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Osmium Tetroxide Oxidation of Protoporphyrin IX and Synthesis of Deuteroporphyrin IX 2,4-Diacrylic Acid

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Protoporphyrin IX has been oxidized with osmium tetroxide to 2,4-di(α,β-dihydroxy)ethyldeuteroporphyrin, which on reaction with sodium periodate formed 2,4-diformyldeuteroporphyrin. This dialdehyde on condensation with malonic acid gave deuteroporphyrin-2,4-diacrylic acid.

It is now commonly accepted that the biosynthetic precursor of protoporphyrin IX (Fig. 1) is coproporphyrinogen (isomer III),[2] but there are still some uncertainties about the oxidative decarboxylation of the two propionic acid chains and at what step the porphyrinogen ring is oxidized to a porphyrin. The oxidative decarboxylation could possibly proceed *via* a concerted mechanism, in which case deuteroporphyrin IX 2,4-diacrylic acid (hereafter referred to as diacrylic porphyrin) or its corresponding porphyrinogen would not be an intermediate in the biosynthesis of protoporphyrin IX. This diacrylic porphyrin was therefore synthesized as one approach to test this hypothesis.

The preparation of this diacrylic porphyrin has been reported by Fischer and Beer,[3] but no criteria of purity were given. The fact that their starting material, 2,4-diformyldeuteroporphyrin IX, had a rhodo type spectra shows it to be impure.[4] Lemberg and Parker[4] obtained a 5% yield of diformyldeuteroporphyrin IX by alumina chromatography of the reaction products between potassium permanganate and protoporphyrin IX dimethyl ester. Lemberg and Falk[5] claimed a 12% yield of the diformyl porphyrin by carefully controlling the reaction time of this oxidation. Several attempts were made to increase this yield by oxidizing protoporphyrin IX or hemin IX dimethyl ester with potassium permanganate, or with the neutral magnesium permanganate under a variety of conditions, but none of these experiments gave encouraging results.

However, when protoporphyrin IX dimethyl ester was oxidized with osmium tetroxide, a previously unknown diglycol, very easily purified through its low hydrogen chloride-number, was obtained in good yield. Fischer and Deilmann[6] obtained a very complex mixture of substances with this reaction from which they were able to isolate the diformyldeutero porphyrin in 6% yield. Under the experimental conditions here described, osmium tetroxide does not affect the porphyrin ring; however, if an excess of osmium tetraoxide is used substances absorbing at 640 and 490 mμ are obtained. The similarity of the spectrum to that of chlorins suggests that the osmium tetroxide has oxidized a peripheral double bond of a pyrrole nucleus giving a dihydroxy compound similar to those postulated by Fischer.[7] This interesting possibility will be studied further.

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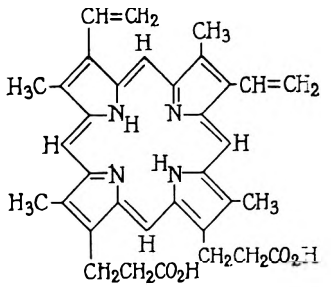
(2) R. A. Neve, R. F. Labbe, and R. A. Aldrich, *J. Am. Chem. Soc.*, **78**, 692 (1956); S. Granick and D. Mauzerall, *Ann. N. Y. Acad. Sci.*, **75**, 115 (1958); L. Bogorad, *J. Biol. Chem.*, **233**, 516 (1958).

(3) H. Fischer and L. Beer, *Z. physiol. Chem., Hoppe-Seyler's*, **244**, 54 (1936).

(4) R. Lemberg and J. Parker, *Australian J. Exp. Biol. Med. Sci.*, **30**, 163 (1952).

(5) R. Lemberg and J. E. Falk, *Biochem. J.* **49**, 674 (1951).

(6) H. Fischer and K. Deilmann, *Z. physiol. Chem., Hoppe-Seyler's*, **280**, 186 (1944).

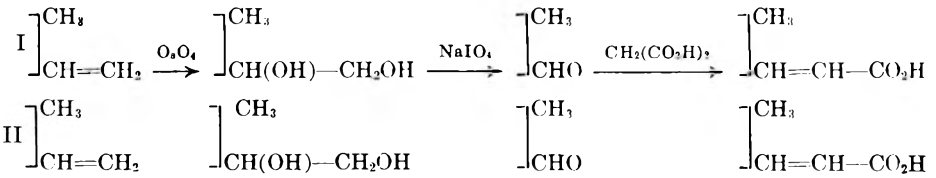


Protoporphyrin IX

Fig. 1.

The diglycol, 2,4-di(α,β-dihydroxy)ethyldeuteroporphyrin IX dimethyl ester (presumably a mixture of the two pairs of enantiomorphs), was oxidized with sodium periodate to diformyldeuteroporphyrin IX dimethyl ester in high yield. The insolubility of the diformyl derivative relative to the glycols makes its purification a simple matter.

The condensation of the diformyl porphyrin with malonic acid was effected by the method of Fischer and Beer[3] with only minor changes. It is interesting that an attempt to condense the diformyl porphyrin with diethyl malonate (using piperidine–piperidinium acetate as catalyst) failed completely.



Models of the diacrylic acid porphyrin showed that only the *trans* acrylic acid group could be made coplanar with the porphyrin ring. In confirmation of this, the infrared spectra showed a *trans* peak[8] at 973 cm.$^{-1}$ which was absent in the closely related coproporphyrin III. Bands were also present in the 1300 cm.$^{-1}$ region, but no new absorption was found in the *cis* regions. The double bonded carbon stretching band was at 1630 cm.$^{-1}$ This steric interference may also explain the lack of reaction of diethyl malonate with the diformylporphyrin. As proof of structure, the diacrylic acid porphyrin was reduced with sodium amalgam giving coproporphyrin III (after oxidation of the porphyrinogen with iodine) in 70% yield. The coproporphyrin was shown to be identical with the naturally occurring isomer III by infrared spectra, mixed melting points, and paper chromatography.[9]

(7) H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. II, part 1, Leipzig, 1937, pp. 269–274.

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., J. Wiley & Sons, Inc., New York, 1958, p. 45 ff.

(9) J. E. Falk, E. I. B. Dresel, A. Benson, and B. C. Knight, *Biochem. J.*, **63**, 87 (1956).

EXPERIMENTAL

2,4-Di(α,β-dihydroxy)ethyldeuteroporphyrin (IX) *dimethyl ester.* Protoporphyrin dimethyl ester (550 mg.) was dissolved in dry dioxane (200 ml.) and osmium tetraoxide (500 mg.) in ether (25 ml.) followed by pyridine (0.35 ml.) was added. This solution was kept in the dark, under nitrogen, for 24 hr. After that time, the ether was removed *in vacuo*, a solution of sodium sulfite (1.1 g.) in water (20 ml.) was added, and the mixture heated on a boiling water bath for 40 min. After partial cooling, the solution was filtered and the black residue was dissolved in warm dioxane. The dioxane solution obtained from four similar preparations was concentrated *in vacuo*, taking care not to allow the mixture to dry. This mixture was extracted with water and the water insoluble material was dissolved in 500 ml. 0.5*N* hydrochloric acid and filtered. The acid solution was diluted with 1 l. of water and was extracted several times with ether and ethyl acetate (1/1, v/v). The organic solvent was back extracted with 0.17*N* hydrochloric acid (500 ml.). The combined acid solutions were neutralized with sodium acetate and the precipitate was centrifuged and washed with water.

The yield was 1.1 g. (45%) of dry 2,4-di(α,β-dihydroxy)-ethyldeuteroporphyrin dimethyl ester. In preliminary experiments with smaller amounts of protoporphyrin the yield was higher (74%).

A crystalline sample was obtained by dissolving a small part of the former product in a warm mixture of methanol and benzene (1/1, v/v) and filtering. Two thirds of the volume of petroleum ether (b.p. 30°–60°) was added and the solution left in the cold. The crystals, dried *in vacuo* melted sharply at 238–240°. The absorption spectrum (Table I) obtained in 1*N* hydrochloric acid agrees quantitatively with that of hematoporphyrin.

Anal. Calcd. for $C_{36}H_{42}N_4O_8$: C, 65.64; H, 6.43. Found: C, 65.10; H, 6.53. Nitrogen determinations by both Dumas and Kjeldahl methods gave low values. Porphyrins often give low values by the former method, but the latter method (with Van Slyke modification) is usually more successful.

Periodate oxidation of 2,4-di(α,β-dihydroxy)ethyldeuteroporphyrin (IX) *dimethyl ester.* To this diglycol (900 mg.), dissolved in 500 ml. of warm dioxane, a solution of sodium periodate (1.15 g.) in water (200 ml.) was added and the mixture left in the dark for 22 hr. Water was added (200 ml.) and the precipitate centrifuged, washed with methanol, and dried *in vacuo;* yield: 680 mg. The absorption spectrum shows the presence of about 20% of monoformylporphyrin. This crude diformyl derivative was extracted with a mixture of 200 ml. of chloroform and 300 ml. of dioxane (solution A) and the insoluble material was then dissolved in 300 ml. of warm chloroform (solution B).

(a) *2-(or 4) Formyl-4-(or 2)-(α,β-dihydroxy)ethyldeuteroporphyrin* IX *dimethyl ester.* Aqueous methanol (45% methanol V/V) was gradually added to solution A so that a mixture of mono and diformyl derivatives (preponderantly diformyl) was precipitated, while in solution there remained only a mixture of the two possible monoformyl derivatives. After diluting the solution with water, the porphyrins were extracted with chloroform; this solution was washed with water and dried with sodium sulfate. The solubility of this porphyrin, the position of its absorption bands (Table II), and the rhodo type spectrum agree with its formulation as the monoglycolmonoformyl derivative

TABLE I

SPECTRA OF 2,4-DI(α,β-DIHYDROXY)ETHYLDEUTEROPHORPHYRIN IX DIMETHYL ESTER

		Maxima					Minima			
		I	II	III	IV	V				
$CHCl_3$ + 20% CH_3OH	λ in mμ	621	568	535	500	400	603	551	519	457
	$\epsilon_M \times 10^{-4}$	0.362	0.65	0.86	1.385	19.1				
	ratio	0.261	0.476	0.621	1.00	13.7	0.05	0.10	0.19	0.10
1*N* HCl	λ in mμ	592	(567)	550		402.5	582		450	
	$\epsilon_M \times 10^{-4}$	0.52	(0.55)	1.56		38.0				
	ratio	0.33	(0.35)	1.00		24.35	0.20		0.028	

TABLE II

SPECTRA OF 2-(OR 4)FORMYL-4-(OR 2)(α,β-DIHYDROXY)ETHYLDEUTEROPORPHYRIN IX DIMETHYL ESTER

Solvent	Maxima					Minima			
	I	II	III	IV	V				
$CHCl_3$									
λ in mμ	643	580	558	519	415	622	572	538	472
Absorbancy ratio	0.20	1.00	1.63	1.00	15.5	0.10	0.81	0.63	0.26

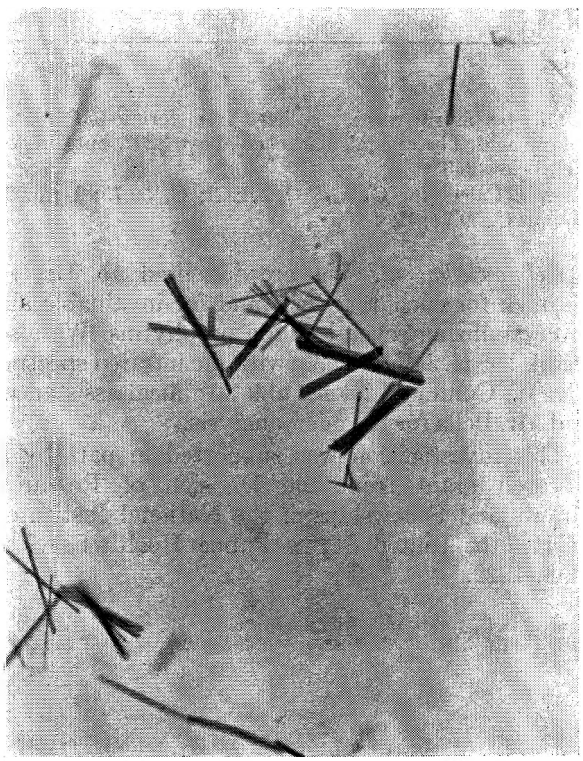


Fig. 2. 2,4-Diformyldeuteroporphyrin IX. Dimethyl ester (×800)

Fig. 3. Deuteroporphyrin IX. 2,4-Diacrylic acid dihydrochloride (×800)

(b) *2,4-Diformyldeuteroporphyrin* IX *dimethyl ester.* Solution B was treated gradually with 350 ml. of methanol and the precipitated porphyrin was centrifuged, washed with methanol, and dried; yield: about 300 mg. of pure diformyl derivative. The spectrum does not show any trace of the Soret band of the monoformyl or glycol derivative. This porphyrin was easily crystallized from hot pyridine (Fig. 2). This porphyrin appeared to crystallize with pyridine, most of which was lost on drying at 60° *in vacuo* over phosphorus pentoxide. The dried crystals melted at 300° dec.; lit., m.p. 301–303°,[4] 280°,[4] and 303–305°,[6] all with decomposition. Melting points were observed with polarized light on a microscope hot stage and are corrected. The spectrum of this compound (Table III) (in chloroform) is in good agreement with that reported by Lemberg and Parker,[4] the bands being somewhat sharper.

The yield was increased by working up the mother liquors and reoxidizing with sodium periodate.

Anal. Calcd. for $C_{34}H_{34}N_4O_6$: C, 68.67; H, 5.76; $C_{34}H_{34}N_4O_6.C_5H_5N$: C, 69.31; H, 5.82. Found: C, 69.13; H, 6.16.

