reaction temperature and the base concentration are reduced, the reaction mechanism may change from elimination-addition to direct substitution.[14]

Sodium and potassium anilides do not react with halobenzenes in liquid ammonia, but potassium anilide and potassium diphenylamide are reported to react with bromobenzene at elevated temperatures[18] to give diphenylamine and triphenylamine, respectively. An improved procedure for this type of reaction has been developed and applied to the preparation of diphenylamine and tolylphenylamines. In order to gain some information regarding the mechanism of such a reaction, *p*-chloro-, *p*-bromo- and *p*-iodotoluenes were treated with potassium anilide in refluxing aniline. Mixtures of *p*- and *m*-tolylphenylamines resulted which were analyzed by means of infrared spectroscopy. The results are summarized in Table I.

TABLE I

PRODUCTS FROM THE REACTION OF *p*-HALOTOLUENES WITH POTASSIUM ANILIDE



X	Total Yield, %	Meta, %	Para, %
Cl	53	53 ± 3	47 ± 3
Br	50	53 ± 3	47 ± 3
I	43	52 ± 3	48 ± 3

If direct substitution were competing with elimination-addition, the ratios of the two isomers should be different for the three *p*-halotoluenes.[2] The fact that all three *p*-halotoluenes give essentially the same product mixtures is strong evidence that these substitutions proceed exclusively by the way of a benzyne-type intermediate. It cannot be excluded, however, that in the case of *p*-iodotoluene a small amount (about 2%) of direct displacement takes place; the analytical procedure, however, was not precise enough to verify this fact.

In order to determine whether alkoxides react with non-activated aryl halides by the way of a benzyne intermediate, the reaction between sodium cyclohexoxide and bromobenzene in refluxing cyclohexanol was investigated. It was found, however, that after 3 days the reaction had proceeded to an extent of less than 10%.

EXPERIMENTAL

Potassium anilide with bromobenzene. Potassium anilide was prepared by adding 4.2 g. (0.107 mole) of potassium metal to 250 ml. of refluxing aniline. Bromobenzene (20 g., 0.128 mole) was added and the solution heated under reflux for 2 hr. At the end of this time, the reaction mixture was allowed to cool and ethanol was cautiously added. Hexane and ether were added; the mixture was washed with water and the solvents evaporated. The residue was distilled through a semimicro column.[19] Diphenylamine (11.0 g., 60%), m.p. 49–52°, whose infrared spectrum was identical with the spectrum of an authentic sample of diphenylamine, was obtained.

Reaction of potassium m- and p-toluidides with bromobenzene. The reaction conditions were the same as above. Five grams (0.128 mole) of potassium and 30 g. (0.198 mole) of bromobenzene were used. The yield of crude *m*-tolylphenylamine was 14.5 g. (61.5%), the yield of *p*-tolylphenylamine was reduced by mechanical losses to 6.2 g. (26%). The products were purified by precipitation with anhydrous hydrogen chloride in ether, followed by treatment with water, extraction with ether, and recrystallization from pentane. The purified *m*-tolylphenylamine had m.p. 28.5–29.5°, lit.,[20] 30°. *p*-Tolylphenylamine had m.p. 87.5–88.5°, lit.,[20] 89°.

Reaction of potassium diphenylanilide with bromobenzene. To 25 g. (0.148 mole) of diphenylamine in 250 ml. of refluxing xylene was added 4.0 g. (0.10 mole) of potassium. The reaction was very slow, and even after 4 hr. of refluxing about 20% of the potassium was still unreacted. Bromobenzene (30 g., 0.198 mole) was added, and the reaction mixture was heated under reflux for 18 hr. Ethanol and a small amount of water were added; the organic layer was washed with water, dried over anhydrous magnesium sulfate, saturated with anhydrous hydrogen chloride, and filtered. The filtrate was evaporated and the residue recrystallized from ethyl acetate. Crude triphenylamine (1.0 g., 2.7%) was obtained. After several recrystallizations from ethyl acetate–ethanol, 500 mg. of pure product, m.p. 126–127°, undepressed by admixture with an authentic sample of triphenylamine, was obtained.

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Reaction of p-chloro-, p-bromo- and p-iodotoluenes with potassium anilide. Potassium (5.6 g., 0.144 mole) was added to 250 ml. of refluxing aniline. The appropriate *p*-halotoluene (0.10 mole) was added, and the reaction mixture was heated under reflux for 15 min. Water was cautiously added to decompose the unreacted bases. Ether was added, the organic layer was washed several times with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and saturated with anhydrous hydrogen chloride. The precipitate was washed with ether, treated with water, extracted with ether, and flash distilled to remove high-boiling tarry materials. The compositions of the distillates were determined by comparison of their infrared spectra in carbon disulfide solution at 11.75–14.00 μ with those of synthetic mixtures of *m*- and *p*-tolylphenylamines.

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Synthesis of 1-Alkyltryptophans

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Considerable effort has been expended on the synthesis of tryptophan analogs for use in the study of enzyme inhibition. This note describes a new general method for the synthesis of 1-alkyltryptophans, in particular the 1-methyl and 1-ethyl derivatives. The only 1-alkyltryptophan previously described is 1-methyltryptophan. This was obtained from 1-methylindole-3-aldehyde *via* the azlactone[1,2] and from 1-methylindole *via* 1-methylgramine.[3] Our starting material was ethyl-α - acetylamino - α - carbethoxy - β - (3 - indole)-propionate.[4] This indole derivative was alkylated on refluxing in an inert solvent with alkyl *p*-toluenesulfonates in the presence of potassium carbonate. Subsequent steps in the synthesis were analogous to those used by Snyder and Smith[4] for the synthesis of DL-tryptophan, namely basic hydrolysis to the malonic acid derivative, decarboxylation to the 1-alkyl-*N*-acetyltryptophan and finally deacetylation by refluxing with dilute hydrochloric acid.

The alkylation of indole using our conditions has led to both 1- and 3-alkyl derivatives[5,6] and since, in our reaction, there was also the possibility of alkylation of the actylamino group, the alkyltryptophans were decarboxylated in molten fluorene at 240–270°. The products were 1-alkyltryptamines, characterized as their phthalimides, hydrochlorides, and picrates. Furthermore, the infrared spectrum of our 1-methyltryptophan was quite different from the spectrum of the isomeric L-abrine [α-methylamino-β-(3-indole)propionic acid]. Our 1-methyltryptophan had a melting point of 250°–251° (dec.). Melting points previously reported for this compound were 289°,[1] 285°,[2] and 223–225°.[3] This variation may be due to partial solvation of the amino acid since a lower melting point was observed in the compound was not extensively dried *in vacuo* at 100°.

EXPERIMENTAL[7]

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-methylindole)propionate (I). Ethyl-α-acetylamino-α-carbethoxy-β(3-indole)-propionate[4] (17.3 g., 0.05 mole) was refluxed in 200 ml. of dry xylene with methyl *p*-toluenesulfonate (10.0 g., 0.06 mole) and anhydrous potassium carbonate (15 g., 0.11 mole) for 5 hr. The mixture was filtered, the residue was washed with benzene, and the combined filtrates evaporated to dryness *in vacuo*. The residue was titurated with ether yielding crystals of I (12.6 g., 70% yield), m.p. 124°. Crystallization from ethanol afforded colorless rhombic crystals, m.p. 125–126°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.70; N, 7.57.

The methylation was also carried out successfully in refluxing *o*-dichlorobenzene resulting in a 62% yield.

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-ethylindole)propionate (II). This 1-ethyl derivative was prepared by substituting ethyl *p*-toluenesulfonate (12.0 g., 0.06 mole) for the methyl ester in the previous synthesis. The crude product (7.0 g., 54% yield), m.p. 107–108°, was crystallized from ethanol to yield short colorless prisms, m.p. 115–116°.

Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00. Found: C, 64.10; H, 6.89.

α-Acetylamino-α-carboxy-β(3-N-methylindole)propionic acid (III). The ester I (18 g., 0.05 mole) was refluxed with 100 ml. of 10% sodium hydroxide solution for 4 hr. The cooled, filtered solution was acidified with concentrated hydrochloric acid. The malonic acid derivative (III) which separated was crystallized from 50% aqueous ethanol to yield colorless rhombic plates (14.1 g., 93% yield), m.p. 147–148°. The crystals became pink on exposure to air.

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 7.77. Found: C, 58.91 H, 5.56; N, 7.57.

α-Acetylamino-α-carboxy-β(3-N-ethylindole)propionic acid (IV). Hydrolysis of II as in the previous preparation yielded IV as colorless prisms (from ethanol) in 85% yield, melting at 128–129°.

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70. Found: C, 60.22; H, 5.94.

1-Methyl-N-acetyltryptophan (V). The malonic acid derivative III (7.6 g.) was heated in a nitrogen atmosphere at 180–190° for 15 min. The pale yellow glass which remained on cooling was crystallized from ethanol (charcoal) to yield large colorless prisms of V (5.6 g., 86% yield), m.p. 169.5–170.5° (lit.[3] 171–172°).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.58; H, 6.20. Found: C, 64.59; H, 6.44.

1-Ethyl-N-acetyltryptophan (VI). The decarboxylation of IV carried out as in the previous preparation yielded colorless plates of VI (from ethanol) in 82% yield, m.p. 185–187°.

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Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61. Found: C, 65.46; H, 6.56.

1-Methyltryptophan (VII). The acetyl derivative V (3.0 g.) was refluxed with 20 ml. of 2*N* hydrochloric acid for 2 hr. The solution was evaporated to dryness *in vacuo* and the residue redissolved in water. The 1-methyltryptophan crystallized (1.8 g., 72% yield) on addition of 1.5 g. of sodium acetate dissolved in a little water. Recrystallization from aqueous ethanol (charcoal) yielded colorless plates of VII, m.p. 250–251°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.59; N, 12.82.

The infrared spectrum of VII, determined as a suspension in potassium bromide, had prominent maxima at 1623, and 735 cm.$^{-1}$

The picrate of the amino acid was obtained on admixture of methanolic solutions of VII and picric acid. Crystallization from water gave fine orange-red needles of the hydrated picrate, m.p. 142–143° (with dec.).

Anal. Calcd. for $C_{12}H_{14}N_2O_2.C_6H_3N_3O_7.H_2O$: C, 46.45; H, 4.11. Found: C, 46.31; H, 4.10.

The amino acid hydrochloride was obtained by addition of ethanolic hydrogen chloride to VII, refluxing, and allowing to cool. Recrystallization from ethanol gave colorless needles of 1-methyltryptophan hydrochloride, m.p. 235–236° (dec.) (lit.[3] 239–242°).

Anal. Calcd. for $C_{12}H_{14}N_2O_2.HCl$: C, 56.59; H, 5.94. Found: C, 56.50; H, 6.01.

1-Ethyltryptophan (VIII). The acetyl derivative VI was refluxed with 2*N* hydrochloric acid for 2 hr. and then evaporated to dryness *in vacuo*. The residue was dissolved in water and brought to a *p*H of 6 by the addition of sodium hydroxide. The 1-ethyltryptophan immediately crystallized in small prisms, m.p. 234–235° (dec.). Crystallization from aqueous ethanol yielded colorless plates, m.p. 225–226° (dec.).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.07; H, 6.95; N, 11.89.

The picrate crystallized in short orange prisms from water as the monohydrate, m.p. 127–129° (dec.).

Anal. Calcd. for $C_{13}H_{16}N_2O_2.C_6H_3N_3O_7.H_2O$: C, 47.60; H, 4.42. Found: C, 47.61; H, 4.47.

Decarboxylation of the 1-alkylamino acids. (*a*) *1-Methyltryptamine.* 1-Methyltryptophan (1.0 g.) was added to molten fluorene (10 g.) heated on a metal bath at 270°. After 2–3 min. all evolution of carbon dioxide ceased and the mixture was cooled, diluted with benzene, and extracted with dilute hydrochloric acid. The aqueous extract was clarified by shaking with ether and then made basic with sodium hydroxide and extracted with ether. The dried ether extract was evaporated and the residue distilled (180°/0.1 mm.) to yield 1-methyltryptamine as a pale yellow oil (0.484 g., 64% yield). The picrate was obtained as yellow prismatic needles from ethanol, m.p. 183–184° (lit.[8] 180–181°). The hydrochloride was obtained as colorless plates from ether-ethanol, m.p. 205–206° (dec.) (lit.[3] 199–202°). The phthalimide was prepared by refluxing the amine with an equal weight of phthalic anhydride in acetic acid. Crystallization from the same solvent yielded pale yellow needles, m.p. 178–179° (lit.[3] 177–177.5°).

(*b*) *1-Ethyltryptamine.* The 1-ethyltryptophan was decarboxylated in molten fluorene at 240–250°. The amine was isolated as described in the previous preparation and was obtained as a pale yellow oil in 53% yield. The picrate was obtained as orange prisms from ethanol, m.p. 182.5–183° (lit.[9] 180–181°). A large depression in melting point was observed on admixture with the picrate of N-ω-ethyltryptamine,[9] m.p. 186–187°. 1-Ethyltryptamine hydrochloride separated from a mixture of ethanol and ether in fine colorless needles, m.p. 193.5–194°.

Anal. Calcd. for $C_{12}H_{16}N_2.HCl$: C, 64.13; H, 7.63. Found: C, 64.20; H, 7.73.

1-Ethyltryptamine phthalimide was obtained as pale yellow prismatic needles from ethanol, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70. Found: C, 75.66; H, 5.78.

Paper chromatography of the amino acids. Chromatography was carried out on Whatman No. 1 paper using a mixture of 1-butanol (400 ml.), acetic acid (100 ml.), and water (250 ml.) as the developing solvent. The R_f values of tryptophan, 1-methyltryptophan, and 1-ethyltryptophan in this solvent were 0.63, 0.71, and 0.79, respectively. The amino acids appeared as brown spots on spraying with Millon reagent.

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Anionic Exchange Resins as Catalysts in the Preparation of Fulvenes

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The preparation of fulvenes by the condensation of cyclopentadiene with aldehydes or ketones in the presence of bases, such as ammonia and the alcoholates or hydroxides of sodium and potassium,[1] has long been known.[2] Work in this laboratory has now demonstrated that ion exchange resins of either the high or medium base strength type also are capable of catalyzing this reaction, giving in many cases yields comparable to those obtained with more conventional catalysts. This system possesses an advantage in that the reaction time can be quite easily controlled simply by regulating the contact time of the reactants with the ion exchange resin. Thus it is possible to achieve some success in the preparation of sensitive monosubstituted fulvenes and of fulvene itself by simply stopping the condensation before the secondary, base-catalyzed reactions start. This also helps to avoid complications caused by the presence of a base during the isolation and purification of the product.

Several fulvenes were prepared using this method, including fulvene, methyl fulvene, ethyl fulvene, and dimethyl fulvene. Of these, only dimethyl fulvene was isolated. In spite of numerous attempts, the remainder of the fulvenes could not be purified due to their extreme instability. Attempts to react them with maleic anhydride in order to prepare their Diels-Alder adducts as derivatives were also unsuccessful because of both their thermal instability and the reactivity of the residual cyclopentadiene in this reaction. Thus it was necessary to depend on the intense color of the products and their characteristic ultraviolet absorption spectra for proof of their presence. This of course, makes it

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impossible to determine yields of these sensitive fulvenes so that only these qualitative results can be given at this time. It is hoped that future refinements in technique may make a more quantitative treatment of this method possible.

EXPERIMENTAL

The ion exchange resins used in these reactions were prepared by first generating their basic forms with 20% aqueous potassium hydroxide, followed by thorough washing with distilled water. They were then washed well with methanol and dried under reduced pressure at room temperature. The dried resins were stored under nitrogen.