Deuteroporphyrin IX *2,4-Diacrylic Acid.* Diformyldeuteroporphyrin IX dimethyl ester (150 mg.) was dissolved in boiling pyridine (100 ml.) containing piperidine (0.03 ml.). The temperature was decreased to 95° and a solution of malonic acid (6 g.) in pyridine (60 ml.) containing piperidine (0.1 ml.) was added dropwise during 6 hr. After that time the temperature was raised to the boiling point and an additional amount of malonic acid (2 g. in 20 ml. of pyridine + 0.02 ml.

TABLE III

SPECTRUM OF 2,4-DIFORMYLDEUTEROPORPHYRIN IX DIMETHYL ESTER

Solvent	Maxima I	II	III	IV	V	Minima			
$CHCl_3$ in mμ	650.5	596	563	527	437	631	581	550	482
Absorbancy ratio	0.265	0.470	0.580	1.00	10.12	0.07	0.23	0.40	0.23

TABLE IV

SPECTRA OF DEUTEROPORPHYRIN IX 2,4-DIACRYLIC ACID

Solvent		Maxima I	II	III	IV	V	Minima			
Pyridine	in mμ	641	586	554	517	428	621	572	537	479
	$\epsilon_M \times 10^{-4}$	0.577	0.805	1.36	1.49	15.1	0.14	0.40	0.73	0.48
	ratio	0.387	0.540	0.913	1.00	10.13	0.094	0.27	0.49	0.32
0.1*M* KOH + 10% pyridine	in mμ	625	581	552	515	402[a]	615	567	534	477
	$\epsilon_M \times 10^{-4}$	0.432	0.705	1.15	1.15	9.90	0.17	0.51	0.61	0.46
	ratio	0.375	0.613	1.00	1.00	8.60	0.15	0.44	0.53	0.40
6.0*M* HCl + +10% pyridine	in mμ	611		566		423[a]		597		485–495
	$\epsilon_M \times 10^{-4}$	0.708		1.66		25.7		0.52		0.11
	ratio	0.426		1.00		15.48		0.31		0.066

[a] These bands were measured in solvents not containing pyridine.

piperidine) was added dropwise during 1 hr. Upon cooling, 800 ml. of petroleum ether (b.p. 30–60°) were added and after standing in the cold, the solution was centrifuged. The precipitate was shaken twice with a mixture of chloroform and ether (2/3, v/v) and centrifuged. The insoluble material showed on paper chromatography[9] (using 2,6-lutidine (50 ml.) and 0.5*N* ammonia (35 ml.) as liquid phase) that it was mainly composed of a dicarboxylic acid porphyrin with only a trace of tricarboxylic acid porphyrin.

This residue was dissolved in 100 ml. of 0.5*N* potassium hydroxide and kept for 64 hr. in the dark at 3° to hydrolyze the two methyl ester groups. The alkaline solution was then acidified with acetic acid and the porphyrins collected by centrifugation, washed with water several times and dissolved in 100 ml. of 0.01*N* potassium hydroxide. This solution was kept frozen. Attempts to dry the free porphyrin led to considerable alteration. Paper chromatography showed that this product was composed of a tetracarboxylic acid porphyrin with a trace only of a pentacarboxylic porphyrin. The spectra of deuteroporphyrin diacrylic acid in different solvents follow (Table IV); the spectrum in pyridine disagrees with the spectrum reported by Fischer and Beer.[3]

This porphyrin was crystallized from formic-6*M* hydrochloric acid. The crystals darkened above 320°, but did not melt below 340°.

Anal. Calcd. for $C_{36}H_{34}N_4O_8 \cdot 2$ HCl: C, 59.75; H, 5.02. Found: C, 59.71; H, 4.90.

Acknowledgment. We are indebted to Dr. S. Garnick for encouragement and for invaluable aid in crystallizing several of the porphyrins. We also thank Dr. H. Jaffe for help with the infrared spectra, Mr. W. Cumming for his able technical assistance, and Mr. Bella for the microanalysis.

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NEW YORK, N. Y.

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

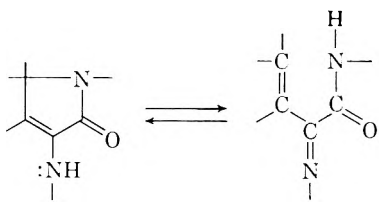
Curtius Rearrangement of α-Oximino Acids[1]

WYMAN R. VAUGHAN AND JOHN L. SPENCER[2]

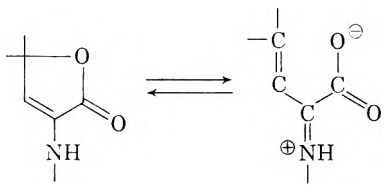
Received January 4, 1960

A new method of synthesis for 3-substituted 5-hydroxy-1,2,4-oxadiazoles is reported. The oxime of an α-ketoester is converted to the acid hydrazide, which in turn is converted to the azide by reaction with nitrous acid. Curtius rearrangement of the azide leads directly to the 1,2,4-oxadiazole.

In connection with studies of lactam-enamide tautomerism[3a] of the type represented by



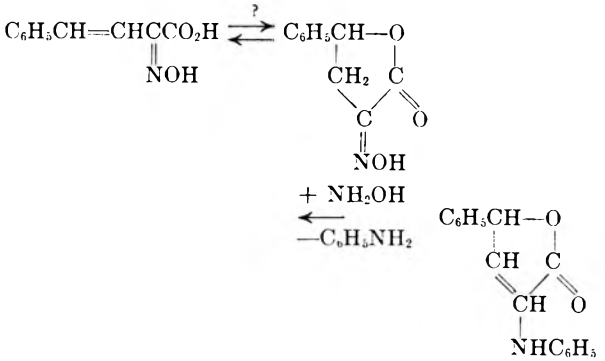
it was of interest to examine the properties of benzylidenepyruvic acid derivatives. The anilide, which is isomeric in the enamide-lactam sense with 1,5-diphenyl-2,3-pyrrolidinedione, does not partake of the tautomerism described above,[3a] but reaction of benzylidenepyruvic acid with aniline leads at once to a system in which lacto-enoic tautomerism obtains, *e.g.*



The reaction of benzylidenepyruvic acid with phenylhydrazine affords the phenylhydrazone,[4] which likewise partakes of lactoenoic tautomerism,[3b,4] but which may be irreversibly cyclized to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxylic acid.[4] The comparative ease of the latter cyclization is illustrated by the reaction of benzylidenepyruvanilide with phenylhydrazine. The phenylhydrazone is probably formed at once, but it is not isolable even though the tautomeric lactam form is known.[3,4] Instead the reaction leads at once to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxanilide.[3a]

The oxime and oxime acetate of benzylidenepyruvanilide, however, are normal and do not cyclize to the isomeric lactams; and in turn these lactams, synthesized by another method, have been shown not to open up to the acyclic isomers.[3a]

Consequently it was deemed of interest to examine the behavior of benzylidenepyruvic acid oxime, which would be especially interesting, since it is potentially tautomeric, in the lacto-enoic sense,[3b] with the oxime derived from 3-phenylamino-5-phenyl-2(5H)furanone (*pseudo*-1,5-diphenyl-2,3-pyrrolidinedione):



On the other hand it might cyclize like the analogous phenylhydrazone,[3a,4] which affords a pyrazoline, *i.e.* like chalcone oxime which affords a 2-isoxazoline.[5-7] However, the open-chain form of benzylidenepyruvic acid oxime proved to be completely resistant to either type of cyclization. Indeed the reaction of 3-phenylamino-5-phenyl-2-(5H)furanone with hydroxylamine leads to replacement of the 3-phenylamino group by hydroxylamino and ring opening to give the oxime of benzylidenepyruvic acid.

In the course of the foregoing studies the oxime of methyl benzylidenepyruvate was prepared, and it, too, resisted cyclization. In the interest of seeing whether this reluctance to cyclize could be overcome, the ester was converted to the hydrazide, which in turn was converted into the acid azide by treatment with nitrous acid. Upon heating, the azide might be expected to afford one of three different products: the amide oxime (C_6H_5CH=$CHC(=NOH)NH_2$), 3-amino-5-phenyl-2-isoxazoline (by cyclization of the amide oxime), or 5-hydroxy-3-styryl-1,2,4-oxadiazole (by cyclization of the intermediate isocyanate).

Upon carrying out the Curtius rearrangement, it was in fact the 1,2,4-oxadiazole which was

(1) Abstracted from a portion of the Ph.D. Dissertation of John L. Spencer, University of Michigan, 1958.

(2) National Science Foundation predoctoral fellow 1956–58.

(3) (a) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1565 (1957). (b) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1560 (1957).

(4) W. R. Vaughan, *J. Org. Chem.*, **20**, 1619 (1955).

(5) A. H. Blatt, *J. Am. Chem. Soc.*, **71**, 1861 (1949).

(6) R. P. Barnes, *et al.*, *J. Am. Chem. Soc.* **76**, 276 (1954).

(7) H. H. Blecker, Dissertation, Rutgers (1955).

obtained. The course of the reaction may be likened to the Curtius rearrangement of β-hydroxy acid azides[8] which afford oxazolidones. Thus, the hydroxy group of the oxime is structurally analogous to the β-hydroxyl of the latter compounds.

In order to determine the generality of the reaction, it was applied to the oximes of benzoylformic acid azide and phenylpyruvic acid azide with identical results. The structure of each of the 3-substituted-5-hydroxy-1,2,4-oxadiazoles was confirmed by unequivocal synthesis from the appropriate amide oxime by treatment with ethyl chloroformate followed by sodium hydroxide.[9]

One might possibly have expected some difficulty arising from the possible interchange of oximino and hydrazido groups or sensitivity of the oximino group to the nitrous acid used in converting the hydrazide to azide, but no undesirable side reactions were encountered. Thus, the procedure appears to be well suited for general synthesis of compounds of this type. It is only necessary to call attention to the rather large melting ranges for the oximes, which may of course be attributed to the presence of both *syn* and *anti* forms, for no attempt was made to separate isomers. However, such ranges were also encountered by Blatt[5] in the course of his work on the chalcone oximes even after the isomers had been separated. In any case the substances had good analyses and upon reaction afforded good yields of products.

EXPERIMENTAL[10-12]

Benzylidenepyruvic acid oxime. Benzaldehyde and pyruvic acid were condensed in methanol by means of methanolic sodium hydroxide according to the directions of Stecher and Ryder.[13] When needed, the free acid was obtained from the salt according to directions of the same authors.

The oxime was obtained under each of the following sets of conditions: (A) From equimolar quantities of the acid salt and hydroxylamine hydrochloride in the presence of excess potassium hydroxide; (B) From the acid salt and hydroxylamine hydrochloride in glacial acetic acid; (C) From equimolar quantities of the free acid and hydroxylamine hydrochloride in aqueous ethanol[14] at room temperature (at reflux,[11] 4 hr., only cinnamonitrile was obtained): m.p. 158–160° dec., reported[15] m.p. 168°, dec. Samples of the oxime were allowed to stand in concd. sulfuric acid for from 3 hr. to 3 days, but upon pouring any of the solutions onto ice, only the unchanged oxime was obtained.

Methyl benzylidenepyruvate oxime. Methyl benzylidenepyruvate,[16] 9.5 g. (0.050 mole) was refluxed with 5.1 g. (0.075 mole) of hydroxylamine in 50 ml. of methanol for 4 hr., during which time the original yellow color of the solution almost completely disappeared. The solution was then cooled and the resulting precipitate collected. An additional quantity of crude product was obtained by concentrating the filtrate and adding water. In this manner there was obtained 8.0 g. (78%), m.p. 115–120°. Recrystallization from methanol-water afforded 6.5 g. of white solid, m.p. 116–126°. Subsequent recrystallizations from the same solvent pair or from benzene–petroleum ether (b.p. 60–75°) did not improve the melting point.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.35; N, 6.88.

A sample of the product was hydrolyzed with 10% sodium hydroxide, and the acid obtained by acidification was shown to be identical with the oxime of benzylidenepyruvic acid by mixed melting point determination and identity of infrared spectra. Attempts to cyclize the ester oxime by standing in concd. sulfuric acid for periods from 1 night to 1 week afforded only unaltered starting material or the acid oxime.

The ester oxime reacts with hydrogen bromide in carbon tetrachloride to produce a white solid, m.p. 75–120°, but this turns yellow on exposure to the atmosphere and upon standing again becomes colorless and identical with the original oxime (mixed melting point determination). However, when a solution of 3.0 g. (0.016 mole) of bromine in carbon tetrachloride was added to a solution of 2.0 g. (0.01 mole) of the ester oxime in warm carbon tetrachloride and the resulting solution refluxed for 2 hr., there was obtained a large quantity of solid from the cooled reaction mixture: 2.9 g. (77%), m.p. 179–186° dec. An analytical sample was prepared by thrice recrystallizing from benzene, m.p. 186–190° dec.

Anal. Calcd. for $C_{11}H_{11}Br_2NO_3$: C, 36.19; H, 3.03; Br, 43.79; N, 3.84. Found: C, 36.04; H, 3.22; Br, 43.79; N, 3.89.

Benzylidenepyruvic acid oxime hydrazide. To a solution of 2.0 g. (0.0097 mole) of methyl benzylidenepyruvate oxime in 12 ml. of methanol was added 2 ml. of hydrazine. The solution was warmed on the steam bath for 20 min., during which time a white precipitate formed. An equal volume of water was added, and the solution was cooled. This afforded 1.9 g. (95%) of crude hydrazide, m.p. 193–202° dec. The melting point was found to be very dependent on the rate of heating. An analytical sample was obtained by two recrystallizations from ethanol, m.p. 192–193° dec. heated at 2°/min.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.51; H, 5.50; N, 20.43.

Benzylidenepyruvic acid oxime azide. A solution of 0.5 g. (0.0024 mole) of the above oxime hydrazide in 20 ml. of acetic acid with 5 ml. of water was cooled in an ice bath, and a solution of 0.25 g. (0.0036 mole) of sodium nitrite in 5 ml. of water was added dropwise to it. This yielded 0.4 g. (76%) of white solid, m.p. 104° vig. dec. A sample for analysis was prepared by dissolving in cold methanol, filtering, and reprecipitating with water, m.p. 108° vig. dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.46; H, 3.81; N, 25.95.

5-Hydroxy-3-styryl-1,2,4-oxadiazole. (a) *By rearrangement of the azide in ethanol.* Refluxing 0.2 g. of the above azide in 30 ml. of ethanol for 2 hr. gave on evaporation of the alcohol and trituration with water 0.1 g. of white solid, m.p. 192–200°. An analytical sample, m.p. 198.5–200.0°, was obtained by recrystallization from ethanol-water.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.54; H, 4.42; N, 14.82.

(b) *By rearrangement of the azide in benzene.* Refluxing 0.2 g. of the above azide in 20 ml. of benzene for 2 hr. gave after filtering and cooling 0.1 g. of white solid, m.p. 187–197°. Recrystallization from carbon tetrachloride raised the melting point to 196–200°.

(c) *From amidoxime.* The oxadiazole was prepared according to the procedure of Wolff[9] from cinnamamidoxime

(8) W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).

(9) H. Wolff, *Ber.*, **22**, 2400 (1889).

(10) Melting points are uncorrected.

(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(12) Infrared spectra of Nujol mulls obtained by means of a Perkin-Elmer model 21 infrared spectrophotometer.

(13) E. D. Stecher and H. F. Ryder, *J. Am. Chem. Soc.*, **74**, 4392 (1952).

(14) A. H. Blatt, *J. Am. Chem. Soc.*, **53**, 1133 (1931).

(15) R. Ciusa and A. Bernardi, *Gazz. chim. ital*, **41**, 152 (1911).

(16) M. Reimer, *J. Am. Chem. Soc.*, **46**, 783 (1924).

and ethyl chloroformate followed by treatment with sodium hydroxide.

The identical nature of these three compounds was shown by superimposable infrared spectra and no depression of the melting points on mixing.

Ethyl benzoylformate oxime. The oxime was prepared according to Gabriel[17] by the treatment of ethyl benzoylformate[18] with hydroxylamine hydrochloride and sodium carbonate in aqueous ethanol.

Benzoylformic acid oxime hydrazide. To a solution of 1.0 g. of ethyl benzoylformate oxime in 6 ml. of ethanol was added 1 ml. of hydrazine. The solution was refluxed for 10 min. and evaporated to approximately one third its volume. The addition of water afforded 1.0 g. of crude solid, m.p. 150–170°. An analytical sample was prepared by recrystallization from alcohol–carbon tetrachloride and alcohol–water, m.p. 164–172°.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.81; H, 5.19; N, 23.45.

Benzoylformic acid oxime azide. To a solution of 0.1 g. of the above hydrazide in 4 ml. of acetic acid and 1 ml. of water was added dropwise a solution of 60 mg. of sodium nitrite in 1 ml. of water. An additional 2 ml. of water was added to yield 70 mg. of white solid, m.p. 110° vigorous dec. It was not purified due to its instability. The infrared spectrum of this compound showed an absorption band at *ca.* 2160 cm.$^{-1}$.

3-Phenyl-5-hydroxy-1,2,4-oxadiazole. (a) *By rearrangement of the azide.* Refluxing 60 mg. of the above azide, in 5 ml. of ethanol for 1 hr., adding water, and cooling afforded 30 mg. of white solid, m.p. 192–199°. Recrystallization from benzene raised the melting point to 197.0–200.5°.

(b) *From amidoxime.* The procedure of Falck[19] was used to obtain the oxadiazole from benzamidoxime.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.23; H, 3.80; N, 17.22.

The identity of these two compounds is shown by identical infrared spectra and undepressed mixture melting point.

Ethyl phenylpyruvate oxime. The oxime was prepared by refluxing ethyl phenylpyruvate (from phenylpyruvic acid[20]) with hydroxylamine in ethanol for 3 hr. The preparation of the same substance by the action of nitrosylsulfuric acid on benzylacetoacetate ester is reported.[21]

Phenylpyruvic acid oxime hydrazide. To a solution of 5.0 g. (0.025 mole) of the above oxime in 25 ml. of ethanol was added 5 ml. of hydrazine. The solution was refluxed 15 min. and 50 ml. of water was added. Cooling afforded 2.3 g. (49%) of white needles, m.p. 138–143° dec. An analytical sample, m.p. 143–146°, was obtained by recrystallizations from benzene, ethanol-water, and chloroform–carbon tetrachloride.

Anal. Calcd. for $C_9H_{11}O_2N_3$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.96; H, 5.73; N, 21.78.

Phenylpyruvic acid oxime azide. To a solution of 1.2 g. of the above hydrazide in 50 ml. of 5% hydrochloric acid cooled in an ice bath was added dropwise 0.6 g. of sodium nitrite in 5 ml. of water. This yielded 1.0 g. of solid, m.p. 95° vig. dec., whose infrared spectrum had an absorption band at *ca.* 2160 cm.$^{-1}$. It was not purified due to its instability.

3-Benzyl-5-hydroxy-1,2,4-oxadiazole. (a) *By rearrangement of the azide.* Refluxing 1.0 g. of the above azide in 25 ml. of benzene for 30 min. caused the solution to darken. Evaporation left a dark residue which was recrystallized from water to give 0.4 g. of solid, m.p. 60–100°. Recrystallizations from carbon tetrachloride, water, and petroleum ether (b.p. 60–75°) with a trace of benzene gave an analytical sample, m.p. 112–115°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.41; H, 4.58; N, 15.94. Found: C, 61.36; H, 4.58; N, 15.90.

(b) *From amidoxime.* Phenylacetamidoxime[22] was converted to the oxadiazole[23] with ethyl chloroformate and base. Identical infrared spectra and undepressed mixture melting point showed these two samples to be the same compound.

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Nitration of Unsaturated Alcohols[1]

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The nitration of several aliphatic alcohols containing carbon-carbon unsaturation has been accomplished using acetyl nitrate as the reagent. In specific cases, the normal nitration procedure could be modified to afford good yields but in most cases only 10 to 30% yields were obtained. These low yields are ascribed to subsequent addition of the elements of acetyl nitrate to the double bond with the formation of high boiling by-products. A number of new unsaturated nitrates, dibromoalcohols, and dibromoalcohol nitrates are described. The last can be obtained in good yields by both nitration of the dibromoalcohols and bromination of the unsaturated nitrates.

The most attractive method for the synthesis of molecules containing both nitrate ester functions and carbon-carbon unsaturation is the nitration of the corresponding unsaturated alcohol. A wide variety of general nitration media have been employed by different workers.[2,3] Most of these media, if not all, are composed of reagents which in

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addition to effecting hydroxyl nitration may also add to unsaturated systems. The successful nitrations of allyl alcohol,[1] both *cis*- and *trans*-2-buten-1,4-diol,[5] 2,2-bis(hydroxymethyl)-3-buten-1-ol,[6] and 2-(hydroxymethyl)-2-methyl-3-buten-1-ol[6] with absolute nitric acid in acetic anhydride (acetic acid was used as a diluent in the last two examples) suggested that this system might serve for the projected investigation. However, it was shown,[7-9] after the study reported herein was nearly complete, that acetyl nitrate, the effective nitrating reagent in this system, can add to olefinic linkages. The report by Bordwell and Garbisch[9] dealing with the addition of acetyl nitrate to aliphatic systems containing carbon-carbon double bonds was of particular value since it outlined the best addition conditions which were exactly the converse of our intention.

Since the eventual goal of our work was to study the polymerization of unsaturated substances containing nitrate ester groups, the unsaturated alcohols of greatest interest were those which contained a terminal or vinyl type carbon-carbon unsaturation. However, for completeness, several alcohols with internal unsaturation were also investigated. Nitration of the corresponding alcohols with acetyl nitrate (threefold excess at $-30°$) in acetic anhydride afforded the nitrates: 1-nitrato-4-pentene, 1-nitrato-5-hexene, 2-methyl-4-nitrato-1-pentene, 1-nitrato-2-butene, and 2-methyl-1-nitrato-2-propene. The yields of unsaturated nitrates obtained by this method, designated herein the standard method, ranged from 10 to 30%. These nitrates are all liquids and the last step in their preparation was distillation under reduced pressure. When the standard nitration method was employed, considerable nondistillable (bath temperature 75° at 0.1 mm. pressure) residues invariably resulted. These residues were viscous and on quantitative analysis always proved to contain more nitrogen than that required for hydroxyl nitration alone.

The reaction of silver nitrate dissolved in acetonitrile[10] with the corresponding unsaturated halogen derivatives gave 1-nitrato-4-pentene and 2-methyl-1-nitrato-2-propene in high yields (83 and 88%, respectively). Although these nitrates were isolated by distillation, as were the products from the standard nitration method, only negligible residues were formed.

These observations suggest that two factors may operate to reduce the yields in the standard nitration method. First, the acetyl nitrate may add to the double bond[7-9] to produce the high boiling acetoxy-nitronitrates. Second, these adducts may decompose on heating to produce radicals serving to initiate the polymerization of the unsaturated nitrates. In a single case, it was possible to isolate one of these adducts, 2-methyl-1-nitrato-2(or 3)-nitropropan-2(or 3)-ol acetate by subjecting the residue from the distillation of the unsaturated nitrate to higher temperature and greatly reduced pressure. Attempts to isolate similar adducts from the other residues by the same technique terminated in minor explosions or detonations.

Bordwell and Garbisch[9] state that acetyl nitrate fails to form on the addition of nitric acid (70%) to acetic anhydride at temperatures below $-10°$. This observation suggested that the solution of nitric acid in acetic anhydride formed in this way might effect hydroxyl nitration without the interference of double bond addition. However, experiments using this technique for the nitration of 2-methyl-2-propen-1-ol gave neither the unsaturated nitrate nor any adduct. Apparently, the alcohol survived this treatment without effect.

Although, as evidenced by the considerable heat of reaction, acetyl nitrate forms on the addition of absolute nitric acid to acetic anhydride at $-30°$, the nitrating mixture is more effective if it is prepared at 20 to 25° and then cooled to $-30°$ prior to addition of the alcohol. Thus, 1-nitrato-2-butene was obtained in 30% yield by the standard method and in 65% yield when the nitrating solution was prepared at 25° (*caution*). The higher temperature may permit more nearly quantitative conversion of the nitric acid to the much more effective[9] nitrating agent acetyl nitrate. A similar increase in yield (25 to 50%) was observed when 2-methyl-2-propen-1-ol was nitrated with the mixture prepared at 25°.

After many experiments, the best method (65% yield) for the nitration of this last alcohol was evolved. This required the use of acetic acid as a diluent for the nitration system.[6] These various modifications appear to be rather specific for a given unsaturated alcohol since their application to the other alcohols studied did not meet with any improvement in yield over the standard method. None of the various methods permitted the preparation of 2-methyl-2-nitrato-3-butene from the corresponding alcohol. Perhaps this tertiary nitrate readily eliminates the elements of nitric acid to form isoprene.

In order to confirm the structures of these unsaturated nitrate derivatives, the original alcohols were brominated (50 to 70% yields) to obtain:

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1,2-dibromo-5-pentanol, 1,2-dibromo-6-hexanol, 1,-2-dibromo-2-methyl-4-pentanol, 1,2-dibromo-2-methyl-3-propanol, 2,3-dibromo-1-propanol, and 1,2-dibromo-3-methyl-3-butanol; the second, third, and fourth compounds in the list are new. Since some of these dibromoalcohols tend to decompose during purification by distillation, conflicts appear in the literature on their physical properties[11] and this problem has not been resolved in our work.

Nitration of these dibromoalcohols by the standard nitration method afforded the new dibromonitrates: 1,2-dibromo-5-nitratopentane, 1,2-dibromo-6-nitratohexane, 2,3-dibromo-1-nitratopropane, 1,2-dibromo-2-methyl-3-nitratopropane, 1,2-dibromo-2-methyl-4-nitratopentane, and 1,2-dibromo-3-methyl-3-nitratobutane in yields of 67, 47, 56, 61, 86, and 50%, respectively. Identical samples of the first four were obtained by bromination of the corresponding unsaturated nitrates (79, 72, 87, and 88% yields, respectively).

EXPERIMENTAL

Materials and methods. The unsaturated alcohols, except 2-methyl-1-penten-4-ol, were commercial samples which were fractionated prior to use. Middle fractions with boiling point ranges of less than a degree were selected.

Prior to analysis of all the various products described below, the infrared spectra were checked to ensure their gross purity. The presence of the proper absorption peaks, following the assignments given by Bellamy,[12] as well as the absence of extraneous absorption peaks was employed for this purpose.

General bromination procedure. The unsaturated compound (0.1 mole) was dissolved in 100 ml. of dichloromethane (or carbon disulfide), stirred at −20° and 0.11 mole of bromine dissolved in 100 ml. of the same solvent was added dropwise. The resulting solution was extracted with 5% aqueous sodium hydroxide until colorless and with water until neutral. After drying with calcium sulfate, the solvent was removed under reduced pressure and the brominated product was purified by distillation under reduced pressure.

2,3-Dibromo-1-propanol. Pure material was isolated in 53% yield; b.p. 109° (20 mm.), n_D^{20} 1.5597. These values are in reasonable agreement with those cited for this substance.[13]

1,2-Dibromo-5-pentanol. This compound decomposed slightly during distillation under reduced pressure. A slightly impure sample was obtained; yield 69%, b.p. 107° (2 mm.), n_D^{20} 1.5417 (lit.,[11] b.p. 132–133° at 16 mm.).