Dimethyl fulvene. Forty-four grams (0.67 mole) of cyclopentadiene was cooled to 0° in a 250 ml. glass-stoppered flask and 23 g. of Dowex 1-X10 (a strongly basic quaternary ammonium hydroxide type ion exchange resin) and 29 g. (0.5 mole) of acetone were added rapidly. The temperature of the mixture was permitted to rise slowly to room temperature and after 1.5 hr. a vigorous exothermic reaction commenced. The flask was shaken until the temperature began to fall and the reaction subsided (about 10 min. were required). The dark mixture was then allowed to stand at room temperature overnight. The Dowex 1-X10 was removed by filtration and thoroughly washed with ether, and the washings were combined with the original filtrate. The ether and unreacted starting materials were removed at 80 mm. pressure and the residue was kept at 30°/10 mm. for 1.5 hr. Fractionation of the residue through an 8 × 3/4 in. column packed with berl saddles gave 29.7 g. of the bright yellow dimethyl fulvene boiling from 41.5–45.5°/10 mm., yield 46.7%.

Methyl fulvene. A mixture of 22 g. (0.5 mole) of acetaldehyde and 44 g. (0.67 mole) of cyclopentadiene was introduced into the top of a 10 × 270 mm. column of Permutit A (an anionic exchange resin of medium base strength, consisting primarily of tertiary amine exchange sites) surrounded by a jacket containing circulating methanol cooled to −22 to −24° by an external Dry Ice–acetone bath. The rate of addition was adjusted so that the reactants were in contact with the resin for 1.25 hr., about 7 hr. being required to complete the reaction. The unreacted starting materials were removed at room temperature by distillation through a Dry Ice–cooled column at *ca.* 17 mm. The column was then permitted to warm to room temperature, the pressure was lowered to 0.75 mm. and the receiver was cooled in a Dry Ice–acetone bath. Under these conditions 16.3 g. of a bright yellow distillate (a solid at −70°) was collected without applying heat to the distilling flask. The ultraviolet absorption spectrum of this distillate in methanol showed a strong maximum at 255 mμ and a very weak one at 290 mμ. The absorption spectrum of dimethyl fulvene has a strong maximum at 265 mμ and a weak one a 357,[1] while that of fulvene is reported[3] to have maxima at 242 mμ (strong) and 362 mμ (weak). Thus the strong peak should be due to methyl fulvene.

Ethyl fulvene. In a 300-ml. three neck flask equipped with a stirrer, thermometer, reflux condenser, and addition funnel were placed 19.8 g. (0.30 mole) of cyclopentadiene and 10 g. of Dowex 1-X10. The mixture was cooled to 0° under nitrogen in an ice bath, and 14.5 g. (0.25 mole) of propionaldehyde was added over a 15-min. period while the temperature rose to 10–12°. After an additional 10 min. the mixture was warmed to 25° and the ion exchange resin was rapidly removed by filtration. The red-orange filtrate was transferred to a 50-ml. distilling flask, 3 g. of anhydrous magnesium sulfate was added, and the low-boiling material was removed at 20 mm., using a water bath at 40–50° for a heat source. After 3 hr. under these conditions no further boiling occurred and the orange oil was filtered to yield 14 g. of material. Its ultraviolet absorption spectrum showed a strong maximum at 256 mμ and a weak maximum at 360 mμ (see the previous section).

Fulvene. A mixture of 18.7 g. of 40% aqueous formaldehyde (equivalent to 0.25 mole of formaldehyde), 70 ml. of methanol, and 19.8 g. (0.3 mole) of cyclopentadiene was introduced into the top of a 20 × 150 mm. column of Amberlite IRA 400 (a strongly basic quaternary ammonium hydroxide type resin) at a rate such that the contact time with the catalyst was about 30 sec., 1 hr. being required to complete the reaction. The temperature of the column was maintained at *ca.* 5° throughout the reaction by circulating tap water. The orange oil which separated was removed and the aqueous layer was extracted 5 times with 10-ml. portions of ether. The extracts were combined with the original oil layer, dried over magnesium sulfate, and the solvent and other low boilers removed under reduced pressure as described in the previous sections. The yield of the orange product was 5.3 g. A single rather weak maximum occurred at 240 mμ in its ultraviolet absorption spectrum. This agrees quite well with the strong peak reported for fulvene[3] (see the preparation of methyl fulvene described previously). The absence of the second, weaker absorption at 362 mμ is probably due to the low concentration of the fulvene indicating a lack of purity in the product.

Acknowledgment. The author wishes to thank J. J. Mannion for the determination of the ultraviolet absorption spectra used in this work.

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Succinoylation of the Chloro- and Bromonaphthalenes

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Although the four halobenzenes have been converted to the corresponding β-(*p*-halobenzoyl)-propionic acids with succinic anhydride and aluminum chloride,[2] no successful succinoylation of the halonaphthalenes has been reported.[3] It is shown below that the chloronaphthalenes and 2-bromonaphthalene can be succinoylated, although the yields of pure products are low and the products are sometimes rearranged.

When 1-chloronaphthalene was treated with aluminum chloride and succinic anhydride in either tetrachloroethane or carbon disulfide solutions, an 87% and a 10% yield, respectively, of a mixture of difficultly separatable crude acids was obtained. Separation could best be effected by conversion of the acid mixture to the methyl esters and separation of the esters. From the mixture of methyl

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(2) E. Berliner in *Org. Reactions*, **V**, Chapter 5 (1949).

(3) The succinoylation of 1-bromo-4-methylnaphthalene has been described as unpromising. R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 2720 (1932).

esters pure β-(1-chloro-4-naphthoyl)propionic acid and β-(6-chloro-2-naphthoyl)propionic acid could be isolated. The ratio of pure acids was about 93:7 and they were identified by conversion to the known chloronaphthoic acids. The rearrangement, which must have occurred in the formation of the 2,6-isomer, is analogous to the rearrangement observed in the acylation of 1-chloronaphthalene, when a small amount of 2-chloro-6-acetylnaphthalene is obtained, in addition to the 1,4-product.[4] The succinoylation of 2-chloronaphthalene afforded chiefly β-(6-chloro-2-naphthoyl)-propionic acid, identical with the acid obtained in small amount from 1-chloronaphthalene, as well as a very small amount of an unidentified acid.

With 1-bromonaphthalene no bromo acid could be isolated. Instead, a mixture of β-(1-naphthoyl)- and β-(2-naphthoyl)propionic acid was obtained, as well as higher brominated naphthalenes, most likely 2,6-di- and 1,2,6-tribromonaphthalene. The acid mixture is similar to that obtained on succinoylation of naphthalene, and the formation of the naphthoylpropionic acids probably constitutes a succinoylation of naphthalene, rather than a debromination of bromonaphthoylpropionic acids. That is, it is assumed that the removal of the bromine atom from the 1-position is faster than the possible succinoylation of 1-bromonaphthalene. The formation of naphthalene and of polybromonaphthalenes from bromonaphthalene, as well as the isomerization of the chloro- and bromonaphthalenes, on treatment with aluminum chloride has been known for many years.[5] With 2-bromonaphthalene, a very small amount of β-(6-bromo-2-naphthoyl)propionic acid, identified by hypohalite oxidation to the known 6-bromo-2-naphthoic acid, was obtained.

EXPERIMENTAL

The succinoylations of 1-chloronaphthalene, as well as of the other halonaphthalenes, were conducted by the general procedures described in the literature.[2] In a typical run, 14 g. of aluminum chloride was added over 1 hr. to an ice-cold solution of 0.05 mole each of 1-chloronaphthalene and succinic anhydride in 100 ml. of tetrachloroethane. After 16 hr. at room temperature, the reaction mixture was worked up as usual. The acid mixture weighed 11.5 g. (87%). Numerous fractional crystallizations did not effect a separation into pure acids, although two main fractions were obtained. The best separation was performed when the crude acid mixture was first recrystallized once from ethanol. From a run conducted on 0.2 mole of 1-chloronaphthalene there was obtained a first crop of 17 g. of crystals, while 26 g. more was obtained by diluting the alcoholic filtrate with ice. The 17 g. was esterified with 150 ml. of methanol and 10 ml. of concentrated sulfuric acid. On cooling, 12.65 g. of brownish crystals, melting at 52–54°, separated. The filtrate of this ester was poured onto ice and the mixture was extracted with ether. After washing with a 10% sodium hydroxide solution and drying, the ether was boiled off and the remaining oil was crystallized from methanol, when 0.5 g. of yellow needles, melting at 110–115°, deposited. Two and one half g. of orange crystals (m.p. 48–50°) was obtained from the mother liquor. The 26 g. was treated in the same way, but the yields of pure product were considerably less. After several more crystallizations and combining of appropriate fractions, the over-all yield was 36.5% of the lower melting pure methyl β-(1-chloro-4-naphthoyl)propionate and 2.5% of pure methyl β-(6-chloro-2-naphthoyl)-propionate.

Methyl β-(1-chloro-4-naphthoyl)propionate forms colorless plates from petroleum ether and melts at 53.0–53.5°.[6]

Anal. Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.13; H, 4.81.

β-(1-Chloro-4-naphthoyl)propionic acid, obtained from the above ester on basic hydrolysis, was crystallized alternately from benzene and aqueous ethanol, and forms small, colorless needles melting at 161.8–163.3°.

Anal. Calcd. for $C_{14}H_{11}O_3Cl$: C, 64.00; H, 4.22. Found: C, 64.26; H, 4.45.

Oxidation of the above acid with hypochlorite solution[7] afforded 4-chloro-1-naphthoic acid of m.p. 220–222°, after one crystallization from aqueous ethanol (lit.[4] 223–224°). The *p*-bromophenacyl ester, recrystallized from aqueous ethanol, melted at 130.7–131.4° (lit.[8] 130–131°).

Methyl β-(6-chloro-2-naphthoyl)-propionate forms white needles from methanol which melt at 120.0–120.4°.

Anal. Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.19; H, 4.89.

β-(6-Chloro-2-naphthoyl)propionic acid, obtained from the above ester, forms white flakes from ethanol, melting at 196.5–197.3°.

Anal. Calcd. for $C_{14}H_{11}O_3Cl$: C, 64.00; H, 4.22. Found: C, 64.09; H, 4.26.

Oxidation of this acid afforded 6-chloro-2-naphthoic acid melting at 280–281°, after two crystallizations from ethanol (lit.[4] 285–286°). The amide was recrystallized from ethanol and melted at 205–206° (lit.[4] 206.5–207°).

The succinoylation of 2-chloronaphthalene (2.5 g.) in tetrachloroethane afforded 3.5 g. (87%) of impure product, melting over a range of 95–133°. Fractional crystallization afforded β-(6-chloro-2-naphthoyl)propionic acid, identical by melting point and mixed melting point with the acid obtained from 1-chloronaphthalene. The residue from the crystallizations contained another acid, but the 0.1 g. of material melting at 145.8–153.2° was not further investigated.

The succinoylation of 1-bromonaphthalene (20.7 g.) in tetrachloroethane afforded in the steam-distillate 9 g. of unchanged starting material, identified by its picrate (m.p. 134–135°), as well as 45 mg. of a solid, m.p. 157.3–158°, from ligroin, which is presumably 2,6-dibromonaphthalene (lit.[9] 160) and 80 mg. of presumably 1,2,6-tribromonaphthalene, m.p. 116.5–117° (lit.[9] 118°). From the acid fraction, about 5–6 g. of yellow material crystallized gradually, from which β-(2-naphthoyl)propionic acid was isolated. It melted at 170.0–172.2° and was identified by a mixed melting point and neutralization equivalent (229.3; calcd. 228.2). The filtrate contained material of neutralization equivalent 231.9, from which the 1-acid was recovered by

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(6) Melting points are corrected.

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fractional acidification;[10] it was identified by melting point and mixed melting point. Small amounts of unidentified acidic material remained behind. The results in runs in nitrobenzene were similar, except that no di- or tribromonaphthalenes were obtained.

2-Bromonaphthalene (10 g.) was succinoylated in nitrobenzene solution. The crude acid weighed 4.4 g. Repeated recrystallizations from methanol afforded eventually 0.35 g. (2.4%) of yellow crystals of β-(6-bromo-2-naphthoyl)-propionic acid, which started to change color at 198° and decomposed at 207°.

Anal. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.74; H, 3.61. Found: C, 54.82; H, 3.70.

Small amounts of β-(2-naphthoyl)propionic acid were obtained from the mother liquor. In tetrachloroethane the yields of pure acid were even smaller.

Hypohalite oxidation of the above acid afforded 6-bromo-2-naphthoic acid, which after two crystallizations from ethanol melted with decomposition at 279–286° (lit.[11] 280° dec.). The methyl and ethyl esters, after crystallizations from methanol and ethanol, respectively, melted at 122.0–123.5° and at 66.5–68.0° (lit.[11] 123–124.5° and 67–68°).

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A Reactive Peptide Intermediate Derived from Ethoxyacetylene

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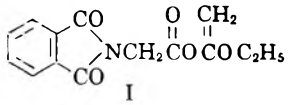
Our studies[2,3] of peptide synthesis in aqueous solution prompted us to investigate the possible utility of ethoxyacetylene[4] under these conditions. An aqueous solution of ethoxyacetylene, phthaloylglycine, and glycine ethyl ester deposited a solid, which was composed of the expected phthaloylglycylglycine ethyl ester[5] and a neutral product in an approximate ratio of 1:8.

The analytical data for the major product supported a structure arising from a 1/1 addition of acid and ethoxyacetylene.

The reaction of the adduct and ethyl glycinate at 60° and at room temperature in anhydrous solvents gave 80% and 75% respectively of phthaloylglycylglycine ethyl ester. These results rule out the symmetrical anhydride of phthaloylglycine, a plausible structure since ethoxyacetylene is known to convert acids to anhydrides,[6]

An infrared spectrum of a chloroform distillate from the reaction of the adduct and ethyl glycinate was identical to that of an ethyl acetate in chloroform solution. The isolation of ethyl acetate is convincing evidence for structure I. Similar results were obtained with phthaloyl-L-phenylalanine.



I

In the examples of peptide synthesis using alkoxyacetylenes published by Arens and coworkers[4] no case was reported in which the possibility of racemization by an azlactonization mechanism existed. We have prepared carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester[7] from carbobenzyloxyglycyl-L-phenylalanine and glycine ethyl ester with no sign of racemization.

EXPERIMENTAL[8]

1-Ethoxyvinyl phthaloylglycinate (I). A solution of 0.6 g. (2.93 mmoles) of phthaloylglycine[9] and 0.302 g. (2.93 mmoles) of glycine ethyl ester in 6 ml. of water and 0.6 ml. of ethoxyacetylene[10] was stirred at room temperature for 2 hr. The solid, which separated slowly, amounted to 300 mg.; m.p. 102–107°. Recrystallization from benzene and petroleum ether (30–60°) gave as a first crop (yield, 36 mg.) a crystalline product which proved to be identical with phthaloylglycylglycine ethyl ester.[5] The filtrate was evaporated to dryness under reduced pressure and the residue was crystallized from ether, 200 mg., m.p. 108–110°.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.36; H, 4.91; N, 5.15.

Phthaloylglycylglycine ethyl ester.[5] *A.* A solution of 50 mg. (0.182 mmole) of the adduct I and 19 mg. (0.182 mmole) of glycine ethyl ester in 1 ml. of dioxane was heated at 50° for 30 min. The dioxane solution was freeze dried and the residue crystallized from ethanol; yield, 42 mg. (80%); m.p. 191–193°. The melting point of a mixture with authentic phthaloylglycylglycine ethyl ester did not show a depression.