1,2-Dibromo-6-hexanol. This new substance also decomposed slowly during distillation; yield 65%, b.p. 120° (2 mm.), n_D^{20} 1.5242.

1,2-Dibromo-3-methyl-3-butanol. A 62% yield of this substance was obtained; b.p. 103° (10 mm.), n_D^{20} 1.5302. This latter value agrees with the reported values[14,15] but the boiling points cited do not correlate exactly with each other or with our data.

1,2-Dibromo-2-methyl-4-pentanol. The required 2-methyl-1-penten-4-ol was prepared following Hudson and Schmerbaile.[16] Bromination gave the new, 1,2-dibromo-2-methyl-4-pentanol; yield 56%, b.p. 104° (5 mm.), n_D^{20} 1.5384.

1,2-Dibromo-2-methyl-3-propanol. Bromination of the unsaturated alcohol in carbon disulfide afforded this new compound; yield 50%, b.p. 104°, n_D^{20} 1.5453.

General nitration procedure. The absolute nitric acid employed was prepared by the reduced pressure distillation of colorless commercial reagent grade 70% nitric acid from an equal volume of concd. reagent grade sulfuric acid; b.p. 35–40° (30 mm.). All work was done behind explosion screens.

To 50 ml. of acetic anhydride, stirred and cooled at −30° in a flask covered with aluminum foil and protected from moisture, was added 12.6 ml. (0.3 mole) of absolute nitric acid. At the same temperature, 0.1 mole of the alcohol was added slowly. After stirring for a few minutes, the mixture was poured rapidly onto cracked ice. This and all subsequent processing in experiments with the unsaturated materials was conducted with a minimum exposure to light. The oily layer which formed was separated and washed with 5% sodium carbonate solution until neutral and then with water. With small volumes, the addition of either dichloromethane or ether facilitated these operations. The neutral material was dried with calcium sulfate (Drierite) and distilled under reduced pressure.

The reported nitrations, employing this method, of 2-propen-1-ol[4] and both *cis*- and *trans*-2-buten-1,4-diol[5] were successfully repeated in this laboratory. In the work described below, nearly all of the distillations produced large yields of viscous pot residues which were found to provide more complex infrared spectra and to contain more nitrogen than the desired product as determined by elemental analysis. Attempts were made to distill the pot residues obtained in most of the nitration experiments. The usual result was at least a fume-off if not an actual explosion.

Unless noted to the contrary, this general method was used for the nitration of the alcoholic substances.

2,3-Dibromo-1-nitratopropane. This new compound was prepared by two methods. Nitration of 2,3-dibromo-1-propanol and bromination of 1-nitrato-2-propene by the methods described afforded pure material of like constants and identical infrared spectra, in yields of 56 and 87%, respectively; b.p. 119° (20 mm.), n_D^{20} 1.5349.

Anal. Calcd. for $C_3H_5Br_2NO_3$: C, 13.90; H, 1.92; Br, 60.79; N, 5.33. Found: C, 14.04; H, 2.02; Br, 61.04; N, 5.55.

1,2-Dibromo-2-methyl-3-nitratopropane. Bromination of 2-methyl-1-nitrato-2-propene gave this new compound; yield 88%, b.p. 58° (0.4 mm.), n_D^{24} 1.5235. Identical constants and infrared spectra were obtained with a sample of this compound prepared by nitration of the dibromoalcohol; yield 61%.

Anal. Calcd. for $C_4H_7Br_2NO_3$: C, 17.35; H, 2.55; Br, 57.71; N, 5.06. Found: C, 17.35; H, 2.66; Br, 57.80; N, 5.11.

1,2-Dibromo-3-methyl-3-nitratobutane. This new compound was prepared from 1,2-dibromo-3-methyl-3-butanol by nitration; yield 50%, b.p. 106° (5 mm.), n_D^{20} 1.5222.

Anal. Calcd. for $C_5H_9Br_2NO_3$: C, 20.64; H, 3.12; N, 4.81; Br, 54.93. Found: C, 20.97; H, 3.21; N, 4.54; Br, 54.74.

1,2-Dibromo-2-methyl-4-nitratopentane. Nitration of the corresponding dibromoalcohol afforded this new compound; yield 86%, b.p. 120° (6 mm.), n_D^{20} 1.5155.

Anal. Calcd. for $C_6H_{11}Br_2NO_3$: C, 23.63; H, 3.64; Br, 52.40; N, 4.59. Found: C, 23.99; H, 3.87; Br, 52.23; N, 4.51.

1,2-Dibromo-5-nitratopentane. This new substance resulted from the nitration of the corresponding dibromoalcohol and the bromination (carbon disulfide) of the un-

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(14) A. A. Petrov, *J. Gen. Chem. (U.S.S.R.)*, **12**, 741 (1943); *Chem. Abstr.*, **39**, 695 (1945).

(15) S. Winstein and L. Goodman, *J. Am. Chem. Soc.*, **76**, 4373 (1954).

(16) J. F. Hudson and G. Schmerbaile, *Tetrahedron*, **1**, 284 (1957).

saturated nitrate; yields 67 and 79%, respectively, b.p. 109° (0.7 mm.), n_D^{20} 1.5263 ± 0.0004, infrared spectra identical.

Anal. Calcd. for $C_5H_9Br_2NO_3$: C, 20.64; H, 3.12; Br, 54.93; N, 4.81. Found: C, 20.77; H, 3.27; Br, 55.05; N, 4.94.

1,2-Dibromo-6-nitratohexane. Nitration of the dibromo-alcohol and bromination of the unsaturated nitrate gave this new compound; yields 47 and 72%, respectively, b.p. 149° (5 mm.), n_D^{20} 1.5182 ± 0.0005, infrared spectra identical.

Anal. Calcd. for $C_6H_{11}Br_2NO_3$: C, 23.63; H, 3.64; Br, 52.40; N, 4.59. Found: C, 23.46; H, 3.91; Br, 52.77; N, 4.52.

1-Nitrato-4-pentene. This new nitrate was isolated in 20% yield; b.p. 27° (5 mm.), n_D^{20} 1.4321.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.91; N, 10.68. Found: C, 46.04; H, 7.06; N, 10.83.

A mixture of 1-bromo-4-pentene (25 g.) and 250 ml. of acetonitrile containing 90 g. of silver nitrate and 2 g. of hydroquinone was stirred for 56 hr. at room temperature. The insoluble material was removed by filtration and the filtrate was dissolved in ether and the solution was washed thoroughly with water. Drying over sodium sulfate and distillation (no residue) afforded 1-nitrato-4-pentene identical in boiling point, refractive index, and infrared spectra with the sample described above; yield 18 g. (83%).

1-Nitrato-5-hexene. An 11% yield of this new compound was obtained; b.p. 30° (0.1 mm.), n_D^{20} 1.4385.

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.75; H, 7.60; N, 9.67.

2-Methyl-4-nitrato-1-pentene. This new, comparatively unstable nitrate was isolated in 19% yield; b.p. 26° (2 mm.), n_D^{20} 1.4308.

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.67; H, 7.78; N, 9.56.

Attempted nitration of 2-methyl-3-buten-2-ol. Numerous attempts to prepare the nitrate of this alcohol by the method described above and by the various alternative methods discussed below were unsuccessful. Large pot residues were normally obtained and in the few cases where any distillate of product resulted, it shortly decomposed violently.

1-Nitrato-2-butene. Anhydrous acetic anhydride (60 ml.) was stirred at 25° while adding dropwise 21 ml. (0.5 mole) of absolute nitric acid (*caution*). The solution was cooled to −25° and 14.4 g. (0.2 mole) of 2-buten-1-ol was added dropwise. After 30 min. at −20°, the solution was poured into ice and water and the nitrate was isolated in the described manner; yield 15.2 g. (65%), b.p. 42° (18 mm.), n_D^{20} 1.4294. Employing the previously described nitration method, the yield was 30%.

Anal. Calcd. for $C_4H_7NO_3$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.24; H, 6.20; N, 12.19.

2-Methyl-1-nitrato-2-propene. A mixture of acetonitrile (250 ml.), silver nitrate (125 g.), and 2 g. of hydroquinone was stirred at 0° in the dark while adding 25 g. of 1-chloro-2-methyl-2-propene dropwise. The mixture was allowed to stir for 36 hr. without further cooling. After filtration, the filtrate was diluted with ether and the resulting solution was extracted with water, 2% aqueous sodium bisulfite, and again with water. Drying over sodium sulfate, evaporation of the ether, and distillation gave colorless 2-methyl-1-nitrato-2-propene; yield 88%, b.p. 37° (25 mm.), n_D^{24} 1.4229.

Anal. Calcd. for $C_4H_7NO_3$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.24; H, 6.10; N, 11.87.

Although the compound was prepared in this way for use as a reference compound in the studies described below, the data given represent significant improvements over those cited in the literature.[17]

Nitration of 2-methyl-2-propen-1-ol, employing the general method described previously, afforded the same nitrate in 25% yield. Almost no nitration was effected if the temperature was held at −55° during the course of the nitration process including the addition of the nitric acid to the acetic anhydride. Following the method of Kuhn and Duckworth,[5] which differs in that acetic acid is used to dilute the nitration system, there was likewise obtained low yields (25%) of unsaturated nitrate and considerable amounts of pot residue on distillation. In either process if the molar ratio of nitric acid to unsaturated alcohol was reduced to 1:1, only traces of unsaturated nitrate could be isolated; under these conditions no pot residue was obtained either.

Following an adaptation of the method of Bordwell and Garbisch,[9] 60 ml. of acetic anhydride was treated at 25° with 21 ml. (0.5 mole) of absolute nitric acid. The solution was cooled to −25° and 14.4 g. (0.2 mole) of 2-methyl-2-propen-1-ol was added dropwise. After 15 min. at −20°, the mixture was poured into ice and water and processed as described; yield 11.8 g. (50%), with only a trace of pot residue. When sulfuric acid (several drops) was added to this mixture before addition of the alcohol,[9] considerable amounts of pot residue and almost no unsaturated nitrate resulted. When the method of Bordwell and Garbisch,[9] employing a much larger ratio of acetic anhydride to 70% nitric acid, was used, no product of any kind was obtained; in these experiments various temperatures between −10 and 25° were employed for the addition of the nitric acid to the anhydride and in all cases the alcohol was added at −20°.

After these many experiments, the following method, comparable to that of Kuhn and Duckworth,[5] was found to give the best results. Acetic anhydride (28.3 ml., 0.3 mole) and acetic acid (57.2 ml., 1.0 mole) were stirred at 10° while adding 21 ml. (0.5 mole) of absolute nitric acid. This solution was cooled to −3° and 14.4 g. (0.2 mole) of 2-methyl-2-propen-1-ol was added slowly. After 15 min. at this temperature, the cooling bath was removed and the mixture was stirred until the temperature reached 10°. Then the solution was poured into ice and water and processed as described; yield 65%.

2-Methyl-1-nitrato-2(or 3)-nitropropan-2(or 3)-ol acetate. Following a modification of the method of Bordwell and Garbisch,[9] 37.8 g. of absolute nitric acid was added to 400 ml. of acetic anhydride stirred at 25°. The solution was cooled to −30° and 3 g. of concd. sulfuric acid was added. After 15 min., 21.6 g. of 2-methyl-2-propen-1-ol was added in one portion. The temperature rose rapidly to 23° and then subsided. After cooling to −35° and maintaining this temperature for 15 min., the mixture was poured into ice and water. Processing in the manner described under the general nitration procedure yielded a small amount of unsaturated nitrate and a pot residue which could be distilled in part. Redistillation afforded pure material; yield 3.5 g. (5%), b.p. 109–110° (1 mm.), n_D^{20} 1.4797.

Anal. Calcd. for $C_6H_{10}N_2O_7$: C, 32.44; H, 4.54; N, 12.61. Found: C, 32.67; H, 4.36; N, 12.89.

COLUMBUS 10, OHIO

(17) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Am. Chem. Soc.*, **75**, 4078 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

General Formation of Aryl Dithiolcarbonates and Ethyl Ethylxanthate in the Leuckart Thiophenol Synthesis[1]

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Study of the reactions of a variety of diazonium salts with potassium ethylxanthate showed that in addition to the aryl ethylxanthate previously considered to be the principal product, other important and general products are the corresponding diaryl dithiolcarbonate and ethyl ethylxanthate. Evidence is given for the structure of typical products and for the probability that the dithiolcarbonate is not formed from the aryl ethylxanthate, either during the Leuckart reaction or subsequently. The yield of a typical dithiolcarbonate was not improved by use of potassium isopropyl- or benzylxanthate. Both heterolytic and homolytic processes apparently occur, at least to some extent. Experiments are described which permit tentative generalizations and conclusions as to the nature of the Leuckart thiophenol synthesis.

The Leuckart reaction for the preparation of thiophenols involves addition of a neutralized solution of a diazonium salt to a hot aqueous solution of potassium ethylxanthate (I). The product, assumed in the past to be an aryl ethylxanthate (II), ordinarily is not purified but is hydrolyzed directly to the thiophenol, as shown by the equations.[3,4]

$$ArN_2X + KS\cdot CS\cdot OC_2H_5 \xrightarrow{70^\circ}$$
$$\text{I}$$
$$ArS\cdot CS\cdot OC_2H_5 + N_2 + KX \quad \ldots(1)$$
$$\text{II}$$
$$\text{II} \xrightarrow{\text{Aq. KOH}} C_2H_5OH + KS\cdot CO\cdot OK + ArSK \xrightarrow{H^+} ArSH$$

thiol III had a refractive index higher than reported. Conversions of IV to V and III in yields exceeding 50% demonstrated that IV could not be the isomeric thionothiolcarbonate.

Information as to how IV might have been formed was sought by an attempt to isolate all reaction products. Washing the crude product with acid removed negligible material, but aqueous alkali extracted a little 2,6-dimethylphenol and what appeared to be an azophenol, a type of compound which could account for the dark red color of the crude product.

Partial distillation of the neutral products then gave ethyl ethylxanthate (VIII), a finding which

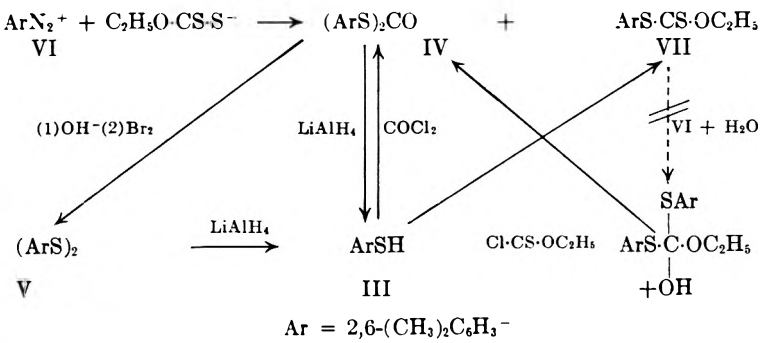


Fig. 1. Identification of bis(2,6-dimethylphenyl) dithiolcarbonate (IV)

In preparing 2,6-dimethylthiophenol (III) by this reaction, we found that the crude product before hydrolysis partially crystallized. The solid, surprisingly, was bis(2,6-dimethylphenyl) dithiolcarbonate (IV). Fig. 1 shows the evidence for its identity; the disulfide V was prepared because the surprised us even more than had the isolation of IV, because of the evident transfer of an ethyl group from I and the necessarily concomitant cleavage of the bond in I between oxygen and a primary carbon atom. The identity of VIII was demonstrated by comparing its infrared spectrum with that of authentic VIII, itself characterized by derivatives. Potassium ethylxanthate (I) gave no VIII when heated in water and therefore its simple decomposition was not responsible for formation of VIII.

$$2\ ArN_2X + 2\ KS\cdot CS\cdot OC_2H_5 \longrightarrow$$
$$\text{I}$$
$$(ArS)_2CO + C_2H_5S\cdot CS\cdot OC_2H_5 + 2N_2 + 2KX \quad \ldots(2)$$
$$\text{IX(in IV, Ar=2,6-(CH}_3)_2C_6H_3^-) \qquad \text{VIII}$$

(1) Largely abstracted from the M.A. thesis of J. R. C., December 1955, and the Ph.D. thesis of C. L. G., May 1959. Presented in part at the Southeastern Regional Meeting of the American Chemical Society at Durham, N. C., Nov. 14–16, 1957.

(2) To whom inquiries should be addressed.

(3) K. H. Saunders, *The Aromatic Diazo Compounds*, 2nd ed., Edward Arnold and Co., London, 1949, p. 324.

(4) E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. 1, Chemical Publishing Co., Inc., New York, N. Y., 1958, p. 31.

The yield of VIII was 44%, calculated using Equation 2, which later seemed likely to apply. For the sake of brevity, the ratio of the yield of ethyl ethylxanthate (VIII) to the yields of various diaryl dithiolcarbonates (IX) will be called the "VIII/IX ratio"; IX will be used to refer to diaryl dithiolcarbonates in a general sense, and II will be used in the same way for aryl ethylxanthates.

Since the dithiolcarbonate IV was isolated in 62% yield, the VIII/IX ratio in this instance was 0.7, rather than 1 as required by Equation 2. A plausible explanation for the discrepancy was that VIII had been destroyed in part, either during the reaction or the isolation. Since VIII was resistant to acid and base, as used in its isolation, an effort was made to approximate its destruction in the reaction (or the subsequent distillation) by determining that proportion of an extraneous amount of VIII which could be recovered after it had been added during the usual reaction; the assumption was made that the amount of VIII actually formed in the reaction would be unchanged. About 81% of the extraneous VIII survived. Correction for the loss suggested that about 55% of VIII had been formed in the conventional reaction. The VIII/IX ratio obtained using the corrected yield was 0.9, which thus rather strongly supports the validity of Equation 2.

Chromatographic separation of the residue from the distillation of VIII gave the aryl xanthate VII in 23% yield and the dithiolcarbonate IV in 62% yield (including IV which had crystallized earlier). VII was identified conclusively by independent synthesis from ethyl chlorothionoformate and the thiol III (Fig. 1); this type of reaction has been used with alcohols but seems to be novel with a thiol.

The effect of varied conditions next was explored in the hope of improving the yield of IV and of obtaining intimations as to the mechanism of its formation. It might be added here that yields as high as 75% of IV have been obtained but that occasionally, in the same procedure, they were as low as 53%. One possible explanation for this variation may be that an important part of the reaction occurs in the water-insoluble organic phase and that there is erratic diffusion of a necessary intermediate within this mass. Another explanation is suggested later. In any event, caution is dictated in the interpretation of results in the various reactions leading to aryl xanthates (II) and dithiolcarbonates (IX) which are to be considered.

In this study of conditions, the proportions of reagents were varied by adding the diazonium salt VI to three molar proportions (usually 1.25) of xanthate I. In an effort to have VI in excess, it also was added, both slowly and rapidly, to 0.5 molar proportion of I. The range of 40–54% in the yield of IV probably is not very significant but does suggest that better yields of IV are obtained with a ratio of VI to I which approximates unity.[5]

A feature of the reaction which undoubtedly plays a highly significant role, both theoretically and practically, is the solid which forms when VI is allowed to react with I in the cold. This solid presumably is a diazoxanthate,[3] $ArN_2S{\cdot}CS{\cdot}OR$, and ordinarily is decomposed immediately when the reaction is effected at 60° (an explosion may ensue if it is not).[3] Attempts to isolate this complex were thought to be hazardous because of its apparent explosive tendency. It was studied, however, *in situ*. When 0.52 molar proportion of the I was added to one equivalent of VI at 0° and the mixture then heated slowly to 60°, IV resulted but only in 25% yield. The same result ensued when the cold mixture of I and VI was added rapidly to water at 60°. It is noteworthy that when 2.1 proportions of I to 1 of VI were used, IV was isolated in only 1% yield. These results, more than those obtained only at 60°, point to the undesirability of a ratio of VI to I which differs much from unity, if IV is sought from the reaction.

The most obvious explanation for the formation of the dithiolcarbonate IV in the Leuckart synthesis was that the anticipated aryl xanthate VII is in fact a major initial product, but that it is attacked by VI and water and thus partially converted into IV, as shown by the cancelled arrow of Fig. 1.

Hölzle had previously isolated bis(5,8-dichloro-1-naphthyl)dithiolcarbonate in 34% yield in the appropriate Leuckart reaction (and the aryl xanthate in 46% yield).[6] In considering the mechanism of its formation, he rejected the aryl ethylxanthate as an intermediate on the ground of its insolubility in water; he also excluded its hydrolysis product, $ArS{\cdot}CO{\cdot}S^-$, on the basis that the aryl ethylxanthate could not be hydrolyzed under the conditions of the reaction and that, even if it were, the hydrolysis product would not be that indicated. We substantiated Hölzle's opinion as to simple direct attack upon the aryl xanthate by recovering the xanthate VII after it had been treated with VI in water. Since it was possible, however, that the VII formed in the Leuckart reaction would appear so finely dispersed that our experiment in bulk would not be representative, VII also was exposed to VI in methanol, which effected homogeneity. Again VII was recovered, despite the fact that a control reaction of VI with I in methanol gave IV in 25% yield. These observations suggest that VII is not an intermediate in the formation of IV, but they are by no means conclusive; for example, the xanthate I normally might function concertedly with VI

(5) Owing to the rapidity of the reaction, I probably was in excess in *all* of these experiments, since the VI had to be added to it. The reverse addition to heated VI obviously is impracticable.

(6) K. Hölzle, *Helv. Chim. Acta*, 29, 1883 (1946).

upon the aryl xanthate VII in a manner that would be difficult to duplicate in a model situation. It might be added that Hölzle's exclusion of a hydrolysis product of VII also is reasonable, if our observation of the slow decrease in *p*H of an alkaline solution of VII indicates only slow hydrolysis.

Hölzle noted that the yield of his dithiolcarbonate was inversely proportional to the acidity of the medium,[6] and concluded that the reactive species was a diazonium hydroxide. His view, as we understand it, was that the xanthate ion, in the form of the mesomeric structure $C_2H_5O\cdot\overset{+}{C}S\cdot\overset{-}{S}$, upon simultaneous attack by the diazonium and hydroxide ions, followed by loss of alcohol, gave the intermediate $ArS\cdot CO\cdot\overset{-}{S}$, which then underwent attack by a second diazonium ion to give the dithiolcarbonate; attack of the xanthate ion in its usual form ($C_2H_5O\cdot CS\cdot\overset{-}{S}$) gave the aryl ethylxanthate. In both paths nitrogen was lost at appropriate points. The formation of VIII, however, cannot be accounted for by Hölzle's mechanism.

One of the most important questions connected with the Leuckart synthesis, and probably one of the most difficult to answer, is whether the reaction is heterolytic, homolytic, or some combination of the two (one path perhaps leading to the dithiolcarbonates IX and the other to the aryl xanthates II).[7] In a consideration of the uncatalyzed reactions of diazonium salts, Ingold has pointed out the probable importance of S_N1 decomposition into arylcarbonium ions, which subsequently react rapidly with nucleophilic species which are at hand;[9] decreased reactivity of the *p*-nitro compound (and perhaps of the *p*-methoxy) and enhanced reactivity of *ortho*-substituted systems are to be anticipated in such reactions (*vide infra*).[9] De Tar and Turetzky found that diazonium salts decomposed homolytically in acetate-buffered methanol[10] but stated their belief that decomposition in water up to about *p*H 7 occurred mainly by an ionic mechanism.[10b] In our reactions, the solution of diazonium salt was neutralized to Congo Red (*p*H 3–5)[11] and added to an essentially neutral solution of I. One is tempted therefore to conclude that the *p*H favors an ionic mechanism; however, the fact that the reaction mixture ultimately had a *p*H of about 7–7.5 makes such a conclusion seem somewhat injudicious.

In an effort to determine whether or not homolysis is involved in the Leuckart synthesis, the usual reaction with VI and I was effected in the presence of acrylamide. The formation of a considerable amount of presumed polyacrylamide was a strong indication that free radicals were in fact present. The yields of IV and VII differed little from that of a control reaction without acrylamide, but this result would be anticipated if the chain length of the polyacrylamide were sufficiently great so that relatively few initiating radicals were trapped. An interesting implication that radicals might form more readily with a hindered diazonium salt was obtained by warming both VI and a benzenediazonium salt in the presence of the diamine-precursor of Wurster's Blue; the deep blue color indicative of a free radical formed at 15–20° and 40–50° respectively. Enhanced reactivity has been noted with diazonium salts of *o-tert*-butylaniline which decompose above about −25°[12]; behavior of this kind, whether it depends upon homolysis or not, demonstrates enhanced reactivity for *ortho*-substituted systems which probably is quite important in relation to the varied yields of IX discussed presently. It is also noteworthy that neutralization at 0° of the solution either of VI or the benzenediazonium salt caused development of the Wurster color, suggesting that radicals may be generated rather easily from the unhindered salt, even though perhaps less easily than from the hindered one.

In probing further into the nature of the Leuckart reaction, it next became desirable to determine whether the formation of VIII and of dithiolcarbonates (IX) was general and, if so, the influence of steric and electronic factors on the ratio of the dithiolcarbonate IX to the aryl xanthate II; this ratio will be referred to subsequently as the "IX/II ratio."

No attention has been paid to the generality of formation of dithiolcarbonates (IX) in the Leuckart reaction, although in at least three instances, besides that of Hölzle,[6] they have been isolated in small or undeclared amounts using *p*-methyl-,[13] *o*-methoxy-,[14] and 2,4,6-tribromo-[15] benzenediazonium salts. Table I shows the results obtained when various representative diazonium salts were subjected to the Leuckart reaction. It is notable that the VIII/IX ratio seems to approximate unity closely enough to support the validity of Equation 2; the variations from unity probably reflect, in

(7) It is worth mentioning that there is a rather suggestive similarity of the Leuckart synthesis to the Sandmeyer reaction, in that the facile oxidation of the cuprous ion[8] has a possible counterpart in the presumably facile oxidation of I to the disulfide.

(8) *Cf.* ref. 3, p. 282.

(9) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 799.

(10) (a) D. F. De Tar and M. N. Turetzky, *J. Am. Chem. Soc.*, **77**, 1745 (1955); (b) **78**, 3925 (1956); (c) **78**, 3928 (1956).

(11) O. Tomicek, *Chemical Indicators*, Butterworths Scientific Publications, London, 1951, p. 50.

(12) F. Greer, Ph.D. thesis, Vanderbilt University, 1955, p. 73.

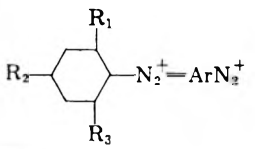
(13) R. Leuckart, *J. prakt. Chem.*, [2] **41**, 190 (1890); *J. Chem. Soc.* (*Abstracts*), **58**, 603 (1890).

(14) F. Mauthner, *Ber.*, **39**, 1347 (1906).

(15) W. H. Hunter and A. H. Kohlhase, *J. Am. Chem. Soc.*, **54**, 2425 (1932).