B. A solution of 19 mg. (0.182 mmole) of ethyl glycinate and 50 mg. (0.182 mmole) of I in 3 ml. of methylene chloride was stored at room temperature for 4 hr. Removal of the solvent and crystallization from ethanol afforded a product (40 mg.; 75%) which was identical to the product obtained in Run A.

Isolation of ethyl acetate from I. A solution of 400 mg. (1.5 mmole) of I and 152 mg. (1.5 mmole) of glycine ethyl ester in 0.5 ml. of chloroform was heated at reflux for 30 min. The solvent was then distilled until 0.25 ml. was collected. An infrared spectrum of this distillate was identical to one of ethyl acetate in chloroform. The residue yielded 480 mg. of phthaloylglycylglycine ethyl ester; m.p. 191–192°.

Carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester.[7] A mixture of 0.15 g. (0.42 mmole) of carbobenzoxyglycyl-L-phenylalanine, 43 mg. (0.42 mmole) of glycine ethyl ester, and 0.5 ml. of ethoxyacetylene was heated under reflux for 30 min. The excess ethoxyacetylene was distilled under reduced pressure. The oily residue was dissolved in 6 ml. of

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ethyl acetate and the solution was washed with 1*N* potassium bicarbonate (2 × 6 ml.). The ethyl acetate layer was dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue after crystallization from ethyl acetate–petroleum (30–60°) amounted to 90 mg. (49%); m.p. 114–116°; $[\alpha]_D^{26.0}$ −12.4°. The reported values[7] are 116–118° and $[\alpha]_D^{25}$ −12.0°.

Phthaloyl-L-phenylalanylglycine ethyl ester.[2] To 0.3 ml. of ethoxy acetylene cooled in a Dry Ice–acetone mixture bath was added 0.1 g. (0.34 mmole) of phthaloyl-L-phenylalanine. The suspension was slowly allowed to warm to 0° and held at this temperature until solution was effected. Dioxane was added at −20° and the resulting solution lyophilized. The residual oil was dissolved in 0.5 ml. of chloroform and to it was added 35 mg. (0.34 mmole) of ethyl glycinate. The solution was heated at reflux for 30 min. after which the solvent was distilled until 0.25 ml. was collected. An infrared curve of this distillate was identical with one of ethyl acetate in chloroform. The residue from the distillation was evaporated to dryness under reduced pressure and the resulting solid crystallized from ethanol, 75 mg. (60%); m.p. 160–161°; $[\alpha]_D^{26.0}$ −146° (ethanol).

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Synthesis from Thiolesters. II. Synthesis of Cyclic Sulfides[1]

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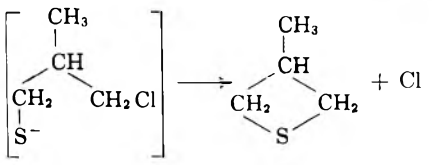
The high yields of thiolacetates obtained by the reaction of thiolacetic acid with most olefins makes these substances attractive as starting materials in the synthesis of a number of types of sulfur compounds including thiols[3] and alkanesulfonyl chlorides.[4] Applied to olefins containing a halogen or potential halogen grouping (*e.g.*, hydroxyl) the formation of thiolacetates by this route can serve as an approach to the synthesis of cyclic sulfides. For example, addition of thiolacetic acid to methallyl chloride gave an 88% yield of 2-methyl-3-chloropropyl thiolacetate. Hydrolysis of the latter by aqueous alkali together with concurrent steam distillation gave an 80% yield of redistilled 3-methylthiacyclobutane. The synthesis of this compound *via* 2-methyl-1,3-propanediol is much more tedious.

$$CH_2{=}C(CH_3)CH_2Cl + CH_3COSH \xrightarrow{\text{light}} CH_3COSCH_2CH(CH_3)CH_2Cl \xrightarrow{OH^-}$$



Over-all yields of 39% of thiacyclopropane (propylene sulfide) and 76% of thiacyclohexane were obtained by a similar route starting with 2-chloropropene and 5-chloro-1-pentene, respectively.

In the present paper this general method has been applied to the synthesis of simple 3-, 4-, and 6-membered ring cyclic sulfides. Its extension to other ring sulfides will be described later. The only previous use of this method that has come to our attention is the preparation of 3-hydroxythiacyclobutane by alkaline hydrolysis of mono- or diacetylated 2-hydroxy-3-chloropropanethiol.[5]

EXPERIMENTAL[6]

General procedure for the preparation of cyclic sulfides. The suspended haloalkyl thiolester was stirred and heated in an aqueous solution containing excess sodium hydroxide. The cyclic sulfide was isolated as it was formed by an internal steam distillation. It was separated mechanically and the aqueous portion of the steam distillate extracted three times with pentane. The sulfide and the pentane extracts were combined and dried over anhydrous magnesium sulfate. Distillation of the combined extracts yielded the product.

2-Methyl-3-chloropropyl thiolacetate. Starting with 45.3 g. (0.5 mole) of 2-methyl-3-chloro-1-propene and 38.1 g. (0.5 mole) of freshly distilled thiolacetic acid, 73 g. (87.8%) of 2-methyl-3-chloropropyl thiolacetate, b.p. 89° (16 mm.), n_D^{25} 1.4575 was obtained by the general procedure previously described.[3,4]

Anal. Calcd. for $C_6H_{11}OSCl$: C, 43.24; H, 6.65. Found: C, 43.60; H, 6.55.

3-Methylthiacyclobutane. A 1-l. flask, fitted with a stirrer and condenser arranged for distillation was charged with 12 g. (0.3 mole) of sodium hydroxide dissolved in 400 ml. of water and 25 g. (0.15 mole) of 2-methyl-3-chloropropyl thiolacetate. Carrying out the general procedure, 10.6 g. (80%) of 3-methylthiacyclobutane, b.p. 108–109°, n_D^{25} 1.4840, was obtained.

Anal. Calcd. for C_4H_8S: C, 54.49; H, 9.15. Found: C, 54.21; H, 9.29.

The monomercuric chloride addition product of 3-methylthiacyclobutane was prepared according to the method of Mann and Purdie.[7] Immediately after formation, the complex was recrystallized from ethanol and then acetone. In a sealed tube softening of the derivative began at about 85° and at 153° decomposition to a purple substance was observed.

Anal. Calcd. for $C_4H_8S{\cdot}HgCl_2$: C, 13.36; H, 2.24. Found: C, 13.81; H, 2.25.

5-Chloro-1-pentyl thiolacetate. Starting with 29 g. (0.23 mole) of 5-chloro-1-pentene (Peninsular Chem. Research, Inc., Gainesville, Fla.) and 17.4 g. (0.3 mole) of freshly distilled thiolacetic acid, 36 g. (87%) of 5-chloro-1-pentyl thiol-

(1) Presented in part at the 126th meeting of the American Chemical Society, New York, September 1954 (p. 6-O of Abstracts).

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acetate, b.p. 135–138° (25 mm.) was obtained by the general procedure previously described.[3]

Anal. Calcd. for $C_7H_{13}OSCl$: C, 46.52; H, 7.23. Found: C, 46.61, 46.54; H, 6.69, 6.87.

Thiacyclohexane. Starting with 34 g. (0.19 mole) of 5-chloropentyl thiolacetate, 16.52 g. (87%) of thiocyclohexane, b.p. 140–141° was obtained. Whitehead, Dean, and Fidler[8] reported the b.p. to be 141.6°.

2-Chloropropyl thiolacetate. Starting with 153 g. (2 moles) of 2-chloropropene (Shell Chemical Co.) and 114.2 g. (1.5 moles) of freshly distilled thiolacetic acid, 216 g. (94.2%) of 2-chloropropyl thiolacetate, b.p. 71° (10 mm.), was obtained by the general method previously described.[3,4] It was necessary to employ an ice water bath to control the exothermic reaction on a run of this size. Culvenor, Davies, and Heater[9] reported the b.p. to be 70–71° (9 mm.).

Thiacyclopropane (propylene sulfide). A. Starting with 68 g. (0.45 mole) of 2-chloropropyl thiolacetate, the above procedure was carried out with the exception that sodium carbonate was substituted for sodium hydroxide, which caused polymerization. Distillation of the combined extracts through a three-plate Vigreux column yielded 8.5 g. (25%) of thiacyclopropane, b.p. 72–75°, and 11 g. (16% recovery) of the starting material. The reaction flask continued a considerable amount of polymeric material.

B. Forty-five grams (0.29 mole) of 2-chloropropyl thiolacetate was stirred overnight with 500 ml. of methanol containing 5 ml. of concentrated hydrochloric acid. The reaction mixture was then neutralized to a *p*H of 7 (indicator paper) with a dilute sodium hydroxide solution. The reaction mixture was stirred at room temperature for an additional hour, and then extracted 4 times with 50-ml. portions of pentane. Distillation through a 3-plate Vigreux column yielded 7 g. (30.5%) of thiacyclopropane, b.p. 72–75°. Considerable polymeric material remained in the distillation flask.

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Synthesis of DL-Norleucine-2-C^{14}

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Since DL-norleucine-2-C^{14} was desired for metabolic studies but had not previously been synthesized, the following synthesis was undertaken:[2–7]

R = $CH_3CH_2CH_2CH_2$

$$RBr \xrightarrow[\text{Ether}]{Mg^\circ} RMgBr \xrightarrow[H_2SO_4]{C^{14}O_2} R{-}C^{14}OOH \xrightarrow[\text{Ether}]{LiAlH_4}$$

$$RC^{14}H_2OH \xrightarrow{PBr_3} RC^{14}H_2Br \xrightarrow[\text{Ether}]{Mg^\circ} RC^{14}H_2MgBr \xrightarrow[H_2SO_4]{CO_2}$$

$$RC^{14}H_2COOH \xrightarrow[PCl_3]{Br_2} R{-}C^{14}HCOOH \xrightarrow{\text{concd. } NH_3}$$

(Br)

$$R{-}C^{14}H{-}COOH$$

(NH_2)

EXPERIMENTAL

Valeric acid-1-C^{14}. *n*-Butylmagnesium bromide (0.203 mole) was prepared according to standard procedures and carbonated with $C^{14}O_2$ in a vacuum manifold at 2-mm. pressure.[3] The acid was recovered from the reaction flask by steam distillation over silver sulfate. The product was separated, washed with ether, dried several hours over anhydrous magnesium sulfate, and redistilled to yield 7.1–9.1 ml. (77–83%), b.p. 170–190°.

n-Amyl alcohol-1-C^{14}. Valeric-acid-1-C^{14} was reduced to *n*-amyl alcohol-1-C^{14} with $LiAlH_4$ using anhydrous ether as a solvent.[4] The product was recovered by separation of the ether phase, removal of the ether and distillation of the fraction boiling between 128–140°. The yield was 76–78% (6.4–7.0 ml.).

Caproic-acid-2-C^{14}. *n*-Amyl bromide-1-C^{14} was prepared by the bromination of *n*-amyl-alcohol-1-C^{14} with PBr_3.[5] The reaction mixture was allowed to stand for 2 hr. The product was recovered by distillation and washed successively with water, concd. H_2SO_4 and 10% Na_2CO_3. The product was dried over anhydrous Na_2SO_4 and redistilled, collecting the fraction boiling between 125–128°. The yield was 70–72% (5.5–5.1 ml.). *n*-Amylmagnesium bromide-1-C^{14} was then prepared and carbonated at −20° by passing inactive CO_2 gas through the solution. Caproic-acid-2-C^{14} was recovered by the method used for valeric acid-1-C^{14} and yielded 55–66% (5.5–7.3 ml.).

DL-*norleucine-2-C^{14}.* α-Bromocaproic acid-2-C^{14} was prepared by brominating caproic acid-2-C^{14} with Br_2 and PCl.[6] The product was recovered by fractional distillation at 10-mm. Hg pressure collecting the product boiling at 128–131°. Yield: 45–67% (5.14–5.91 g.). α-Bromocaproic acid-2-C^{14} was then added to a flask containing concentrated NH_3, tightly stoppered and heated in a 50–55° water bath for 24 hr. The flask was then cooled to and kept at 4° for 24 hr. The shiny white flakes which crystallized were recovered by filtration, washed with cold methanol, and dried at 105°.[7] The yield was 59–62% (2.16–2.24 g.). The over all yield was 8.2–8.3% based on $BaC^{14}O_3$, and the over all isotopic yield based on the specific activity of $BaC^{14}O_3$, was 6.7–7.2% (3.67–3.97 mc.). The specific activities of the final products were 1.64 μc./mg. and 1.85 μc./mg. for 2 successive syntheses. These specific activities were determined by the oxidation of the product to $C^{14}O_2$ with $K_2S_2O_8$.[8] The $C^{14}O_2$ was then precipitated as $BaC^{14}O_3$ and counted at infinite thickness in a Tracerlab windowless Geiger flow gas counter and autoscaler. The total isotopic yield was increased by 0.2 mc. by the addition of inactive norleucine to the filtrate and subsequent recrystallization. Paper chromatograms developed with butanol–acetic acid–H_2O and phenol-H_2O systems in one and/or two dimensions and sprayed with ninhydrin showed a single spot which coincided with known samples of norleucine. Mixed chromatograms also showed a single spot. Autoradiograms of these papers showed only a single radioactive spot matching the ninhydrin spot showing the radioactive purity of the norleucine.

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Anal.[9] Calcd. for $C_6H_{13}O_2N$; C, 54.94; H, 9.99; N, 10.68. Found: C, 55.00, 55.16; H, 9.81, 9.75; N, 10.56, 10.55.

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Crystallizable Polystyrene. II. Polymerization of Styrene with Triphenylmethyl Potassium and Related Compounds

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In preceding publications[1,2] the preparation of crystallizable polystyrene with Alfin-type catalysts was reported. The present work deals with the extension of the organometallic catalysts for the polymerization of styrene to include alkali metal derivatives of triphenylmethane and related compounds. Triphenylmethylpotassium, diphenylcyclohexylmethylpotassium, and diphenylmethylpotassium have been found to produce crystallizable polystyrene, having the same range of crystallizability as the polymers prepared using the Alfin catalyst. The highest degree of crystallizability comparable to that produced by the Alfin catalysts was obtained by use of triphenylmethylpotassium. 1,1-Diphenylethylpotassium, benzylpotassium, triphenylmethylsodium, sodium hydride, potassium amide, and potassium gave noncrystallizable polystyrene. Table I contrasts the results obtained when styrene was polymerized using the above catalysts.

In accord with previous observations using the Alfin catalysts,[1,2] polymerizations with triphenylmethylpotassium conducted in a benzene medium, produced high yields of noncrystallizable polystyrene. The heterogeneous isotactic polymerization system was thus converted to a homogeneous nonisotactic polymerization since benzene acted as a solvent for triphenylmethylpotassium. A hexane medium, however, provided the required heterogeneous system, facilitating isotactic polymerization.

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EXPERIMENTAL

Polymerizations. The polymerizations and crystallizations were carried out as previously described.[1]

Catalysts. The catalysts were bottled under dry nitrogen with self-sealing caps and were dispensed by means of hypodermic syringes and needles.

Triphenylmethylpotassium. Triphenylmethylpotassium was prepared according to the method of Levine, Baumgarten, and Hauser.[3] The triphenylmethylpotassium was transferred to a hexane suspension by removal of ether by distillation. The hexane suspension was transferred from the reaction flask by nitrogen pressure and was stored in a bottle capped with a self-sealing cap.

Diphenylmethylpotassium. Diphenylmethylpotassium was prepared in ether solution according to the method of Yost and Hauser.[4] The ether was subsequently replaced with hexane.