TABLE I

YIELDS,[a] FROM REPRESENTATIVE DIAZONIUM SALTS, OF ARYL DITHIOLCARBONATES (IX), ARYL ETHYLXANTHATES (II) AND ETHYL ETHYLXANTHATE (VIII)



				$(ArS)_2CO$ IX		$ArS{\cdot}CS{\cdot}OC_2H_5$ II		Ratio	$C_2H_5S{\cdot}CS{\cdot}OC_2H_5$ VIII	Ratio
No.	R_1	R_2	R_3	No.	Yield, %[b]	No.	Yield, %[b]	IX/II[b]	Yield, %[c]	VIII/IX[d]
VI	CH_3	H	CH_3	IV	62[e]	VII	23	2.7	55	0.9
X	C_2H_5	H	C_2H_5	XI	40	XII	29	1.4	33	0.8
XIII	CH_3	H	H	XIV	50	XV	42	1.2	45	0.9
XVI	H	H	H	XVII	30(11)	XVIII	50(36)	0.6	22	0.7
XIX	H	OCH_3	H	XX	20(12)	XXI	36	0.6	25	1.3[f]
XXII	H	NO_2	H	XXIII	27	XXIV	42	0.6	21[g]	0.8

[a] Yields are based on material before final purification. When substantial losses were incurred in purification, the yield of pure material follows in parentheses. [b] Crude yield % of the particular aryl dithiolcarbonate/crude yield % of the aryl ethylxanthate. [c] Corrected (see Experimental) for estimated decomposition after its formation. [d] Corrected yield %[c] of VIII/yield %, crude, of the particular aryl dithiolcarbonate. [e] 72% in a large-scale operation (see Experimental). [f] This unusually high value may simply be a result of greater loss than usual in the isolation of the XX. [g] Possibly an artifact.

part, differences in stabilities of products and ease of isolation in the various instances.

Consideration of most of the dithiolcarbonates which previously had been isolated from the Leuckart reaction suggested that steric hindrance about the diazonium function might have been an important factor in their formation and in the IX/II ratio. Table I shows that the yield of the dithiolcarbonate and the IX/II ratio are indeed greater when *ortho* substituents are present (*i.e.* with VI, X, and XIII). On the other hand, the isolation of IX after the reaction of XVI, XIX, and XXII, which contained no *ortho* substituents, shows that the formation of IX is general. The diazonium reagents XIX and XXII, containing a *p*-methoxy and a *p*-nitro group respectively, were used to determine the extent to which electron donation or withdrawal might affect the reaction; the rough similarity of these results to those obtained with the benzene-diazonium salt (XVI) indicates that electronic effects do not play a major role in determining the IX/II ratio.

The structures of the various dithiolcarbonates (IX) and aryl xanthates (II) probably need not be regarded with suspicion, since reactions of diazonium salts in which nitrogen is replaced appear invariably to result in entrance of the replacing group at the carbon atom which bore the nitrogen originally, irrespective of whether the reaction is heterolytic or homolytic.[16] Nevertheless, to obviate any possibility that the orientations of the products differed from those of the parent amines, the infrared spectra of all of the compounds of types IX and II were carefully scrutinized, especially in those regions which characterize the nature of aromatic substitution (1650–2000 cm.$^{-1}$, 950–1225 cm.$^{-1}$, and 670–1000 cm.$^{-1}$).[17] Correspondence of the spectra with expectation and with those of the parent amines appeared to support the validity of the various structures proposed.[18]

The experiments which led to the data of Table I were without notable incidents, except for those involving the benzene-(XVI) and *p*-nitrobenzenediazonium salts (XXII), which deserve some comment: (a) The melting points of the dithiolcarbonates XVII and XXIII differed from reported values. Evidence supporting our constants appears in the Experimental part (furthermore, absorption occurred in the infrared region[18] common to the other dithiolcarbonates). (b) Phenyl disulfide was obtained along with XVII and XVIII; XVII and XVIII seemed likely sources (*e.g.* dibenzyl dithiolcarbonate decomposes to the disulfide),[19] but, since both proved to be rather stable to heat, the origin of the disulfide still is unknown. (c) A red solid appeared when the nitro salt XXII was added to the I, even at 60°. This solid undoubtedly was a more stable counterpart of the presumed diazoxanthates. Another anomaly in this reaction was our inability to secure unequivocal evidence for the formation of VIII. As Table I shows, VIII was isolated, but the temperature required for distillation was sufficiently greater than usual to induce suspicion that VIII actually was an artifact; chromatography separated material which gave VIII upon distillation, but again

(16) *Cf.* ref. 3, Chapter VIII.

(17) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, 2nd ed., Methuen and Co., Ltd., London, 1958, Chap. 5. For the series from VI, the thiol III was used below 1000 cm.$^{-1}$ instead of IV and VII.

(18) The six dithiolcarbonates (IX) showed two medium (m) to strong (s) bands in the range of 830–880 cm.$^{-1}$ which accordingly may be characteristic of structure IX. The six xanthates (II), as well as VIII, showed six bands in the region of 1000–1300 cm.$^{-1}$ which may be characteristic: 1000–1015 cm.$^{-1}$ (m); 1020–1075 cm.$^{-1}$ (s; often as two overlapping bands); 1105–1110 cm.$^{-1}$ (m); 1139–1150 cm.$^{-1}$ (m); 1212–1235 cm.$^{-1}$ (s); 1265–1300 cm.$^{-1}$ (m).

(19) G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 666 (1945).

only with excessive heating. In the experiments with XXII, both VIII and XXIII conceivably could have formed according to Equation 3. This

$$2\ p\text{-}NO_2C_6H_4S\text{-}CS\text{-}OC_2H_5 \longrightarrow (p\text{-}O_2NC_6H_4S)_2CO + C_2H_5S\text{-}CS\text{-}OC_2H_5 \quad (3)$$

XXIV → XXIII + VIII

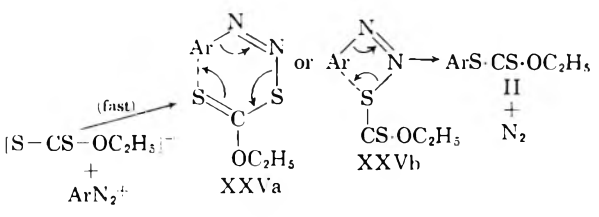
possibility was dismissed for the nitroaryl xanthate XXIV by demonstrating reasonable thermal stability for it. As a precaution, thermal stability under the conditions used to remove VIII also was established for the solid xanthates VII and XII. The other aryl xanthates (XV, XVIII, and XXI) were liquids which were considered to be stable, since no indication of behavior according to Equation 3 had been noticed when each was twice distilled for purification.

Since VIII evidently was an authentic product of the Leuckart reaction, an effort was worthwhile to determine the effect of using alkylxanthate salts other than I in the reaction, in order to facilitate the transfer of the alkyl group. The 2,6-diethyl compound X was found to give the dithiolcarbonate XI in a yield of between 50% (crude) and 18% (recrystallized) with potassium benzylxanthate, and of 37–28% with potassium isopropylxanthate (an effort to prepare potassium *tert*-butylxanthate was unpromising); both results thus approximate those obtained using I. No special effort was made to isolate products other than the XI, but 2,6-diethylphenyl benzylxanthate (43%) was isolated because it happened to crystallize nicely; the ratio of dithiolcarbonate XI to this xanthate resembles the IX/II ratio obtained with the ethyl xanthate I (approximately the same ratio resulted also with the isopropylxanthate if unpurified material which appeared at the expected point is considered to be the aryl isopropylxanthate).

Conclusions regarding the Leuckart process which now *seem* to be justified are these: (1) Formation is general of aryl xanthates (II), dithiolcarbonates (IX) and ethyl ethylxanthate (VIII; one possible exception); IX is not formed from II alone, in the reaction or subsequently. (2) Substituents in IX and II are oriented as in the parent amines. (3) The molar amount of VIII formed usually is smaller than of IX, but only slightly so. (4) Replacement of the ethyl group of I by isopropyl or benzyl has little effect on the yield of IX. (5) A diazonium salt and I at −5° give a solid diazoxanthate, which usually decomposes rapidly at 60°. (6) A 1:1 ratio of diazonium salt to I best produces IX. With solid diazoxanthate, excess I gives nearly no IX: excess diazonium salt produces IX, even though in low yield. (7) Free radicals are present. An unsubstituted diazonium salt yields radicals at 0° in neutral solution; a hindered salt probably does so more readily. (8) No biaryl coupling products were isolated (saponification of crude reaction product from XIX and steam distillation gave no 4,4′-dimethoxybiphenyl; however, aryl radicals may not survive long enough to couple). (9) Aryl carbonium ions are present, since a phenol was isolated. (10) Less IX forms in methanol than in water. Side reactions in methanol may be responsible but, since solvents of high dielectric constant favor heterolytic rather than homolytic processes,[20a] the result may signify that IX forms chiefly by a heterolytic path. (11) Substituents *ortho* to the diazonium function effect some increase in the yield of IX and in the IX/II ratio. (12) The yields of IX and II and the IX/II ratio are little affected by replacement of hydrogen by methoxy or nitro in the *para* position in the diazonium salt. (13) The yield of IX decreases with increasing acidity.[6] The reason may be that the diazotate anion is required,[6,20b] that a homolytic dissociation of the diazonium salt (known to be favored by a high *p*H) occurs, or simply that at low *p*H the concentration of ethylxanthate ion is reduced relative to the less nucleophilic free acid. Variation of *p*H may be a factor in the variable yields of IV which were mentioned earlier.

Mechanisms for the Leuckart synthesis cannot be offered now with much assurance. Thus, in addition to the quandary of heterolysis *versus* homolysis, the extent is unknown to which *syn*, *anti* stereoisomerism of diazoxanthates might determine whether IX or II predominates. Nevertheless, the fact that long-known reactions of diazonium reagents often are poorly understood leads us to believe that definitive evidence on the Leuckart process may appear only slowly and prompts us to suggest processes which may play a role. We wish to emphasize that these suggestions are quite speculative and are intended to be more provocative than definitive in explaining an unusual combination of reactions which results in the formation of a dithiolcarbonate and ethyl ethylxanthate along with the aryl xanthate.

An attractive pathway to the aryl ethylxanthates (II) involves the quasi-ring structures XXV A or XXV B for the diazoxanthate.



(20) (a) W. A. Waters, *The Chemistry of Free Radicals*, 2nd ed., Oxford University Press, London, 1948, p. 16.

(20) (b) H. Zollinger, *Experientia*, **12**, 165 (1956); C. Wittwer and H. Zollinger, *Helv. Chim. Acta*, **37**, 1954 (1954).

Formation of the diaryl dithiolcarbonates (IX) might follow one or more of the sequences outlined in Fig. 2.

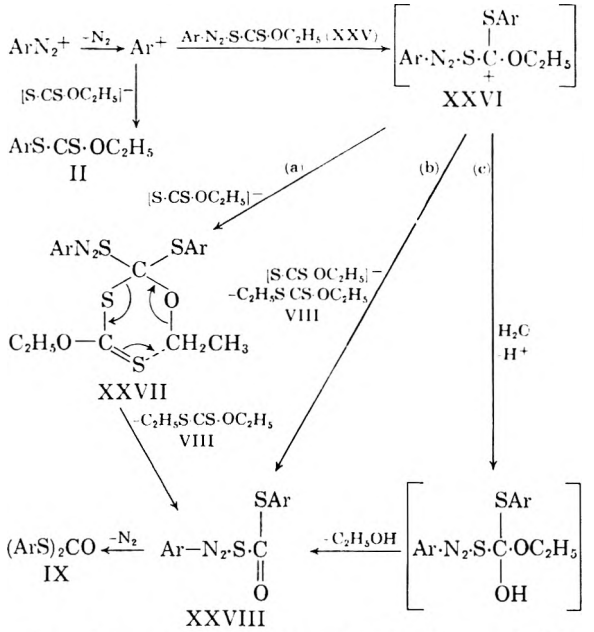


Fig. 2. Formation of the diaryl dithiolcarbonates (IX)[21]

EXPERIMENTAL[23]

Starting materials and general procedures. Potassium ethylxanthate (I)[24] was dried under vacuum and stored at 0–10°; no decomposition was evident after 3.5 years, the longest any was kept. Potassium isopropyl- (86%) and benzylxanthate (88%) were prepared in essentially the standard manner,[24] except that with the benzylxanthate the proportion of the alcohol was reduced by *ca.* one half and the product was precipitated with ether: both xanthates were completely soluble in acetone, showing the absence of potassium trithiocarbonate.

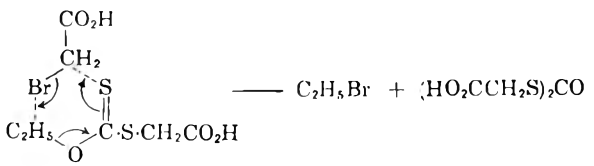
Amines used were purified commercial products. Sulfuric acid gave more soluble amine and diazonium salts with 2,6-dimethylaniline (XXIX) than did hydrochloric acid and accordingly was used for convenience in diazotizing all of the amines; hydrochloric acid, however, gave comparable results with XXIX. No explosions were encountered during the work, although the solids obtained by treating I with the nitro compound XXII or with the dimethyl salt VI in the low-temperature experiments gave indication of decomposing violently if handled incautiously in quantity; nevertheless care should be taken in the diazonium salt reactions generally, owing to the possibility of explosion.[25] In the Leuckart reactions, unless otherwise stated, the procedure of 1(a) was used with specified amounts of amines, and of other reagents in the molar proportions of 1(a), for diazotization, neutralization, reaction with I, and isolation of crude product by ether extraction; however, most diazotizations and neutralizations were done at 0–3° instead of at −5° to avoid solidification. Ether extracts of the reaction products usually were dried over anhydrous sodium sulfate and solvent then was removed under reduced pressure, most often by means of a rotating-flask evaporator (moist extracts in general were handled similarly); the term "red oil" refers to the residue left after removal of ether from the extract of the crude product of the Leuckart reaction. Chromatography was effected usually with a 3 × 32-cm. column of aluminum oxide ("Merck, Acid Washed, Suitable for Chromatographic Adsorption").