Benzylpotassium. Benzylpotassium was prepared from chlorobenzene and potassium in a toluene medium, according to the procedure of Gilman, Pacivitz, and Baine.[5]

Potassium amide. Potassium amide was prepared in liquid ammonia.[3] The liquid ammonia was replaced by hexane.

Diphenylcyclohexylmethylpotassium. Diphenylcyclohexylmethylpotassium was prepared according to the directions of Ziegler and Schnell,[6] with some modifications. The potassium compound was prepared using diphenylcyclohexylchloromethane (m.p. 83–84°) which was prepared from the carbinol *via* acetyl chloride. Diphenylcyclohexylchloromethane was treated with potassium amide, according to the directions used for the preparation of diphenylmethylpotassium.[4] Diphenylcyclohexylacetic acid was obtained in 92% crude yield by the carbonation of diphenylmethylcyclohexylpotassium and melted at 202–203° upon recrystallization from acetic acid. This melting point is in agreement with that obtained by Ziegler and Schnell[6] by carbonation of the diphenylcyclohexylmethylpotassium which they obtained by reaction of potassium on diphenylcyclohexylcarbinol methyl ether. The catalyst was transferred to hexane solution as already described.

1,1-Diphenylethylpotassium. 1,1-Diphenylethylene[7] was reduced to 1,1-diphenylethane with sodium ethylate, according to the directions of Klages.[8] 1,1-Diphenylethylpotassium was prepared by essentially the same method as that used for diphenylmethylpotassium. However, in this case, hexane was used in place of ether since 1,1-diphenylethane was soluble in hexane. 1,1-Diphenylpropionic acid obtained by carbonation of the potassium salt was obtained in 94% crude yield and melted at 171–172° on crystallization from benzene. This melting point is in agreement with that obtained by Ziegler and Schnell[6] on carbonation of 1,1-diphenylethylpotassium which they obtained by the action of potassium on 1,1-diphenylethylcarbinol methyl ether.

Potassium. A 0.1-g. piece of freshly cut potassium was used. The polymer grew outward from the surface of the potassium.

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TABLE I

POLYMERIZATION OF STYRENE

Catalyst	Run	Catalyst Concentration Moles/liter	Ml.	Catalyst Medium	Polymerization Medium	Ml.	Ml. Styrene	Time	Temp.	Crystallinity[a,b]	Inherent Viscosity[a]	Yield G.	Yield %
Triphenylmethylpotassium	1	0.19	30	Hexane	Hexane	200	30	7 hr.	Reflux	High	1.3	1.5	5.5
	2	0.19	30	Hexane	Hexane	200	30	18 hr.	Reflux	High	0.79	21.0	7.7
	3	0.19	30	Hexane	Hexane	200	30	2 wk.	40°	Medium	2.76	15.0	55.5
	4	0.19	5	Hexane	...	...	5	5 days	25°	High	1.61	3.5	78.0
	5	0.53	30	Hexane	...	...	30	5 days	25°	Medium	0.93	24.0	89.0
	6	0.53	60	Hexane	...	...	30	2 days	25°	High	0.96	9.5	35.2
	7	0.19	30	Hexane	Benzene	200	30	8 hr.	Reflux	Nil	0.19	14.0	51.7
	8	0.19	30	Hexane	Benzene	200	30	18 hr.	Reflux	Nil	0.2	26.3	97.5
Diphenylcyclohexylmethylpotassium	9	0.5	30	Hexane	Hexane	200	30	8 days	40°	High	0.68	24.0	88.8
Diphenylmethylpotassium	10	0.8	15	Hexane	Hexane	200	30	3 days	40°	Medium	0.48	22.6	84.0
	11	0.8	30	Hexane	...	...	30	3 days	40°	Low	0.32	27.0	100.0
1,1-Diphenylethylpotassium	12	0.1	30	Hexane	Hexane	100	30	4 days	25°	Nil	1.41	7.0	25.9
Benzylpotassium	13	0.66	5	Toluene	Hexane	200	30	1 day	28°	Nil		19.0	70.0
	14	0.66	10	Toluene	Hexane	200	30	15 min.	25°	Nil	1.0	27.0	100.0
Triphenylmethylsodium	15	0.96	20	Ether	Hexane	200	30	14 days	25°	Nil	0.24	23.0	88.8
Sodium hydride	16	10 g.		...	Hexane	200	30	72 hr.	25°	Nil	0.88	24.3	90.0
Potassium amide	17	0.2		Hexane	Hexane	100	30	24 hr.	25°	Nil	0.29	5.0	18.5
Potassium	18	0.1		Hexane	Hexane	200	30	60 days	25°	Nil	2.45	5.0	18.0

[a] Viscosity and crystallinity measurements were made as described previously.[2] [b] The samples of polymers were crystallized by immersion in boiling heptane for 16 hr.

Pyridinaldazines

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Although 2-pyridinaldazine was described as long ago as 1915,[3] and in spite of a widespread interest in the physiological properties of various pyridine aldehyde derivatives,[4-11] we have been unable to locate any later reference to the azines of the pyridine aldehydes.[12]

As part of a fungicidal study,[13] we have prepared 2-, 3- and 4-pyridinaldazine in alkaline media using the convenient method of *Organic Synthesis* for benzalazine.[14] In each case the yield was excellent (over 90%). Azine formation under these conditions is not conventional and to check the generality of this procedure we have prepared the known 1-naphthaldazine,[15] 2,2′-dichlorobenzalazine,[16] and 3,3′-dinitrobenzalazine[17] in similar yield.

EXPERIMENTAL[18]

2-Pyridinaldazine. 4.6 g. (0.43 mole) of pyridine-2-carboxaldehyde was added dropwise to a solution of 2.4 g. (0.185 mole) of hydrazine sulfate in 180 ml. of water and 25 ml. of concentrated ammonium hydroxide with vigorous stirring at room temperature. Stirring was continued for 3 hr. The yellow product which had separated was recrystallized from aqueous methanol to give 4.1 g. of the azine

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(12) After this note had been prepared, the Abstracts of Papers of the 132nd Meeting of the American Chemical Society, New York, Sept. 8–13 (1957), appeared which contain an abstract (12N, paragraph 32) concerning complexes of 2-pyridinaldazine with iron (II) and nickel (II) by W. J. Stratton and D. H. Busch.

(13) Details of which we hope to publish later elsewhere.

(14) *Org. Syntheses*, **Coll. Vol. II**, page 395.

(15) M. L. Rousset, *Bull. soc. chim. France* [3], **17**, 304 (1897).

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(17) Th. Curtius and A. Lublin, *Ber.*, **33**, 2462 (1900).

(18) Melting points are uncorrected.

(yield 91%) as long golden yellow blades, m.p. 151–152°. Lit.[3] m.p. 149°.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.63; H, 4.63; N, 26.40.

The following five azines were similarly prepared.

3-Pyridinaldazine, golden yellow prismatic needles (4.1 g., yield 91%) from aqueous methanol, m.p. 148–149°. A specimen on admixture with 2-pyridinaldazine melted at 126–128°.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.45; H, 4.69; N, 26.45.

4-Pyridinaldazine, golden yellow needles (4.15 g., yield 92%) from aqueous methanol, m.p. 192–193°.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.60; H, 4.91; N, 26.35.

1-Naphthaldazine, yellow needles (3 g., yield 90%) from acetone-methanol, m.p. 155–156°. Lit.[15] m.p. 152°.

2,2'-Dichlorobenzalazine, long yellow needles (2.6 g., yield 87%) from methanol, m.p. 150–151°. Lit.[6] m.p. 143–145°.

3,3'-Dinitrobenzalazine, yellow blades (2.9 g., yield 89%) from acetic acid, m.p. 196–197°. Lit.[17] m.p. 194°.

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Preparation of 2-Cyanotetrahydropyran[1]

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Received July 29, 1957

Although substituted 2-cyanotetrahydropyrans have been reported in the literature, they have been prepared either by addition of hydrogen cyanide to substituted dihydropyrans[3] or by reaction of appropriate acroleins and vinyl cyanides[4] in reactors at moderate pressure. There appeared to be no simple laboratory procedure for 2-cyanotetrahydropyran which was needed for other research. Accordingly the metathesis of 2-bromotetrahydropyran with metal cyanides has been partly evaluated as a method of synthesis.

2-Bromotetrahydropyran[5] solutions were treated in toluene with cuprous, mercuric, potassium, and silver cyanides in the manner reported for open chain, α-chloro ethers.[6] Maximum conversions were obtained in experiments at 20–30°. None of the desired product was formed when potassium cyanide was used and the yield was only 12% from cuprous cyanide. However, silver and mercuric cyanides gave 27–30% yields of 2-cyanotetrahydropyran.

The compound was characterized by hydrolysis in 63% yield to tetrahydropyran-2-carboxylic acid[7] and by reaction with benzylmagnesium chloride to form 2-(phenylacetyl)tetrahydropyran.

EXPERIMENTAL

2-Cyanotetrahydropyran. A solution of 85 g. (1.0 mole) of 2,3-dihydro-4*H*-pyran in 300 ml. of dry toluene was maintained at −10 to 0° while a stream of hydrogen bromide was added with stirring until 73 g. (0.90 mole) had been absorbed. The 2-bromotetrahydropyran so obtained was used for the preparation of the 2-cyano compound since attempts to isolate the halopyran by vacuum distillation resulted in decomposition.[8]

The toluene solution was added dropwise with stirring to a suspension of 252 g. (1.0 mole) of mercuric cyanide in 200 ml. of dry toluene in an exothermic reaction that was kept at 20–25°. After 2 hr. the mixture was filtered and the filtrate was washed with water, dried, and distilled to give 21–30 g. (21–30%) of 2-cyanotetrahydropyran, b.p. 90–92°/18 mm., n_D^{25} 1.4430.

In a similar way, 40 g. (0.30 mole) of silver cyanide added over 30 min. to 51 g. (0.31 mole) of the bromopyran in 200 ml. of dry toluene at 25–30° gave 9.0 g. (27%) of 2-cyanotetrahydropyran, b.p. 77–83°/16 mm., n_D^{24} 1.4455.

Anal. Calcd. for C_6H_9ON: C, 64.85; H, 8.16; N, 12.60. Found: C, 65.15; H, 8.16; N, 12.63.

Reaction of equimolar amounts of 2-bromotetrahydropyran and cuprous cyanide in a similar manner at 20–25° gave 12% of product, b.p. 75–79°/15 mm., n_D^{25} 1.4422, provided the reaction mixture was washed with 10% ammonium hydroxide before distillation.

2-Tetrahydropyrancarboxylic acid. A mixture of 55.6 g. (0.50 mole) of 2-cyanotetrahydropyran was boiled for 7 hr. with 40.0 g. (1.00 mole) of sodium hydroxide in 200 ml. of water. The alkaline solution was extracted with three 50-ml. portions of ether and exactly neutralized with one equivalent of hydrochloric acid. Ether extraction in a liquid-liquid extractor and distillation of the ether extract gave 41 g. (63%) of 2-tetrahydropyrancarboxylic acid, b.p. 142–145°/20 mm., n_D^{25} 1.4620.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75; neut. equiv., 130. Found: C, 55.50; H, 7.82; neut. equiv. 129.

The acid was further characterized by conversion to phenacyl 2-tetrahydropyrancarboxylate, m.p. 74–76°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.92; H, 6.65.

2-(Phenylacetyl)tetrahydropyran. A solution of 16.8 g. (0.15 mole) of 2-cyanotetrahydropyran in 100 ml. of ether was added dropwise to the Grignard reagent prepared from 7.2 g. (0.30 mole) of magnesium and 38 g. (0.30 mole) of benzyl chloride in 400 ml. of anhydrous ether. One hour after addition was complete, hydrolysis with ice and dilute hydrochloric acid and distillation of the dried ether layer gave 13 g. (42%) of 2-(phenylacetyl)tetrahydropyran, b.p. 155–165°/3–4 mm., n_D^{25} 1.5241. An analytical sample was obtained as a fraction, b.p. 140–141°/3 mm., n_D^{25} 1.5218.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.54; H, 8.00.

This product was further characterized as the 2,4-dinitrophenylhydrazone, m.p. 139–142°.

(1) Abstracted from the senior thesis of Kenneth Yorka, De Paul University, 1955. Preliminary experiments were conducted by A. M. Laurinaitis.

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Anal. Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.36; H, 5.24; N, 14.59. Found: C, 59.23; H, 5.29; N, 14.60.

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p-(*p*-Benzoylbenzoyl)benzoic Acid

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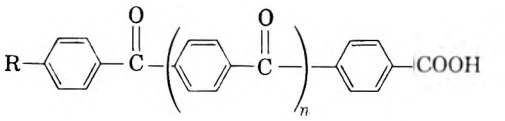
Information concerning the synthesis of linear polybenzoylbenzoic acids of type I is sparse. Koelsch and Bryan[2] prepared dibasic acids (Ia, n



Ia, R = COOH
Ib, R = H

= 1, 2, 3) by acylating toluene with acid chlorides such as those derived from terphthalic acid, *p,p'*-benzophenonedicarboxylic acid, etc., and subsequently oxidizing the end methyl groups to carboxylic acid groups. Acylation of benzene with *p,p'*-benzophenonedicarbonyl chloride gave *p*-(*p*-benzoylbenzoyl)benzoic acid as a by-product.[3] Finally, the acid catalyzed condensation of benzyl alcohol yields polymers which oxidized to a mixture of polyketones containing both ortho and para linkages.[4]

A possible route to compounds of type Ib is the Friedel-Crafts aroylation of *p*-benzylbenzoic acid by halides such as benzoyl chloride and *p*-benzoylbenzoyl chloride. In this way the preparation of *p*-(*p*-benzoylbenzyl)benzoic acid and its oxidation product, *p*-(*p*-benzoylbenzoyl)benzoic acid, was readily achieved. However, the few attempts to extend the synthesis were unsuccessful.

EXPERIMENTAL

p-(p-Benzoylbenzyl)benzoic acid. A solution of 0.05 mole of benzoyl chloride in 30 ml. of carbon disulfide was added with stirring to 0.04 mole of *p*-benzylbenzoic acid[5] and 0.16 mole of aluminum chloride in 30 ml. of carbon disulfide. The mixture was stirred and heated under reflux for 3 hr. after which it was hydrolyzed with ice and hydrochloric acid. The carbon disulfide was removed by steam distillation and the residue was dissolved in aqueous alkali and filtered. Acidification precipitated the crude acid which was twice recrystallized with decolorization from 150-ml. portions of methanol to give 6.6 g. (52%) of *p*-(*p*-benzoylbenzyl)-benzoic acid, m.p. 181.5–182.5°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10; N.E. 316. Found: C, 79.50; H, 5.17; N.E. 316.

p-(p-Benzoylbenzoyl) benzoic acid. A solution of 3.5 g. of sodium dichromate in 5 cc. of water, 8 cc. of acetic acid, and 1.7 cc. of concentrated sulfuric acid was added dropwise over a 20-min. period to a boiling solution of 3.0 g. of *p*-(*p*-benzoylbenzyl)benzoic acid in 25 ml. of acetic acid. After 45 min. it was poured into water and the precipitate was collected. This was difficultly soluble in dilute sodium hydroxide and methanol. Crystallization from 30 ml. of dioxane gave 2.0 g. (64%) of *p*-(*p*-benzoylbenzoyl)benzoic acid, m.p. 268.5–269.5° (lit., m.p. 268°).[3]

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Estrogen Esters[1]

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In the stercid field the same acylating group can promote a desirable physiological response in more than one hormone category.[2,3]

This study extended our observations with the acylation of androgens[4] to the synthetic estrogens diethylstilbestrol (I) and hexestrol (II). More particularly, we were interested in varying the character of the acylating group so that the estrogenic activity inherent in I and II would be increased as well as decreased. This objective is an outgrowth of the provocative concept of Myers[5] and coworkers who have stressed the importance of the steroid sex

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TABLE I

BIS ESTERS OF DIETHYLSTILBESTROL AND HEXESTROL

Compound No.	Acylating Group	M.P.,[a] °C.	Yield,[c] %	Molecular Formula	Carbon[b] Calcd.	Carbon[b] Found	Hydrogen Calcd.	Hydrogen Found
1.	$ClCH_2CH_2CO$	144–145	15	$C_{24}H_{26}Cl_2O_4$	64.1	64.2	5.8	5.9
2.	$BrCH_2CH_2CO$	137–139	19	$C_{24}H_{26}Br_2O_4$[d]	53.6	54.1	4.8	5.2
3.	ICH_2CH_2CO	107–108[e]						
4.	$(CH_3)_3CCH_2CO$	123–124	52	$C_{30}H_{40}O_4$	77.6	77.7	8.7	8.7
5.	$(C_6H_5CH_2)_2CHCO$	170–172	43[ca]	$C_{50}H_{48}O_4$	84.2	84.1	6.8	6.9
			HEXESTROL					
6.	$ClCH_2CH_2CO$	132–134	15	$C_{24}H_{28}Cl_2O_4$	63.9	63.7	6.2	6.4
7.	$BrCH_2CH_2CO$	129–130[e]	14[ca]	$C_{24}H_{28}Br_2O_4$[f]	53.4	55.1	5.2	5.5
8.	ICH_2CH_2CO	108–109[e]						
9.	$(CH_3)_3CCH_2CO$	173–175	83	$C_{30}H_{42}O_4$	77.2	77.3	9.1	9.3
10.	$(C_6H_5CH_2)_2CHCO$	187–189[cb]	52	$C_{50}H_{50}O_4$	84.0	83.8	7.0	7.1

[a] All melting points are uncorrected. [b] Analyses by Drs. Weiler and Strauss, Oxford, England. [c] Unless otherwise indicated the recrystallizing solvent was ethanol; [ca] acetone-water; [cb] heptane, then ethanol. [d] Calcd.: Br, 29.7. Found: Br, 29.4. [e] The compound could not be obtained analytically pure since it apparently suffered dehydrohalogenation on treatment. [f] Calcd: Br, 29.6. Found: Br, 28.2.

hormones on chemical regulation of the endocrine balance.

In the estrogen field, in particular, a wide range of clinical utility is indicated if the primary hormonal effect on the target organs could be modified. Such applications include modification of hypercholesteremia,[6] cupremia,[7] mammary gland growth,[8] calcemia,[9] acne,[10] clinical management of the climacteric,[11] increased feed efficiency in lambs,[12] adjunct to chloropromazine therapy,[13] and protective action against toxic effects of digoxin on the myocardium.[14]

Whereas Myers[5] varied the nuclear character of I and II, we investigated different acylating groups on I and II which insured an inherently active estrogenic function as part of the completed molecule with the potential that esters more active than I and II could then be evaluated at sub-threshold doses, and those esters which were less active could be assessed as to their influence on the non-target functions described above.

The selection of acylating groups was confined to bis-β-halopropionates which were expected to enhance activity and the bis-*tert*-butylacetate and bis-α,α-dibenzylacetates which were expected to afford steric resistance to *in vivo* saponification.[4]

TABLE II

ESTROGENIC ACTIVITY[a] OF BIS-ACYLATED DIETHYLSTILBESTROL (I) AND HEXESTROL (II)

Compound No.	Dosage γ/kg.	Dosage Molar Equivalent[b] to Standard Drug	Activity
1.	1.7	1	1.75
2.	2.0	1	1.94
	1.5	0.75	1.41
	1.0	0.50	1.53
3.	2.4	1	1.98
	1.8	0.75	1.52
	1.2	0.50	0
4.	1.7	1	0.61
5.	2.7	1	0
6.	1.7	1	1.07
7.	2.0	1	1.11
8.	2.4	1	0.42
9.	1.7	1	0.51
10.	2.7	1	0

[a] Estrogenic test was done by the Allen-Doisy method. (See ref. 15). Spayed female rats were given two subcutaneous doses of the compounds and estrus evaluated by two daily vaginal smears until disappearance of the reaction. Results are expressed as per cent animals showing signs of estrus, taking into account duration of the reaction. The results of the count of cornified epithelial cells were plotted on the ordinate, as a function of time, plotted on the abscissa, and the entire area under the curve was weighted and compared to the standard compounds. Each test represents the average response of six rats. The reaction produced by 1 γ of diethylstilbestrol (I) per kg. of rat is arbitrarily taken as 1 (1 γ of hexestrol (II) so evaluated = 1.04). [b] Compounds 1–5 based on I, Compounds 6–10 based on II.

(6) M. F. Oliver and G. S. Boyd, *Circulation*, **13**, 82 (1956).

(7) E. M. Russ and J. Raymunt, *Proc. Soc. Exptl. Biol. Med.*, **92**, 465 (1956).

(8) a H. Yamamoto and C. W. Turner, *Proc. Soc. Exptl. Biol. Med.*, **92**, 130 (1956); b D. Jacobsohn, *Acta Physiol. Scand.*, **32**, 304 (1954).

(9) a R. E. Clagg, A. S. Rosenthal, and P. E. Sanford, *Poultry Sci.*, **33**, 1197 (1954); b M. D. Bogdonoff, N. W. Shock, and J. Parson, *J. Gerontol.*, **9**, 262 (1954).

(10) S. M. Peck, E. G. Klarmann, and H. J. Spoor, *Arch. Dermatol. and Syphilol.*, **70**, 452 (1954); C. Lapière, *Compt. rend.*, **147**, 1302 (1953).

(11) R. C. Benson and J. W. Garetz, *J. Clin. Endocrinol. and Metabolism*, **13**, 258 (1953).

(12) F. N. Andrews, M. Stoh, T. W. Perry, and W. M. Beeson, *J. Animal Sci.*, **15**, 575 (1956).

(13) M. Hyvert, H. Fagard, and J. Huchon, *Annales Médico-psychologiques (Paris)*, **113**, 645 (1955).

(14) E. H. Grinell and P. W. Smith, *Proc. Soc. Exptl. Biol. Med.*, **94**, 524 (1957).

(15) C. W. Emmons, *Hormone Assay*, Academic Press, Inc., New York, N. Y., 1950, p. 396.

The compounds prepared are described in Table I, and the noted estrogenic activity as evaluated by the Allen-Doisy method[15] is shown in Table II.

The estrogenic activity tests reflect the capacity of the β-halopropionate linkage (Compounds 1–3, 6, and 7) to enhance the estrogenic response inherent in I and II. These compounds show a marked response when compared with previously assessed derivatives.[16]

The effect of the acylating group is much more pronounced in the derivatives of I than in those of II, and peak activity is found in Compound 2, the bis-β-bromopropionate of diethylstilbestrol. The use of these acylating groups in the androgen series also reflected a superiority of the β-bromo-propionate derivative.[4] The bis-*tert*-butyl acetates (Compounds 4 and 9) yielded activity below that of the parent structures, while the bis-α,α-dibenzyl acetates (Compounds 5 and 10) were inactive. It is of interest that both of these acylating groups above failed to give a hormonal response in the androgen work.[4]

EXPERIMENTAL[17]

The acid chlorides have been described.[4]

Bis(β-chloropropionate) of diethylstilbestrol (Compound 1). To a cooled (−10°) solution of 20 ml. of β-chloropropionyl chloride in 150 ml. of toluene was added dropwise with continued cooling and stirring over a 1-hr. period, a solution of 5 g. (0.0186 mole) of diethylstilbestrol in 20 ml. of pyridine and 150 ml. of toluene. After 20 hr. the reaction mixture was successively treated with water, 3*N* hydrochloric acid, water, saturated sodium bicarbonate, and water. The toluene layer was separated, dried over anhydrous magnesium sulfate, filtered, the toluene removed, and the residue recrystallized from ethanol yielded 1.37 g. (15%), m.p. 144–145°.

Bis(α,α-dibenzylacetate) of hexestrol (*Compound 10*). To a cooled (−10°) solution of 10 ml. of α,α-dibenzylacetyl chloride in 150 ml. of toluene was added dropwise with continued stirring and cooling, a solution of 5 g. (0.0185 mole) of hexestrol in 10 ml. of pyridine and 120 ml. of toluene. After standing 20 hr. the reaction mixture was processed as described for Compound 1. There was obtained 6.93 g. (52%) of product after successive recrystallizations from heptane and ethanol, m.p. 187–189°.

Acknowledgment. We are grateful to Dr. G. Ungar of our Pharmacology Division for evaluation of the estrogen activities and to A. Lawrence for his technical assistance in the preparation of the compounds.

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(16) J. A. Hogg and J. Korman, *Medicinal Chemistry*, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 34.

(17) All of the compounds described in Table I were prepared by the same general procedures and representative examples are described.

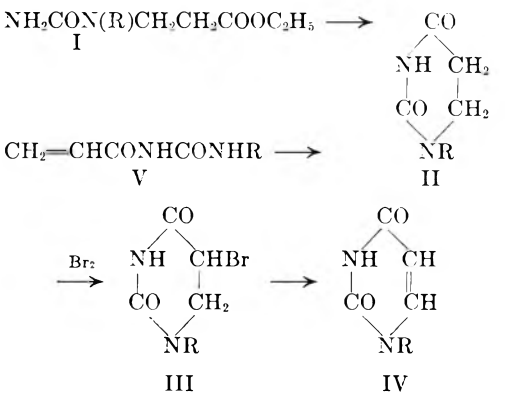
Synthesis of 1-Aryluracils[1]

NORMAN W. GABEL AND S. B. BINKLEY

Received October 15, 1957

Most of the biologically active synthetic pyrimidines have been shown to effect nucleic acid metabolism.[2,3] Since all naturally occurring pyrimidine nucleosides are pyrimidines substituted with a sugar moiety in the one position, 1-aryluracils might be expected to have significant biological activity. A careful survey of the literature and an examination of the review article by Kenner and Todd[4] revealed that no synthetic preparations for 1-arylpyrimidines has been reported.

There were two general methods for synthesizing uracils substituted in the one position. Either a halogen derivative of the group to be attached is treated with a metallic salt of the pyrimidine[5] or a substituted ureidopropionic acid (I) is cyclized to a dihydrouracil (II), brominated in the five position (III), and dehydrobrominated to the uracil (IV).[6,7] The former method is obviously inapplicable for substitution by an aromatic group and the latter was found to be unsuitable after many unsuccessful attempts to synthesize I having an aromatic group.



To obtain the 1-aryluracils it was necessary to develop a new synthetic preparation which, it is hoped, can also be adapted to nucleoside synthesis since there is no satisfactory method for the introduction of the carbohydrate group into the one position of the pyrimidine ring.

While this investigation was in progress, 1-phenyl-

(1) Based upon a dissertation submitted by N. W. Gabel in partial fulfillment of the requirements for the M. S. degree in The Graduate College at the Chicago Professional Colleges of the University of Illinois.

(2) R. J. Winzler, *Ann. Rev. Biochem.*, **18**, 535 (1949).

(3) G. H. Hitchings, *Am. J. Clin. Nutrition*, **3**, 321 (1955).

(4) G. W. Kenner and A. Todd, *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, Chap. 7.

(5) R. Behrend, *Ann.*, **253**, 67 (1889).

(6) E. Fisher and G. Roeder, *Ber.*, **34**, 3751 (1901).

(7) J. E. Gearien and S. B. Binkley, presented at the 131st ACS National Meeting, Miami, 1957.

uracil was synthesized by Atkinson *et al.*[8] They treated propiolic anhydride with urethane to obtain *N*-propiolylurethane. The aniline addition product of this compound yielded 1-phenyluracil upon treatment with dilute alkali.

In 1951 Lieser and Kemmner[9] reported the synthesis of 1-acrylyl-3-phenylurea from acrylyl isocyanate and aniline. Several 1-acrylyl-3-arylureas (V) were prepared in this investigation in 50% yields from the arylamine and a solution of acrylyl isocyanate in anhydrous ethyl ether. These ureas were light-sensitive. The mixing of the reactants required caution because the reaction is sometimes violent and acrylyl isocyanate is a strong lachrymator.

The 1-acrylyl-3-arylureas were cyclized to 1-aryldihydrouracils (II) by refluxing for 2–3 days in *N*,*N*-dimethylformamide to which had been added a small amount of glacial acetic acid. The dihydrouracils were converted to 1-aryl-5-bromodihydrouracils (III) by reaction with bromine in refluxing glacial acetic acid after the method of Gearien and Binkley.[7] The 1-aryluracils (IV) were obtained by dehydrobromination with lithium chloride in *N*,*N*-dimethylformamide. The over-all yield of 1-phenyluracil based on aniline was 13%.

In this synthetic scheme the only reaction which has not been previously reported is the cyclization of 1-acrylyl-3-arylureas to 1-aryldihydrouracils. This reaction apparently occurs through the nucleophilic attack of the nitrogen atom (originally from the arylamine) on the β-carbon of the acrylyl portion of the urea. This is similar to the nucleophilic addition of alkylamines[7] and arylamines[10] to acrylic acid derivatives. The factors facilitating this cyclization are (*a*) the positive charge residing on the β-carbon of one of the resonance forms of acrylic acid derivatives and (*b*) the formation of a stable six-membered ring.

Although no alkyl derivatives of uracil were attempted, there is no apparent reason why they could not be synthesized by this method. If this preparative scheme can be adapted to nucleoside synthesis, it would be possible to prepare pyrimidine nucleosides with either the alpha or beta configuration at the anomeric carbon atom by starting with either an α- or β-1-amino sugar derivative.

EXPERIMENTAL[11]

Acrylyl chloride and isocyanate. Acrylyl chloride was prepared according to the procedure of Stempel, Cross, and Mariella[12] from acrylic acid and benzoyl chloride. The method of Lieser and Kemmner[9] was followed for obtaining a solution of acrylyl isocyanate in anhydrous ethyl ether from acrylyl chloride and a suspension of silver cyanate in ethyl ether.

1-Acrylyl-3-arylureas. A procedure similar to the one described by Lieser and Kemmner[9] was followed. An Erlenmeyer flask containing the acrylyl isocyanate solution was placed in an ice bath. An equimolar amount of the arylamine was added slowly while the flask was being swirled. The precipitate was washed over a Büchner funnel with ethyl ether to remove unreacted materials and was recrystallized from 95% ethanol. *1-Acrylyl-3-phenylurea*: 27 g. (0.29 mole) of aniline yielded 27 g. (50%) of 1-acrylyl-3-phenylurea; m.p. 146°. Lieser and Kemmner[9] reported 147°. *1-Acrylyl-3-α-naphthylurea:* 42 g. (0.29 mole) of α-naphthylamine yielded 34 g. (50%) of 1-acrylyl-3-α-naphthylurea; m.p. 172–174°. *1-Acrylyl-3-p-chlorophenylurea:* 16.6 g. (0.13 mole) of *p*-chloroaniline yielded 15 g. (52%) of 1-acrylyl-3-*p*-chlorophenylurea; m.p. 203°. *1-Acrylyl-3-p-ethoxyphenylurea:* 35 g. (0.25 mole) of *p*-phenetidine yielded 24 g. (41%) of 1-acrylyl-3-*p*-ethoxyphenylurea; m.p. 124°.