Yields in the Leuckart reaction were based on the amine, those of the aryl alkylxanthates being calculated on the basis of Equation 1 and those of the aryl dithiocarbonates (IX) and of ethyl ethylxanthate (VIII) on that of Equation 2. The identity of the samples of VIII isolated always was established by comparison of the infrared spectrum with that of authentic VIII.

1. *Reactions of the 2,6-dimethylbenzenediazonium salt* VI.

(a) *Preparation of bis(2,6-dimethylphenyl) dithiolcarbonate* (IV). A solution of 60.5 g. of 2,6-dimethylaniline (XXIX) in 500 ml. of water containing 42 ml. of sulfuric acid (sp. gr., 1.84) was diazotized below −5° by dropwise addition of a cold solution of 34.5 g. of sodium nitrite in 200 ml. of water (unless a positive starch-iodide test resulted 1 min. after addition, more nitrite solution was added). The resulting solution of the diazonium salt VI was neutralized to Congo Red by adding 30% aqueous sodium carbonate below −5°; the color changed from light yellow to light brown.[26] The solution (containing some precipitated sodium sulfate) then was poured (*ca.* 1 min.) into a solution, kept at 50–60° of 100 g. of I in 500 ml. of water. Nitrogen evolved smoothly and oil separated. Upon completion of gas evolution at 60°, the mixture was cooled. An ether extract was washed with

(21) In Fig. 2, ArN_2^+ (like Ar^+) could attack XXV, nitrogen being lost at once or subsequently. The formation of II shown could be competitive with or alternative to its formation *via* XXV A or XXV B. Paths (a), (b), and (c), shown for conversion of XXVI to IX, may be concomitant or alternative. In (a), XXVII is particularly speculative, since models are strained if the ring is coplanar; nevertheless, XXVII provides an attractive explanation for the unusual facile transfer of a primary alkyl group, especially since an otherwise rather puzzling reaction[22] can be formulated similarly:



In (b), the ethylxanthate anion is regarded as effecting nucleophilic displacement on the ethyl group of XXVI. Path (c) explains why the ratio of VIII/IX can be less than 1 [*cf.* (3)]. Compound XXVIII, however formed, may lose nitrogen essentially as in conversion of XXVB to II; loss of nitrogen is reserved to this point only for convenience. Fig. 2 rationalizes (6); with excess I, ArN_2^+ or Ar^+ presumably gave II, and hence negligible XXVI or IX; excess ArN_2^+ could produce IX *via* path (c), but in low yield since lack of I precluded paths (a) and (b).

(22) E. Bülmann, *Oversigt over det kgl. Danske Videnskabernes Selskabs Forhandlinger*, 1907 [2], 83; *Chem. Abstr.*, 2, 1269 (1908).

(23) Melting points are corrected and boiling points are uncorrected. Analyses mainly were by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were obtained using a Perkin-Elmer Model 137 Infracord spectrophotometer; most substances, being liquid or low melting, were used as liquid films (XXIII in Nujol mull; XI, solid film; IV, VII in carbon tetrachloride).

(24) C. C. Price and G. W. Stacy, *Org. Syntheses*, 28, 82 (1948).

(25) W. E. Bachmann and R. A. Hoffman, *Org. Reactions*, Vol. II, 224 (1944).

(26) In later Leuckart reactions, the *p*H was adjusted to *ca.* 5 using pHydrion test paper and was checked using Congo Red. Variations within the Congo Red transition range[11] may have been responsible for the variation in yields of IV mentioned in the discussion.

5% hydrochloric acid (100 ml.), 5% aqueous sodium hydroxide (200 ml.) and finally with water until neutral. Concentration of the dried extract to *ca.* 150 ml. and cooling gave the dithiolcarbonate IV, which was washed with cold petroleum ether; yield 35.2 g. (47%), m.p. 101–103.5°. Further concentration to *ca.* 75 ml. and chilling (Dry Ice–acetone) gave a second crop of 18.5 g. (25%), m.p. 98–101°. Recrystallization from ether (low yields) and carbon tetrachloride–methylcyclohexane gave colorless IV with a constant m.p. of 103–104.5°.

Anal. Calcd. for $C_{17}H_{18}OS_2$: C, 67.51; H, 6.00; S, 21.20. Found: C, 67.60; H, 6.06; S, 20.94.

(b) *Conversion of* IV *to 2,6-dimethylphenyl disulfide* (V) *and 2,6-dimethylthiophenol* (III). A mixture of 10 g. of IV and 20 g. of sodium hydroxide in 100 ml. of 1:1 water-ethanol was heated under reflux for 4 hr. The mixture was diluted with water and filtered. After removal of alcohol by distillation, bromine was added dropwise with shaking until its color persisted. Filtration removed 7.8 g. (86%) of the disulfide (V), m.p. 100–102°, which after recrystallization from aqueous alcohol and pentane had a constant m.p. of 103–104°; reported m.p., 105.5°–106°,[27] 103–104°.[28]

Anal. Calcd. for $C_{16}H_{18}S_2$: C, 70.03; H, 6.61. Found: C, 70.24; H, 6.76.

A solution of 1.52 g. of lithium aluminum hydride in 30 ml. of dry ether was added dropwise to 7.5 g. of IV in 50 ml. of ether. After 8 hr., moist ether was added, then dilute hydrochloric acid. The ether layer was washed with water and dried. Distillation gave 4.45 g. (64%) of the thiophenol III, b.p. 61–64° (2 mm.), n_D^{24} (each of four fractions) 1.5734; reported b.p. 91° (50 mm.),[28] 111° (25 mm.);[29] n_D^{20} 1.5712,[28] n_D^{25} 1.5712.[29] The thiol III also was obtained (75% yield) by reduction of V with lithium aluminum hydride,[30] b.p. 62–64° (2 mm.), n_D^{24} 1.5733.

Anal. Calcd. for $C_8H_{10}S$: C, 69.51; H, 7.29. Found: C, 69.32; H, 7.41.

(c) *Material balance in the reaction of* VI *with the xanthate* I. VI from 12.12 g. of XXIX was added in 2 min. and the ether extract of the product washed and dried (Extract XXX), all as usual.

In another experiment, with 60.5 g. of XXIX, the alkaline wash solution was strongly acidified and extracted with ether. This extract, dried and concentrated, left 0.98 g. of brown solid (XXXI). Sublimation of the XXXI gave 0.3 g. of 2,6-dimethylphenol, m.p. and mixture m.p. 45–47°. Reduction of the residue from this sublimation with aqueous sodium hydrosulfite resulted in an acid-soluble precipitate; since the precipitate apparently was an aminophenol and since the color of XXXI in water was *p*H-variable, XXXI presumably contained an azo coupling product along with 2,6-dimethylphenol. In this same experiment, only a trace of solid resulted when the usual acid wash was made basic.

Removal of ether from Extract XXX gave "red oil" which partially crystallized in 3 hr. at 5°; solid IV, removed and washed with cold hexane, amounted to 6.42 g. (43%), m.p. 100–103°.

The remaining oil (and hexane wash) was cautiously distilled through an 8 × 250 mm. tube until low boiling material was removed; 3.28 g. (44%) of ethyl ethylxanthate (VIII) distilled, b.p. 80–82° (9 mm.), n_D^{25} 1.5353–1.5354; reported, b.p. 78° (18 mm.),[19] n_D^{19} 1.5375.[31] The identity of VIII first was suggested by analysis of material from an earlier experiment, n_D^{25} 1.5349.

Anal. Calcd. for $C_6H_{10}OS_2$: C, 39.97; H, 6.71; S, 42.68. Found: C, 40.65; H, 6.92; S, 43.13.

For evidence that the VIII was not formed simply by decomposition of I, 9.9 g. of I in 50 ml. of water was heated at 50–55° for 1 hr; the *p*H rose from 7 to 8 but no insoluble oil (*i.e.* VIII) was observed at any time.

Undistilled residue (10.17 g.) from the distillation was dissolved in enough hexane to give 50 ml. of solution, which was chromatographed. Fractions were discerned by evaporating occasional small amounts of effluent in a bath at 50° (VII melted, IV did not). Elution with hexane removed 5.12 g. of VII (23%, m.p. 45–49°), which was followed by oil (1.51 g., probably a mixture of VII and IV). Benzene then eluted greasy IV in three fractions (2.91 g.; 19%). Ether and ethyl acetate subsequently removed 0.34 g. of gum (similar gum previously had nitrogen but no sulfur). All weights were obtained after drying to constant values.

The combined fractions of crude VII, recrystallized from hexane, had a melting point and mixture melting point with authentic VII [see 1(e)] of 48.5–49.5°. The combined fractions of crude IV, recrystallized (hexane), had a melting point and mixture melting point with authentic IV [see 1(e)] of 99–102°.

(d) *Modified conditions in the formation of* IV. The procedures of 1(a) were followed in preparing and neutralizing the diazonium salt VI and in isolating IV (m.p. in the range of 101–103.5°). Solutions of VI from one molar proportion of amine XXIX were added dropwise to solutions at 50–60° containing 0.52 (Expt. 1) and 3.00 molar proportions of the xanthate I; the yields of IV were 40% and 54%, respectively; since repetition of Expt. 1 with rapid addition of the VI gave IV in 42% yield, reasonable variations in the mode of addition probably are unimportant.

In experiments with the solid presumed diazoxanthate, solutions containing 2.1 (Expt. 2) and 0.52 (Expt. 3) molar proportions of the xanthate I were added rapidly at −5° to a solution of VI, and the mixtures then were warmed slowly to 60°; the yields of IV were 1% and 25% respectively. The same result (25% of IV) ensued as in Expt. 3 when the mixture of VI and I, prepared at −5°, was added quickly to water at 60°. It is worth adding that nearly half of the chromatographed product from Expt. 2 contained no sulfur, nitrogen, or halogen; since this material was soluble in concd. sulfuric acid, it evidently contained oxygen.

In the studies of VI and VII in methanol, a control experiment first established that I itself would react reasonably well: Sodium nitrite (1.4 g.) in water (2 ml.) was added at *ca.* −5° to 2.4 g. of the amine XXIX in methanol (20 ml.) containing concd. hydrochloric acid (5 ml.). The mixture was neutralized with saturated methanolic sodium hydroxide and decanted from salt into a boiling solution of 4.5 g. of I in methanol (30 ml.). After rapid evolution of gas was complete, methanol was distilled (reduced pressure), the residue was dissolved in ether, and IV was isolated as in 1(a); yield 0.75 g. (25%), m.p. 101–103.5°. Replacement of I by 3.8 g. of VII resulted in no isolable IV and in recovery of 3.2 g. (84%) of VII, m.p. 48–49°.

When a neutralized solution of the diazonium salt VI was added to an equimolar amount of the xanthate VII in a vigorously stirred water suspension at 55°, VII was recovered in 88% yield.

In the search for free radicals in the usual Leuckart reaction, 0.1 mole of the diazonium salt VI in neutralized solution was added to an aqueous solution of 0.12 mole of I and 71.1 g. of acrylamide, all essentially according to 1(a); the first few drops caused a vigorous reaction—the temperature rose to *ca.* 90° and the solution became quite viscous. After completion of addition and separation of oil, addition of the aqueous layer to acetone or ethanol gave a dough presumed to be polyacrylamide, which eventually hardened (Acrylamide itself is quite soluble in ethanol and acetone; further evidence that the dough was polyacrylamide was afforded by its failure to diffuse through a cellophane membrane). In a similar experiment, 0.2 mole of acrylamide was added to

(27) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, **17**, 221 (1955).

(28) H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Am. Chem. Soc.*, **77**, 2479 (1955).

(29) E. Campaigne and S. W. Osborn, *J. Org. Chem.*, **22**, 561 (1957).

(30) L. Field and F. A. Grunwald, *J. Org. Chem.*, **16**, 946 (1951).

(31) H. Reihlen, E. Elben, and J. Everet, *Ann.*, **485**, 43 (1931).

the solution of VI which then was added to the I; chromatography of the resulting "red oil" gave crude IV and VII in yields of *ca.* 48% and 27% respectively (a control experiment gave IV in 53% yield and VII in *ca.* 23% yield); the water layer contained solid which was apparently polyacrylamide. That free radicals could form from diazonium salts under the conditions of the Leuckart reaction was suggested by diazotizing aniline and XXIX (0.1 molar solutions in 0.3*N* hydrochloric and sulfuric acid respectively), destroying excess nitrous acid (urea), and adding tetramethyl-*p*-phenylenediamine; with either solution, neutralization at 0° (sodium carbonate) resulted in the deep blue color of the Wurster salt. Similar unneutralized solutions were not colored at 0° but that from XXIX reacted vigorously and quickly became blue at 15–20°, unlike that from aniline which reacted vigorously only at 40–50° and became blue only near the end of reaction.

(e) *Independent synthesis of reaction products.* In the synthesis of IV, 2.77 g. of the presumed thiol III, prepared as described in 1(b), in benzene (10 ml.) was added to 0.99 g. of phosgene[32] in benzene (15 ml.). Dry pyridine (2.27 g.) was added. After the exothermic reaction, the mixture was heated 0.5 hr. under reflux and then was washed with 5% hydrochloric acid and water. Drying and removal of solvent left bis(2,6-dimethylphenyl) dithiolcarbonate (IV), m.p. 102–103.5°. After recrystallization, the melting point and mixture melting point with IV prepared as described in 1(a) were 103–104.5° (infrared spectra identical). A pungent chlorine-containing oil resulted when phosgene was bubbled through an alkaline solution of III; since it gave IV with more III and pyridine, it probably was the chlorothiolformate, $2,6\text{-}(CH_3)_2C_6H_3S\text{-}CO\text{-}Cl$.