1-Aryldihydrouracils. Eight to sixteen grams of the 1-acrylyl-3-arylurea, 50 ml. of *N*,*N*-dimethylformamide, and 15–20 ml. of glacial acetic acid were added to a round-bottomed flask fitted with a reflux condensor. After refluxing the mixture for 2–3 days, the solvent was removed by heating under reduced pressure (10–20 mm.). The residue was recrystallized from dioxane to yield the dihydrouracil as clumps of colorless needles. *1-Phenyldihydrouracil:* 11 g. (0.058 mole) of 1-acrylyl-3-phenylurea yielded 9 g. (82%) of 1-phenyldihydrouracil; m.p. 182–184°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.73. Found: C, 63.18; H, 5.31; N, 14.70.

1-α-Naphthyldihydrouracil: 8 g. (0.033 mole) of 1-acrylyl-3-α-naphthylurea yielded 1.5 g. (19%) of 1-α-naphthyldihydrouracil; m.p. 250–252° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: N, 11.24. Found: N, 11.21.

1-p-Chlorophenyldihydrouracil: 14 g. (0.062 mole) of 1-acrylyl-3-*p*-chlorophenylurea yielded 5.4 g. (39%) of 1-*p*-chlorophenyldihydrouracil; m.p. 224°.

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: N, 12.47. Found: N, 12.54.

1-p-Ethoxyphenyldihydrouracil: 16 g. (0.068 mole) of 1-acrylyl-3-p-ethoxyphenylurea yielded 13 g. (81%) of 1-*p*-ethoxyphenyldihydrouracil; m.p. 202–204°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.49; H, 5.96; N, 12.14.

1-Aryl-5-bromodihydrouracils. The procedure of Gearien and Binkley[7] was followed. To a refluxing solution of the 1-aryldihydrouracil in 20 ml. of glacial acetic acid was added slowly an equimolar amount of bromine dissolved in a few milliliters of glacial acetic acid. The reaction flask was cooled under running tap water and the *p*H of the contents was adjusted to *ca.* 5 with 10% sodium hydroxide. Water was then added to induce precipitation. The heavy flocculent precipitate was washed three times with distilled water over a Büchner funnel and recrystallized from dioxane. *1-Phenyl-5-bromodihydrouracil:* 2.7 g. (0.014 mole) of 1-phenyldihydrouracil yielded 2.6 g. (71%) of 1-phenyl-5-bromodihydrouracil; m.p. 192–193° dec.

Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.61; H, 3.34; N, 10.41; Br, 29.74. Found: C, 44.61; H, 3.34; N, 10.46; Br, 29.95.

1-α-Naphthyl-5-bromodihydrouracil: 1.4 g. (0.006 mole) of 1-α-naphthyldihydrouracil yielded 1.8 g. (94%) of 1-α-naphthyl-5-bromodihydrouracil; m.p. 275°.

Anal. Calcd. for $C_{14}H_{11}BrN_2O_2$: Br, 25.04. Found: Br, 24.97.

1-p-Chlorophenyl-5-bromodihydrouracil: 3.9 g. (0.017 mole) of 1-*p*-chlorophenyldihydrouracil yielded 2.7 g. (53%) of 1-*p*-chlorophenyl-5-bromodihydrouracil; m.p. 211–212° dec.

Anal. Calcd. for $C_{10}H_8BrClN_2O_2$: N, 9.23. Found: N, 9.19.

(8) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).

(9) T. Lieser and K. Kemmner, *Chem. Ber.*, **84**, 4 (1951).

(10) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

(11) Analyses were conducted by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points are uncorrected.

(12) G. H. Stempel, R. P. Cross, and R. P. Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950)

1-Aryluracils. The dehydrobromination of 1-aryl-5-bromodihydrouracils was accomplished by a procedure similar to the one described by Holysz.[13] A solution of equimolar amounts of lithium chloride and 1-aryl-5-bromodihydrouracil in 50 ml. of *N,N*-dimethylformamide was heated on a steam cone for 3 hr. Water was now added to the contents to bring about precipitation. The precipitate was washed with distilled water over a Büchner funnel, air-dried, and recrystallized from dioxane as fine colorless needles. The ultraviolet absorption spectrum in methanol (c = 20 μg./ml.) was obtained on a Beckman Ratio Recording Spectrophotometer. *1-Phenyluracil:* 2.3 g. (0.009 mole) of 1-phenyl-5-bromodihydrouracil yielded 0.7 g. (44%) of 1-phenyluracil; m.p. 247°; E_{max} = 11,100 at 265 mμ. Atkinson *et al.*[8] reported m.p. 247°. *1-p-Chlorophenyluracil:* 2.4 g. (0.011 mole) of 1-*p*-chlorophenyl-5-bromodihydrouracil yielded 1.1 g. (45%) of 1-*p*-chlorophenyluracil; m.p. 258°; E_{max} = 15,670 at 264 mμ.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.90; H, 3.16; N, 12.59. Found: C, 53.85; H, 3.27; N, 12.58.

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(13) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

Action of Grignard Reagents on β-Substituted Propiomesitylenes[1]

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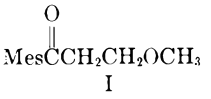
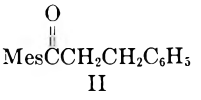
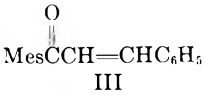
α-Hydrogen elimination reactions produced by the action of Grignard reagents on β-substituted mesityl ketones are followed by 1,4-addition of the Grignard reagent to the resulting α,β-unsaturated ketone. Thus β-methoxypropiomesitylene (I) reacts with two equivalents of phenylmagnesium bromide to give β-phenylpropiomesitylene (II).



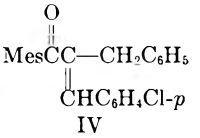
I



II



III

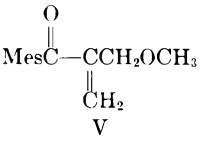


IV

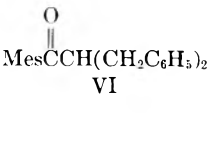
The phenylated ketone proved to be identical with that prepared by catalytic hydrogenation of benzalacetomesitylene (III) according to the method of Barnes.[3] The *p*-chlorobenzal derivative (IV) was made also.

With mesitylmagnesium bromide β-methoxypropiomesitylene (I) yielded β-mesitylpropiomesitylene previously produced by condensing β-chloropropionyl chloride with mesitylene by the method of Friedel and Crafts[4] and by catalytic hydrogenation of mesitoylmesitylacetylene.[5]

An interesting variant was furnished by 3-methoxyisopropenyl mesityl ketone (V),[6] a product of the interaction of formaldehyde, acetomesitylene, and methanol. When this unsaturated ketone was allowed to condense with phenylmagnesium bromide the product was dibenzylacetomesitylene (VI).



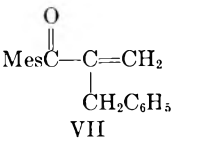
V



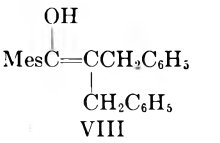
VI

This change differs from the preceding examples in that the enolate that loses the methoxide ion is formed by 1,4-addition of the Grignard reagent to an α,β-unsaturated ketone rather than by enolization of a saturated ketone. Presumably α-benzylvinyl mesityl ketone (VII) was formed as an intermediate.

In addition to the major product, dibenzylacetomesitylene, small amounts of mesitoic acid and dibenzyl ketone were isolated also. These compounds could be produced by air oxidation of the enolic form (VIII) of dibenzylacetomesitylene.



VII



VIII

EXPERIMENTAL[7]

Reaction of β-methoxypropiomesitylene (I) *with phenylmagnesium bromide.* To a refluxing solution of phenylmagnesium bromide, prepared from 62.8 g. (0.4 mole) of bromobenzene, 9.6 g. (0.4 g.-atom) of magnesium, and 200 ml. of dry ether, was added with stirring 20.6 g. (0.1 mole) of β-methoxypropiomesitylene over a period of 10 min. The heating and stirring were continued for 5 hr. The reaction mixture was cooled in an ice bath and treated with a cold dilute solution of hydrochloric acid. The organic layer, after being washed with water and dried over anhydrous sodium sulfate, was freed of solvent by distillation, and the residual yellow oil was distilled through a 12-in. Vigreux column. The small amount of forerun solidified and had the odor characteristic of biphenyl. The main fraction was β-phenylpropiomesitylene, b.p. 149–153°/0.5 mm.; n_D^{20} 1.5570; yield 16.4 g. (65%).

(1) This investigation was supported by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) Socony-Vacuum Oil Co. Fellow, 1954–1955.

(3) R. P. Barnes, *J. Am. Chem. Soc.*, **57**, 937 (1935).

(4) R. C. Fuson and C. H. McKeever, *J. Am. Chem. Soc.*, **62**, 2088 (1940).

(5) R. C. Fuson and J. S. Meek, *J. Org. Chem.*, **10**, 551 (1945).

(6) R. C. Fuson and C. H. McKeever, *J. Am. Chem. Soc.*, **62**, 999 (1940).

(7) All melting points are corrected; all boiling points are uncorrected.

The infrared spectrum[8] of this compound is identical with that of a sample of β-phenylpropiomesitylene prepared according to the method of Barnes.[3] It shows bands assignable to a hindered unconjugated ketone (1697 cm.$^{-1}$) and to a mesityl group (852 cm.$^{-1}$).

The *p*-chlorobenzal derivative (IV) was made by allowing a mixture of 1.0 g. (0.007 mole) of *p*-chlorobenzaldehyde, 0.6 g. (0.002 mole) of β-phenylpropiomesitylene (prepared by the method of Barnes or by the methoxyl elimination reaction), 50 ml. of ethanol, and 10 ml. of a 10% solution of sodium hydroxide to stand at room temperature for 22 hr. When the pale yellow reaction mixture was refrigerated white crystalline plates were deposited; m.p. 108–109.5°, after one recrystallization from ethanol.

Anal. Calcd.[9] for $C_{25}H_{23}OCl$: C, 80.11; H, 6.18. Found: C, 80.09; H, 6.15.

The infrared spectrum of the compound, determined in carbon disulfide, shows absorption at 1655 cm.$^{-1}$, assignable to the conjugated carbonyl function. Bands at 850, 820, and 695 cm.$^{-1}$ suggest the presence of mesityl as well as *p*-disubstituted- and monosubstituted benzene groups.

Reaction of β-methoxypropiomesitylene with mesitylmagnesium bromide. A Grignard reagent was prepared from 4.2 g. (0.18 g.-atom) of finely divided magnesium, 40 g. (0.2 mole) of freshly distilled bromomesitylene, 175 ml. of anhydrous ether, and a small crystal of iodine. To the refluxing solution was added, dropwise and with stirring, 10.3 g. (0.05 mole) of β-methoxypropiomesitylene in 150 ml. of anhydrous benzene. The heating and stirring were continued for 10 hr. The work-up was conducted as described in the previous experiment. Hot ethanol was added to the oily yellow residue, and the solution was refrigerated. The solid which separated was recrystallized from ethanol. Seven grams (50%) of white powdery material was obtained; m.p. 79.5–80.5°.

A mixed melting point determination with an authentic sample of β-mesitylpropiomesitylene[5] showed no depression. The infrared spectrum (chloroform) of the compound exhibits strong bands at 1693 cm.$^{-1}$ and at 855 cm.$^{-1}$ These can be assigned to the hindered carbonyl function and to the mesityl group, respectively.

Reaction of 3-methoxyisopropenyl mesityl ketone (V) *with phenylmagnesium bromide.* The reaction was conducted in an atmosphere of nitrogen. A Grignard reagent was prepared from 11.3 g. (0.072 mole) of bromobenzene, 1.7 g. (0.07 g.-atom) of magnesium, and 50 ml. of dry ether. To the Grignard solution was added, dropwise and with stirring, a solution containing 3.9 g. (0.018 mole) of the methoxy ketone, 50 ml. of dry ether, and 75 ml. of dry benzene. One hour was required for the addition. The reaction mixture, grey-white because of suspended solid material, was heated under reflux for 10 hr., and then allowed to stand overnight at room temperature. The suspension was cooled in an ice-bath and hydrolyzed with cold dilute hydrochloric acid. The work-up was conducted in the usual manner.

A portion of the oily residue was taken up in hot ethanol, and the solution cooled in the refrigerator. Pale yellow prisms separated; m.p. 81–83°. Recrystallization from an ethanol-water mixture gave white pellets, m.p. 83.5–85°.

Anal. Calcd. for $C_{25}H_{26}O$: C, 87.67; H, 7.65. Found: C, 87.84; H, 7.75.

The carbonyl region of the infrared spectrum (carbon disulfide) of the compound contains a strong band at 1700 cm.$^{-1}$ A band at 854 cm.$^{-1}$ is assignable to a mesityl group, and a mono-substituted benzene nucleus is indicated by strong absorption at 750 and 700 cm.$^{-1}$

Addition of cyclohexane to the remainder of the oily residue caused the separation of white, star-like crystals, m.p. 151–153°. A mixture melting point determination and the infrared spectrum showed the compound to be mesitoic acid. The cyclohexane solution from which the mesitoic acid had been removed, was subjected to chromatographic treatment. Three products, biphenyl, dibenzylacetomesitylene, and a yellow oil were obtained. The infrared spectrum (carbon disulfide) suggested that the liquid was dibenzyl ketone. The oxime formed silky white needles, m.p. 120–120.5°; no mixture melting point depression was observed with an authentic sample of the oxime of dibenzyl ketone. The total yield of dibenzylacetomesitylene was 2.2 g. About 0.1 g. of mesitoic acid and a similar amount of dibenzyl ketone were isolated.

(8) The infrared spectra were determined and interpreted by Mr. James Brader, Mrs. Louise Griffing, Mr. Sy Portnow, and Mr. Brian Cloonan.

(9) The microanalyses were performed by Mr. J. Nemeth, Mrs. R. Maria Benassi, Mr. Rolo Nesset, Miss Claire Higham, Mrs. Ruby Ju, and Mrs. Stingl.

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Isolation of Carbonyl Compounds under Neutral Conditions Using the Girard Reagent

C. L. TEITELBAUM

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In the course of an investigation of the constituents of an essential oil, an attempt was made to isolate the carbonyl compounds present by means of the Girard "T" reagent.[1] The literature indicated that this reagent was suitable for the isolation of aldehydes as well as ketones.[2,3] However, application of this procedure resulted in a much lower yield than was indicated by analysis of the oil for carbonyl compounds by the standard hydroxylamine hydrochloride procedure.

Studies using citral as a model carbonyl compound showed that the Girard complex formed smoothly but that the acid regeneration procedure failed to yield any detectable amount of citral. The product had an infrared spectrum indicative of the presence of a complex mixture containing *p*-cymene. This finding is not surprising in view of the known instability of citral in the presence of strong acids and the occurrence of *p*-cymene in the decomposition products.[4]

It has been found that regeneration of a carbonyl compound from its Girard complex can be effected by merely adding a large excess of aqueous formaldehyde to the neutral solution of the complex. In the case of stable carbonyl compounds, the

(1) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, 19, 1095 (1936).

(2) E. Lederer and G. Nachmias, *Bull. soc. chim. France*, 400 (1949). These authors' results in recovering citral from its Girard derivative in 89 per cent yield by acid hydrolysis could not be repeated. Using their procedure, a small yield of organic material containing no detectable (infrared spectrum) citral was recovered.

(3) A. Weissenberg and D. Ginsburg, *Bull. Research Council Israel, Sect. A.*, 5A, 268 (1956).

(4) J. L. Simonsen and L. N. Owen, *The Terpenes*, 2nd ed., Cambridge Univ. Press, Vol. I, p. 91 (1947).

yields are comparable to those obtained by the use of mineral acid. However, in the case of relatively unstable aldehydes, the yields from the new procedure are distinctly superior. Typical results are given in Table I.

TABLE I

Carbonyl Compound	Regeneration Procedure	Yield, %
Citral	CH_2O	81
	HCl	10[a]
n-Octanaldehyde	CH_2O	78
	HCl	64
Acetophenone	CH_2O	72
	HCl	84
Benzaldehyde	CH_2O	50
	HCl	27[b]
2-Octanone	CH_2O	96
	HCl	85

[a] Product was a complex mixture exhibiting the major infrared spectral bands of *p*-cymene. [b] The product consisted of a mixture of solid (apparently benzoic acid) and liquid (solution of benzoic acid in benzaldehyde).

An attempt was also made to eliminate the use of acetic acid as catalyst for formation of the Girard complex. It was found that a cation exchange resin[5] is equally efficient as a catalyst and can be readily removed by decantation, leaving a neutral solution. This avoids the troublesome necessity of neutralizing the acetic acid and eventually extracting traces of it from both the carbonyl and non-carbonyl products.

These modifications of the Girard procedure have proven to be of particular value in isolating carbonyl compounds from mixtures where it is desirable to avoid acidic conditions.

EXPERIMENTAL

Girard "T" reagent (50 g.),[6] 25 g. carbonyl compound, 1 g. cation exchange resin,[5] and 100 ml. ethanol were placed in a flask. The mixture was refluxed 1 hr., during which time the Girard reagent dissolved; the solution was then decanted from the exchange resin into 400 ml. of water. The resulting solution was divided into two equal aliquots. To one half was added 100 ml. 37% formalin solution, and to the other half 50 ml. concentrated hydrochloric acid. Both solutions were allowed to stand overnight at room temperature. Each solution was extracted with pentane and the extract was washed five times with water and dried over anhydrous sodium sulfate. The pentane was evaporated from each extract by heating on a water bath and briefly applying water aspirator vacuum to remove the last traces of solvent. A control experiment demonstrated that the evaporation procedure does not cause any significant loss of the carbonyl compounds used in this work. The recovered carbonyl compound was checked for purity by means of its infrared spectrum.

Acknowledgment. The technical assistance of John Lenard is gratefully acknowledged.

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(5) Amberlite IRC 50, Rohm & Haas Co.
(6) Arapahoe Chemicals, Inc.

Preparation of 3-Hydroxymethyl-5-pyrazolone from 3-Carbethoxy-5-pyrazolone[1]

TAKUC OKUDA AND CHARLES C. PRICE

Received October 28, 1957

A compound believed to be 3-hydroxymethyl-5-pyrazolone has been previously synthesized by Gillespie and Price[2] by condensation of ethyl tetronate with hydrazine hydrate. The preparation of the same compound from 3-carbethoxy-5-pyrazolone[3] through reduction with lithium aluminum hydride confirms the structure assigned earlier.

EXPERIMENTAL

Reduction of 3-carbethoxy-5-pyrazolone to 3-hydroxymethyl-5-pyrazolone. 3-Carbethoxy-5-pyrazolone[3] (10 g., 0.0641 mole) was placed in a Soxhlet extractor mounted on a flask containing a solution of 5 g. (0.132 mole) of lithium aluminum hydride in 400 ml. of dry ether. The ether was refluxed with stirring for 7 hr. After cooling, 14 ml. of ethyl acetate was added with stirring, and then 5 ml. of water. The solid precipitate was filtered after standing overnight. The filtrate gave only a negligible amount of oily residue when the solvent was removed by distillation. The filtered precipitate was extracted with ethanol using a Soxhlet extractor for 6 hr. The ethanol was distilled from the extract *in vacuo* leaving a viscous residue which was cooled to 0° for a week. The resulting crystalline precipitate was filtered with suction. The viscous filtrate gave no more crystalline produce on further concentration and cooling. Attempts to make picrate and benzoyl derivatives from the filtrate also failed.

The filtered product, which weighed 1.2 g., showed the presence of lithium by flame color test. The material was dissolved in 2 ml. of water and the solution was neutralized with acetic acid. On scratching the wall of the container, 0.35 g. of crystals precipitated. Recrystallized from *ca.* 1 ml. of ethanol, the material melted at 156–158° and showed no melting point depression when mixed with a sample of Gillespie's material. The two samples also had the same infrared spectra with the following major characteristics (in potassium bromide, wave length and % absorption): 2.93 (61), 3.45 (67), 3.6 (72), 6.15 (87), 6.49 (71), 6.61 (78), 6.87 (74), 7.90 (39), 8.18 (35), 8.51 (50), 9.34 (38), 9.59 (65), 9.92 (42), 10.20 (37), 12.2 (58), 12.9 (56), 14.0 (52).

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(1) Supported in part by U. S. Public Health Service Grant CY 2714.
(2) J. F. Gillespie and C. C. Price, *J. Org. Chem.*, **22**, 780 (1957).
(3) R. v. Rothenburg, *J. Prakt. Chem.*, [2] **51**, 53 (1895).

Dimeric Pyrolysis Products of Polypropylene Oxide

ALLEN NOSHAY AND CHARLES C. PRICE

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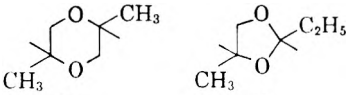
Price and St. Pierre[1] have reported that the py-

(1) C. C. Price and L. E. St. Pierre, *J. Am. Chem. Soc.*, **78**, 3432 (1956).

rolysis of polypropylene oxide in the presence of *p*-toluenesulfonic acid produced propionaldehyde, propionic and acrylic acids, and dimethyldioxane. Dr. R. K. Summerbell has suggested to us[2] that the properties we reported for the latter substance indicated it to be the isomeric 2-ethyl-4-methyldioxolane. We have therefore reinvestigated the identity of this pyrolysis fraction and find it does indeed contain considerable quantities of 2-ethyl-4-methyldioxolane (II), as well as an isomer, probably *trans*-2,5-dimethyldioxane (I).



I II

The presence of II was proven by the acid hydrolysis of the pyrolysis product in the presence of 2,4-dinitrophenylhydrazine to produce propionaldehyde 2,4-dinitrophenylhydrazone, by infrared spectra, by vapor chromatography,[3] and by nuclear magnetic resonance.[4]

The latter three measurements also indicated the presence of an isomer, probably *trans*-2,5-dimethyldioxane, in roughly equal amounts.

Since II is readily prepared by acid-catalyzed condensation of propylene glycol with propionaldehyde, it is not clear whether this compound is a direct product of pyrolysis or is formed from the glycol and aldehyde as a secondary product.

EXPERIMENTAL

Pyrolyses. A 29-g. sample of polypropylene oxide and 0.3 g. of *p*-toluene sulfonic acid were heated together in a sand bath at 270–330° to give 25.5 g. of yellow distillate and 2 g. of black residue. Redistillation through a 6-inch Vigreux column gave 8.5 g., b.p. 51–87°; 10 g., b.p. 87–113° and 3.0 g., b.p. 113–165°. Two redistillations of the main fraction gave three fractions corresponding to dimer, 0.5 g., b.p. 117–120°, n_D^{28} 1.4073; 2.5 g., b.p. 121–123°, n_D^{28} 1.4088; 1.5 g., b.p. 123–128°, n_D^{28} 1.4102.

A similar pyrolysis of 114 g. of polypropylene oxide (Ucon "2025," Carbide Chemicals Corporation) gave the following dimer fractions, after three redistillations: 1.5 g., b.p. 117–119°, n_D^{19} 1.4090; 2.0 g., b.p. 119–120°, n_D^{19} 1.4112; 2.0 g., b.p. 120–122, n_D^{19} 1.4130; 1.5 g., b.p. 122–125°, n_D^{19} 1.4141.

The infrared spectra of all seven dimer samples were almost identical, except for changes in relative intensity of bands, and all were very similar to the spectra reported earlier by St. Pierre.[1]

The infrared spectrum of 2-ethyl-4-methyldioxolane, b.p. 117.5°, n_D^{20} 1.4048, prepared by condensation of propionaldehyde and propylene glycol,[3] was similar to the dimer fractions, except for the absence of bands at 7.86 μ and 11.86 μ. These are the only two major bands for *trans*-2,5-dimethyldioxane[5] not present also in the dioxolane. The strong band in *cis*-2,5-dimethyldioxane at 8.23 μ is almost entirely absent in the pyrolysis product. The bands at 7.1, 9.65, 10.75, and 11.03 μ in the dioxolane are considerably weaker in pyrolysis product fractions boiling at 122–125° than those boiling at 117–119°. A rough approximation from band intensities would suggest that the main components of the pyrolysis are 2-ethyl-4-methyl dioxolane and *trans*-2,5-dimethyldioxane in roughly equal amounts.

The fact that the dimer fractions are not pure dioxolane is further supported by the spread in boiling point and refractive index.[6] Assuming a two component mixture and a linear relation between composition and refractive index, the material from the second pyrolysis would be about 40% dioxolane and 60% dioxane. From this same material, vapor chromatography[3] gave a fraction identified as the dioxolane (55%) and another fraction, probably the dioxane (45%).

A comparison of the nuclear magnetic resonance spectrum[4] of the pyrolysis product with the markedly different spectra of 2-ethyl-4-methyldioxolane and *trans*-2,5-dimethyldioxane was entirely consistent with the conclusion that the pyrolysis mixture contained roughly equal amounts of these isomers.

It was also noted that the synthetic dioxolane crystallized in a Dry Ice–acetone bath whereas none of the dimer fractions did so.

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(2) Private communication.

(3) Courtesy of Dr. L. E. St. Pierre, Research Laboratories, General Electric Company, Schenectady, N. Y.

(4) Courtesy of Dr. J. D. Roberts, California Institute of Technology, Pasadena, Calif.

(5) Samples of *trans*-2,5-dimethyldioxane and the mixed *cis-trans* isomers were kindly supplied by R. K. Summerbell and D. Dalton, Northwestern University.

(6) E. Augdahl, *Acta Chem. Scand.*, 9, 1237 (1955) has reported *trans*-2,5-dimethyldioxane, b.p. 121.5°, n_D^{22} 1.4147.

Nitrosodecarboxylation

Ronald A. Henry

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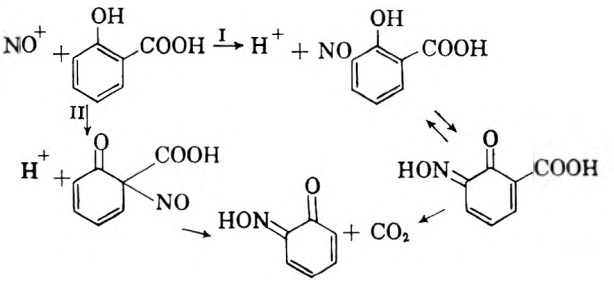
The addition of sodium nitrite to an aqueous ethanolic solution of salicylic acid causes an immediate and rapid evolution of carbon dioxide; some 2-nitrophenol can be distilled from the resulting solution. This decarboxylation could conceivably occur by either of the following reaction paths:



The resulting *ortho*-quinone monoxime or 2-nitrosophenol would then be oxidized by excess nitrite to the 2-nitrophenol. From the nature of the product recovered, it is not possible to differentiate between these two routes. Similarly, the formation of 2-nitro-4-methylphenol from sodium nitrite and 5-methylsalicylic acid does not permit a differentiation between the two mechanisms. However, a determination of the products formed in the reac-

tions of sodium nitrite and the two other isomeric methylsalicylic acids leads to the conclusion that this decarboxylation occurs primarily through II. With 3-methylsalicylic acid the 2-nitro-6-methylphenol which is isolated can only result from an attack of the nitrosonium ion on the carbon atom containing the carboxyl group (or carboxylate ion). Furthermore, the product recovered from 4-methylsalicylic acid was the 2-nitro-5-methylphenol expected by route II.

4-Hydroxybenzoic acid also undergoes some decarboxylation when treated with sodium nitrite; 4-nitrophenol was ultimately recovered in about 6% yield.

In most of these nitrosodecarboxylations, the nitrosophenol was not recovered *per se* and the derived nitrophenol was only recovered in small yields (5 to 15% conversions). That the nitroso compound is an intermediate and that it can be isolated in good yield were demonstrated with a reaction analogous to the well known decarboxylation of 3,5-dibromo-4-hydroxybenzoic acid by bromine to furnish 2,4,6-tribromophenol.[1] When a solution of 3,5-dibromo-4-hydroxybenzoic acid was treated with sodium nitrite, carbon dioxide was evolved rapidly; acidification of the solution after the reaction was complete gave a quantitative yield of the known 2,6-dibromo-4-nitrosophenol, which in turn was oxidized to the corresponding nitrophenol for purposes of further characterization. The bromodesulfonation of 3,5-dibromo-4-hydroxybenzenesulfonic acid is another related reaction which has recently been shown[2] by kinetic studies to involve an intermediate with a para-quinonoid structure.

The partial decarboxylation or desulfonation of certain hydroxybenzoic acids or phenolsulfonic acids, respectively, during nitration has been frequently observed and reported.[3] An examination of this literature leads to the conclusion that in many cases the products which are formed can only result from a direct attack of an electrophilic reagent such as NO_2^+ or NO^+ on the carbon atom with the carboxyl or sulfonate group.

Methyl salicylate and sodium nitrite in aqueous ethanol react very slowly to yield small quantities of dimethyl 5,5′-azosalicylate, identified by its hydrolysis to the known 5,5′-azosalicylic acid.

EXPERIMENTAL[4]

Salicylic acid. From 27.6 g. (0.2 mole) of salicylic acid, 14.0 g. of sodium nitrite, and 250 ml. of water, allowed to stand at room temperature for 5 hr., then steam distilled, there was recovered 0.53 g. of 2-nitrophenol, m.p. 46°.

A rerun, in which the solvent was 200 ml. of 25% aqueous ethanol (by volume) and the reaction time 6.5 hr., gave 0.8 g. of 2-nitrophenol, m.p. 46–47° (undepressed in admixture with authentic 2-nitrophenol). The evolution of gas from this ethanolic system occurred almost immediately and very rapidly; carbon dioxide was qualitatively determined by passing the gas through a freshly filtered solution of barium hydroxide. The nitrophenol was recovered from the alcoholic steam distillate by making the latter strongly basic with sodium carbonate, evaporating to remove the alcohol, acidifying, and cooling.

3-Methylsalicylic acid. 3-Methylsalicylic acid (30.4 g.; 0.2 mole), 14.0 g. (0.2 mole) of sodium nitrite, and 200 ml. of water were mixed. The system was thoroughly flushed with nitrogen and maintained under a nitrogen blanket. After 4 hr. at room temperature with occasional swirling, the solution was warmed during 45 min. to the boiling point and then steam distilled. The yield of nitrocresol was 1.1 g., m.p. 68–70°. By acidifying the aqueous mother liquors and cooling, there was recovered 20.2 g. of starting acid. The conversion to nitrocresol amounted to 10.7%. Recrystallization from 70% aqueous ethanol yielded flat yellow needles, m.p. 71–72°; reported,[5] 70°.

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 9.27, 9.21.

4-Methylsalicylic acid. The same quantities and procedure were used as in the previous experiment, except that 4-methylsalicylic acid, m.p. 179–180°, was employed. One gram of yellow-brown solid, m.p. 54–55°, was obtained by steam-distilling the unacidified reaction mixture; an additional 0.3 g., m.p. 54°, was obtained, by acidification and further steam distillation. The mother liquors were chilled to 0°, the solid was removed by filtration, dried, and extracted with methylene chloride. Impure starting acid (19.4 g.) remained. Oxidation of the dried methylene chloride extracts with peroxytrifluoroacetic acid[6] and work-up in the usual manner yielded 0.2 g. of nitrocresol, m.p. 54–55°. The total recovery corresponded to a conversion of 13.5%. Recrystallization from aqueous ethanol gave yellow needles, m.p. 55–56°; reported[7] for 2-nitro-5-methylphenol, 56°.

5-Methylsalicylic acid. From 0.1 mole of 5-methylsalicylic acid there was obtained 0.4 g. of yellow, steam-distillable solid, melting at 32–33°C; reported[8] for 2-nitro-4-methylphenol, 33–34°. Six grams of starting acid, m.p. 152–153°, was recovered.

4-Hydroxybenzoic acid. A solution consisting of 6.9 g. (0.05 mole) of 4-hydroxybenzoic acid, 3.5 g. of sodium nitrite, and 50 ml. of water was held at 48–52° for 10 min.; carbon dioxide was evolved. The solution was then cooled to

(1) For example, see E. Grovenstein, Jr. and U. V. Henderson, Jr., *J. Am. Chem. Soc.*, **78**, 569 (1956).

(2) L. G. Cannell, *J. Am. Chem. Soc.*, **79**, 2927 (1957). See this reference for a list of earlier references on bromodesulfonation.

(3) Typical examples can be found in the following references: (a) Marchand, *J. prakt. Chem.*, [1], **26**, 397 (1842); (b) H. Hubner, *Ann.*, **195**, 1 (1879); (c) A. Deninger, *J. prakt. Chem.*, [2], **42**, 550 (1890); (d) W. Borsche and A. D. Berkhout, *Ann.*, **330**, 98 (1904); (e) I. J. Rinkes, *Rec. trav. chim.*, **45**, 848 (1926); (f) F. V. Hemmelmayr, *Monatsh.*, **25**, 25 (1904); **26**, 185 (1905); (g) E. Diepolder, *Ber.*, **29**, 1756 (1896); (h) F. Reverdin, *Bull. soc. chim.*, [4] **3**, 591 (1908); (i) J. Biehringer and W. Borsum, *Ber.*, **48**, 1314 (1915); (j) H. Salkowski, *Ann.*, **367**, 350 (1909); (k) H. E. Armstrong, *J. Chem. Soc.*, 869 (1872); (l) H. E. Armstrong and F. D. Brown, *J. Chem. Soc.*, 857 (1872); (m) R. L. Datta and P. S. Varma, *J. Am. Chem. Soc.*, **41**, 2041 (1919); (n) G. Dahmer, *Ann.*, **333**, 363 (1904); (o) W. Robertson, *J. Chem. Soc.*, 1482 (1902).

(4) The melting points are uncorrected.

(5) G. P. Gibson, *J. Chem. Soc.*, 42 (1925).

(6) This is the procedure of W. D. Emmons, *J. Am. Chem. Soc.*, **76**, 3468, 3470 (1954). A trial experiment with 2-methyl-4-nitrosophenol indicated a quantitative conversion to the nitro compound.

(7) G. P. Gibson, *J. Chem. Soc.*, 1269 (1923).

(8) A. Deninger, *J. prakt. Chem.*, [2], **40**, 299 (1889); H. T. Upson, *Am. Chem. J.*, **32**, 13 (1904).

15°, acidified with 4 ml. of concentrated hydrochloric acid, and immediately extracted with three 25-ml. portions of methylene chloride. The combined extracts were dried and then oxidized by the Emmons procedure.[8] Evaporation of the washed and dried methylene chloride solution left 0.45 g. (6.5%) of solid which melted at 112–113.5° after one recrystallization from water. A mixture with an authentic sample of 4-nitrophenol melted at 113.5–114.5°; admixture with 2,4-dinitrophenol depressed the melting point to 75–80°.

2,4-Dihydroxy- and 3-nitro-4-hydroxybenzoic acids. Carbon dioxide was evolved when these acids were warmed with aqueous sodium nitrite on the steam bath; only tars and some starting acid were recovered.

3-Nitrosalicylic acid, 5-nitrosalicyclic acid, 3,5-dinitrosalicylic acid, and 3,5-dinitro-4-hydroxybenzoic acid. Essentially no carbon dioxide was evolved when these acids were heated with aqueous sodium nitrite solution; oxides of nitrogen were liberated, and the starting acids were recovered unchanged when the reaction solution was acidified.

3,5-Dibromo-4-hydroxybenzoic acid. Sodium nitrite (0.7 g.) was added to a solution of 2.96 g. of the acid in 25 ml. of ethanol and 15 ml. of water. There was an immediate evolution of carbon dioxide and the solution became yellow-green. After the solution had stood overnight at room temperature, it was heated on the steam bath for 10 min., cooled to 5°, and acidified with 1 ml. of concentrated hydrochloric acid. The tan platelets which separated were filtered and washed with cold water. A second crop was obtained by diluting the mother liquors with water. The total yield of compound, which turned dark about 160°, was 2.29 g. Recrystallization from aqueous methanol gave tan needles, decomposing at 168–169°. Forster and Robertson[9] reported that 2,6-dibromo-4-nitrosophenol darkened about 160° and detonated between 168 and 175°.

Anal. Calcd. for $C_6H_3NO_2Br_2$: N, 4.99; Br, 56.90. Found: N, 4.82, 4.76; Br, 56.16.

Some of this nitroso compound was oxidized in methylene chloride with peroxytrifluoroacetic acid. The impure product melted at 139–140°; recrystallization from ethanol raised the melting point to 142°; Forster and Robertson[9] reported 142°; Pope and Wood,[10] 144–145°.

3,5-Dibromosalicylic acid was not decarboxylated by aqueous sodium nitrite.

Methyl salicylate and sodium nitrite. Methyl salicylate (30.4 g.; 0.2 mole), 14.0 g. of sodium nitrite, 500 ml. of 95% ethanol, and 400 ml. of water were mixed and allowed to stand at room temperature for 2.5 months. The solution became dark-orange in color, and orange needles slowly crystallized. The product was removed by filtration, washed with 50% ethanol, and dried; 1.3 g., m.p. 200–205°. Two recrystallizations from large volumes of 95% ethanol gave flat orange needles and raised the melting point to 227–229°, without decomposition but with preliminary shrinking at 222–226°. The compound is soluble in dilute, aqueous sodium hydroxide and can be reprecipitated by acidification; it is very soluble in cold acetone and can also be recrystallized from glacial acetic acid. Both the analyses and the infrared spectrum indicate a dimethyl azosalicylate.

Anal. Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.97; H, 4.16; N, 8.58.

Some of the compound (0.3 g.) was heated on the steam bath for 1 hr. with 50 ml. of 0.1*N* sodium hydroxide. Cooling, followed by acidification with glacial acetic acid, furnished a light yellow powder, which was filtered and washed well with cold water. The product was dissolved in aqueous sodium bicarbonate, filtered, heated to boiling, and reprecipitated by the addition of dilute acetic acid. The water-washed, dried compound did not melt up to 300° although some sublimation started between 290 and 295°. The infrared spectrum and the x-ray powder pattern were essentially identical with the respective patterns from an authentic sample of 5,5′-azosalicylic acid.[11]

Anal. Calcd. for $C_{14}H_{10}N_2O_6$: C, 55.63; H, 3.34. Found: C, 55.18; H, 3.70.

Reaction of the silver salt of authentic 5,5′-azosalicylic acid with methyl iodide also yielded an ester (Found: N, 8.59) whose ultraviolet absorption spectrum in 95% ethanol was identical with that for the product obtained in the methyl salicylate-sodium nitrite reaction (λmax. = 226, 248, 337, and 352 mμ). The infrared spectra corresponded closely. However, this ester partially melted at 183–184°, resolidified, then melted in the range 205–220°C. The reason for this difference in behavior was not determined.

Acknowledgment. The author gratefully acknowledges the assistance of William G. Finnegan.

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China Lake, Calif.

(9) M. O. Forster and W. Robertson, *J. Chem. Soc.*, 686 (1901).

(10) F. G. Pope and A. S. Wood, *J. Chem. Soc.*, 1823 (1912).

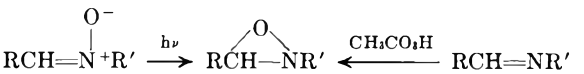
(11) See British Patent **408,676**, April 16, 1934 [*Chem. Abstr.*, **28**, 5680^2 (1934)] for one method of preparing the sodium salt of this acid.

Communications TO THE EDITOR

Preparation of Oxaziranes by Irradiation of Nitrones

Sir:

In previous work,[1] α-(*p*-dimethylaminophenyl)-*N*-phenylnitrone (I) had been prepared and found to be very photosensitive in solution. When irradiated in absolute ethanol, *N*-(*p*-dimethylaminophenyl)formanilide was obtained in good yield (m.p. 74–75°; λ_{max} 268 mμ, ϵ_{max} 21,800 in ethanol. Found: C, 75.06; H, 6.58; N, 11.60; mol. wt. 232). When α-(*p*-dimethylaminophenyl)-*N*-(*m*-nitrophenyl)nitrone (II) is irradiated in benzene to complete disappearance of the nitrone spectrum, it will reform nitrone to the extent of 60% after 24 hr. in the dark at room temperature. A hydrolytic reaction leading to 4-dimethylaminobenzaldehyde accounts for the remainder.



Although the oxazirane (Ia), as well as other 2,3-diaryloxaziranes, could not be synthesized by the oxidation of the imine, the properties and reactions of the products of the irradiation of several *N*,α-diarylnitrones are consistent with the oxazirane structure. The irradiation product of α-(*p*-nitrophenyl)-*N*-phenylnitrone rapidly rearranged to 4-nitrobenzanilide. This anilide also was formed in the oxidation of *p*-nitrobenzylideneaniline with peracetic acid, presumably the oxazirane being formed first. *N*,α-Diphenylnitrone on irradiation gave a product which rearranged, depending on conditions, to give either benzanilide or *N*, *N*-diphenylformanilide. These reactions together with the return of the irradiation product of nitrone II to the nitrone are analogous to the reactions of the oxaziranes described by Emmons.[4]

TABLE I

OXAZIRANES FROM THE IRRADIATION OF NITRONES

R	R′	Nitrone, Mg.	Solvent, Ml.	Irrad. Time	Oxazirane, % Yield
p-$NO_2C_6H_4$	Et	III, 10	CH_3CN, 70	1 hr.[a]	IIIa, 35[b]
p-$NO_2C_6H_4$	*t*-Bu	IV, 10	EtOH, 70	25 min.[a]	IVa, 40[b]
C_6H_5	*t*-Bu	V, 10	CH_3CN, 50	2 hr.[c]	Va, 95[d]

[a] Between two RSP2 photospots, 20 in. apart; solution thickness, 8 mm. [b] Isolated. [c] In quartz flask, 14 in. above a Hanovia mercury arc lamp, type 16200; solution thickness, 2 cm. [d] From active oxygen content and reconversion to nitrone.

Recently the oxazirane structure has been suggested as the first product of the irradiation of nitrones.[2,3] Since Emmons[4] has reported that certain oxaziranes can, by peracetic acid oxidation, be prepared from imines, it is now possible to show that the products of the irradiation of some of the corresponding nitrones (Table I) are the same oxaziranes.

To establish the oxazirane structure for IIIa, IVa, and Va, comparison was made in each case with the oxazirane obtained by oxidation of the corresponding imine.[4] The properties used for identification of each are as follows: IIIa, ultraviolet and infrared (in CCl_4) spectra; IVa, m.p. 58–60°, mixture m.p. 59.5–61.5° with oxazirane of m.p. 61–62°, ultraviolet spectrum, 95% active oxygen;[4,5] Va, ultraviolet spectrum, almost quantitative isomerization to the nitrone V, 90% active oxygen.

Thus, it seems evident that the initial product in the irradiation of nitrones is an oxazirane. Since, as is clear from the reversion, the oxazirane is, in general, at a higher energy level than the nitrone, this photochemical reaction constitutes a conversion and storage of electromagnetic energy as chemical energy. Further details and discussion will appear in a forthcoming publication.

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Mechanism of the Darzens Condensation. Isolation of Two Aldol Intermediates

Sir:

It is generally believed[1,2] that a Darzens condensation, *i. e.*, the oxirane-yielding base-catalyzed reaction of a carbonyl compound and a halogenomethylene substance, occurs *via* aldol addition intermediates.

$$R_1R_2CHX + O{=}CR_3R_4 \overset{\text{base}}{\rightleftharpoons} R_1R_2CX{-}C(OH)R_3R_4$$

$$R_1R_2CX{-}C(OH)R_3R_4 \xrightarrow{\text{base}} R_1R_2C\underset{\diagdown\,\diagup}{\overset{\diagup\,\diagdown}{}}CR_3R_4 \quad (O)$$

Some features of certain Darzens condensations have been recently reasoned from this assumption.[2] However, no such intermediates have ever been isolated under the condensation conditions.

A mechanism involving bivalent radicals formed by 1,1-elimination of hydrogen chloride at the halogenomethylene component has been favored by some authors.[3]

$$R_1R_2CHX \xrightarrow{\text{base}} R_1R_2C$$

$$R_1R_2C + O{=}CR_3R_4 \longrightarrow R_1R_2C\underset{\diagdown\,\diagup}{\overset{\diagup\,\diagdown}{}}CR_3R_4 \quad (O)$$

Furthermore, recent kinetic[4a] as well as structural[4b] evidence for bivalent radical formation from certain halogenomethylene substances upon attack by base has given to this mechanism some circumstantial support.

In this connection the authors wish to report that the hydroxyl ion–catalyzed condensation of *m*-nitrobenzaldehyde and 2,4,6-trimethoxyphenacyl chloride at 0°, in aqueous dioxane, gives 98.8% yield of *m*-nitrophenyl-2,4,6-trimethoxybenzoyloxirane, I, m.p. 170–171°. *Anal.* Calcd. for $C_{18}H_{17}NO_7$: C, 60.2; H, 4.8; N, 3.9. Found: C, 60.1; H, 4.8; N, 4.1. When the reaction is run so that only a small fraction of the starting materials are converted into condensation product it is possible to isolate two intermediate chlorohydrins, II, melting at 163.0–164.5° and 111–112°. *Anal.* Calcd. for $C_{18}H_{18}ClNO_7$: C, 54.6; H, 4.6; Cl, 9.0; N, 3.5. Found (m.p. 163–164.5°); C, 54.9; H, 4.7; Cl, 9.0; N, 3.5. Found (m.p. 111–112°): C, 54.7; H, 4.5, Cl, 9.2; N, 3.6. They give almost quantitative yields of I when treated with the base under the usual conditions. The trimethoxyphenacyl chloride is perfectly stable towards hydroxyl ion.

These results are therefore the first compelling evidence ruling out the "bivalent radical" mechanism and showing that *the Darzens condensation is essentially of aldol-addition type.*

$$(CH_3O)_3C_6H_2COCH{-}CHC_6H_4NO_2 \quad (O)$$

(I)

$$(CH_3O)_3C_6H_2COCHCl{-}CH(OH)C_6H_4NO_2$$

(II)

The details and full discussion of the above-mentioned and other related experimental results will be reported in a forthcoming publication.

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(2) N. H. Cromwell and R. A. Setterquist, *J. Am. Chem. Soc.*, **76**, 5752 (1954); H. Dahn and L. Loewe, *Chimia*, **11**, 98 (1957); H. Kwart and L. G. Kirk, *J. Org. Chem.*, **22**, 116 (1957). See also Kwart's correction to his paper, *J. Org. Chem.*, **22**, 1755 (1957). This correction which concerns one of our previous papers contains an important error: "diastereomerically related intermediates" should be substituted for "diastereomerically related transition states."

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