In the synthesis of VII, 4.00 g. of ethyl chlorothionoformate[33] (50% yield, but in carbon tetrachloride) was added to 4.5 g. of III in benzene (15 ml.) at 5°. Dry pyridine (5 g.) in benzene (15 ml.) then was added dropwise below 10°. The mixture was stirred overnight and allowed to warm to room temperature. The benzene solution was decanted from pyridine hydrochloride, washed with water, 5% hydrochloric acid, 5% aqueous sodium hydroxide, and dried. Removal of benzene left 4.2 g. of oil which was distilled in a short-path apparatus. The distillate (b.p. *ca.* 110–114°, 0.4 mm.), recrystallized from ethanol, gave 2.36 g. (32%) of 2,6-dimethylphenyl ethylxanthate (VII), m.p. 48–49°. Further recrystallization (ether) gave VII with a constant melting point, 48.5–49.5°.

Anal. Calcd. for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.56; H, 6.41; S, 28.33.

The *p*H of a solution of 0.11 g. of VII in ethanol (25 ml.)-water (6 ml.) containing 14 ml. of 0.11*N* aqueous sodium hydroxide remained that of a control (VII omitted) during 2 hr. at 25°. Heating at 50° caused a gradual decrease in *p*H from 10.7 to 10.1 in 2 hr.; after 24 hr. the *p*H was 10.6 and V had separated. When VII was heated at 133–139° (0.3 mm.) for 1.3 hr., 95% was recovered, m.p. and mixture m.p. 48–50°.

Authentic VIII was obtained[19,34] by heating 40.1 g. of I, 32.7 g. of ethyl bromide and 30 ml. of ethanol at 50° for 4.5 hr.; removal of solid, then of solvent, drying over sodium sulfate, and distillation gave 30.8 g. (82%); b.p. 85–87° (15 mm.), n_D^{25} 1.5350; phenylhydrazide m.p. 71–73.5° (reported,[19] m.p. 72–24°(*sic*); Chloramine-T derivative, m.p. 185–186° (reported,[19] m.p. 186–187.5°).[35]

Stability of VIII to conditions used in its washing after Leuckart reactions was demonstrated by shaking 10 drops with 1 ml. of 5% acid or base for 1 min. and allowing the mixture to stand for 2 hr.; there was negligible change in the volume of VIII (similar result after 2 hr. at 80°). In assessing stability under conditions of the Leuckart reaction itself (and the subsequent distillation), the reaction was performed exactly as in 1(c) but with addition of 6.91 g. of VIII along with the solution of VI to 19.9 g. of I in 100 ml. of water. Of the 8.86 g. of VIII isolated (n_D^{25} 1.5340–1.5354), the result of 1(c) had indicated that *ca.* 3.28 g. was formed in the reaction proper; hence the difference (5.58 g.) represented VIII which had survived from that added, indicating that only *ca.* 81% (5.58 × 100/6.91) of VIII formed in the Leuckart reaction can be expected to survive. Accordingly, to convert the % yield of VIII actually isolated to the yield probably formed in Leuckart reactions (the correction referred to in footnote c of Table I), it was multiplied by 1.24 (i.e., 6.91/5.58).

2. *Reactions of the 2,6-diethylbenzenediazonium salt* X. (a) *With* I. The diazonium salt X, prepared from 29.8 g. of 2,6-diethylaniline at −4 to −2° was poured during *ca.* 2 min. into 200 ml. of a hot solution of I as usual. The "red oil", subjected to careful partial distillation through a 6 × 260-mm. tube with a heated jacket, gave 3.98 g. (27%) of VIII, b.p. 47–48°, n_D^{25} 1.5290–1.5350. Of the 39.41 g. of undistilled residue, 9.65 g. was chromatographed. Elution with hexane gave 3.61 g. (29%) of 2,6-diethylphenyl ethylxanthate (XII), m.p. 40–43°, which was recrystallized from alcohol to a constant melting point, 43–44°.

Anal. Calcd. for $C_{13}H_{18}OS_2$: C, 61.37; H, 7.13; S, 25.20. Found: C, 61.44; H, 7.13; S, 24.87.

Thermal stability of the XII was demonstrated by recovery of 99% (m.p. and mixture m.p. 43–44°) after keeping under nitrogen for 6 hr. at 133–135°.

Further elution with hexane gave 1.10 g. of oil, probably XII mixed with bis(2,6-diethylphenyl) dithiolcarbonate (XI). Benzene elution then gave 3.51 g. (40%) of XI, m.p. 49–54°, which was recrystallized from ethanol to a constant melting point, 56.5–57.0°.

Anal. Calcd. for $C_{21}H_{26}OS_2$: C, 70.34; H, 7.31; S, 17.89. Found: C, 70.63; H, 7.36; S, 17.92.

More benzene gave 0.61 g. of unidentified solid, m.p. 32.5–36° (depressed by XI), after which benzene, ether, and ethyl acetate eluted 0.6 g. of gum.

(b) *With potassium benzylxanthate.* The salt X, prepared as in (a), was added rapidly to 55.14 g. of potassium benzylxanthate in 200 ml. of water at 50–60°. The "red oil" (61.57 g.) was isolated as usual. With no attempt to distil, 12.37 g. was chromatographed on alumina containing 1% by weight of "Luminescent Chemical 2 Yl."[36] Hexane eluted 5.41 g. (43%) of colorless 2,6-diethylphenyl benzylxanthate, m.p. 57–64.5°; recrystallization from alcohol gave material with a constant melting point, 65.5–66.0°.

Anal. Calcd. for $C_{18}H_{20}OS_2$: C, 68.31; H, 6.37; S, 20.26. Found: C, 68.07; H, 6.35; S, 20.26.

Further elution (hexane) gave 0.9 g. of oil and then 3.61 g. (50%) of oily XI. Three recrystallizations from ethanol gave XI, m.p. and mixture m.p. 53–57°, (1.32 g., 18%; the apparently low recovery probably resulted actually because of the presence of considerable benzyl benzylxanthate in the 3.61 g. of crude XI). Elution with more hexane, then benzene, gave 0.84 g. of oil.

(c) *With potassium isopropylxanthate.* The salt X, prepared as in (a), was added rapidly to 42.9 g. of potassium isopropylxanthate in 200 ml. of water at 50–60°. The "red oil" (50.99 g.) was isolated as usual, but as in 2(b) without distillation, and 10.06 g. was chromatographed. Hexane eluted 3.08 g. (29%) of presumed crude 2,6-diethylphenyl isopropylxanthate as oil, n_D^{25} 1.5452–1.5730. Benzene eluted 2.64 g. (37%) of crude XI, m.p. 51–56°, which after recrys-

(32) H. Erdmann, *Ber.*, **26**, 1993 (1893).

(33) H. Rivier and P. Richard, *Helv. Chim. Acta*, **8**, 496 (1925).

(34) A. I. Vogel, *J. Chem. Soc.*, 1848 (1948).

(35) In our experience, this derivative should be purified immediately; delay may result in a compound melting at 121–122°.

(36) Photo Products Dept., Du Pont Co., Wilmington, Del. This mixture, which fluoresced under ultraviolet light except in regions containing fairly large amounts of adsorbed product, is similar to one used by J. F. Carson and F. F. Wong, *J. Org. Chem.*, **22**, 1725 (1957).

tallization (ethanol) amounted to 2.00 g. (28%), m.p. and mixture m.p. 54–56.5°.

3. *Reaction of the o-toluenediazonium salt* XIII. The procedures of 1(c) were duplicated with 10.7 g. of *o*-toluidine in lieu of XXIX. The "red oil" left after removal of ether was partially distilled as in 2(a); yield of VIII, 2.72 g. (36%), b.p. 44–70° (1–5 mm.) n_D^{25} 1.5354–1.5356. A portion (15.58 g.) of the undistilled residue (16.24 g.) was chromatographed. Hexane eluted 8.52 g. (42%) of *o*-tolyl ethylxanthate (XV), n_D^{25} 1.6050–1.6139, intermediate fractions of which after two distillations gave XV, b.p. 89° (0.5 mm.), n_D^{25} 1.6001.

Anal. Calcd. for $C_{10}H_{12}OS_2$: C, 56.56; H, 5.70; S, 30.20. Found: C, 56.31; H, 5.77; S, 30.77.

Elution with hexane and then benzene gave 6.57 g. (50%) of crude bis(*o*-tolyl) dithiolcarbonate (XIV; m.p. 40–47°) which, recrystallized from ethanol, gave 5.92 g. (45%) of XIV, m.p. 46–48°; after further recrystallization, the melting point was constant, 49–49.5°.

Anal. Calcd. for $C_{15}H_{14}OS_2$: C, 65.66; H, 5.14; S, 23.37. Found: C, 65.73; H, 5.12; S, 23.45.

Continued elution gave only 0.21 g. of gum.

4. *Reaction of the benzenediazonium salt* XVI. The usual procedure was followed, as in 1(c), with 18.6 g. of aniline, but with 21.8 ml. of sulfuric acid and with diazotization and neutralization at −4°. Partial distillation of the "red oil" as in 2(a) gave 2.67 g. (18%) of VIII, b.p. 55–72° (3 mm.), n_D^{25} 1.5353–1.5358. Of 30.61 g. of undistilled residue, 11.54 g. was chromatographed. Hexane eluted 7.4 g. (50%) of oily phenyl ethylxanthate (XVIII), n_D^{25} 1.6043–1.6267, which upon distillation gave 5.30 g. (36%) of XVIII, b.p. 92–120° (0.4–0.6 mm.), n_D^{25} 1.6064–1.6156; recrystallization of the less volatile pot residue (1.3 g.) gave 0.3 g. of phenyl disulfide, m.p. and mixture m.p. 59.5–61° (9% of phenyl disulfide was obtained in another experiment in which an attempt was made to separate the products in the "red oil" by distillation). Fractional distillation of the crude XVIII gave material boiling at 110–111° (1.3 mm.), n_D^{25} 1.6078; reported,[37] b.p. 155° (16 mm.).

Anal. Calcd. for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; S, 32.34. Found: C, 54.82; H, 4.85; S, 31.83.

Elution with benzene then gave 2.8 g. (30%) of crude phenyl dithiolcarbonate (XVII). Recrystallization from ethanol left 1.00 g. (11%), m.p. 40–42°; further recrystallization gave XVII, m.p. and mixture m.p. 41–43° (authentic XVII was prepared in 73% yield using phosgene as described for IV, m.p. 41–43°).[38] Elution finally with ethyl acetate gave only gum (0.6 g.).

In determining the thermal stability of XVII, it was heated at 160–170° for 6 hr. with 100% recovery (m.p. and mixture m.p. 42–43°), and at 304° for 0.5 hr. with 35% conversion to phenyl disulfide (m.p. and mixture m.p. 58–60°); 85% was recovered (m.p. and mixture m.p. 42.5–44°) after distillation at 164–170° (0.6–1 mm.).

5. *Reactions of the p-methoxybenzenediazonium salt* XIX. So that the reactions of XIX and XXII would be comparable, the diazotization of 12.3 g. of *p*-anisidine was performed much like that in 6, by dissolving it in water (120 ml.) containing sulfuric acid (10 ml.), cooling rapidly in ice-salt and adding, in one portion, 35 ml. of a cold solution of sodium nitrite (6.9 g.) in water (40 ml.); 7 ml. more was required for a positive starch-iodide test. The neutralized solution was added to I and the "red oil" was partially distilled as in 1(c). The yield of VIII was 1.51 g. (20%); b.p. 34–38° (1.3 mm.), n_D^{25} 1.5355–1.5367.

Chromatography of 7.14 g. of the 18.66 g. of undistilled residue and elution with hexane gave 3.12 g. (36%)[39] of crude *p*-methoxyphenyl ethylxanthate (XXI), n_D^{25} 1.6082–1.6272. Two distillations gave XXI, b.p. 82–84° (0.05 mm.), n_D^{25} 1.6073.

Anal. Calcd. for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30; S, 28.08. Found: C, 52.12; H, 5.46; S, 28.86.

Further elution gave 1.19 g. (20%) of crude bis(*p*-methoxyphenyl) dithiolcarbonate (XX), m.p. 94–109°; recrystallization (ethanol-benzene) gave 0.72 g. (12%), m.p. 107–110°, and ultimately XX with a constant m.p. of 110–111°.

Anal. Calcd. for $C_{15}H_{14}O_3S_2$: C, 58.80; H, 4.60. Found: C, 59.03; H, 4.65.

Benzene and ethyl acetate eluted only gum (0.5 g.).

To ascertain whether 4,4′-dimethoxybiphenyl might have been formed, part of the "red oil" was saponified and the mixture then steam distilled. No biaryl was isolated, although biphenyl easily steam-distilled when a sample was added to the saponification mixture.

6. *Reaction of the p-nitrobenzenediazonium salt* XXII. *p*-Nitroaniline was diazotized[40] by dissolving 13.8 g. in water (60 ml.) and conc. sulfuric acid (15 ml.), adding ice (100 g.), chilling to −3°, and adding in one portion a cold solution of 7.68 g. of sodium nitrite in water (40 ml.). The mixture was stirred for 15 min., neutralized, and added to I (2 min.). Instead of immediate evolution of nitrogen and formation of oil, a bright red solid formed; it persisted for several seconds and then decomposed with a loud hiss to a dark oil. Heat was removed and the mixture was stirred for 15 min. (once, the red solid decomposed only during this period). The ether (and 100 ml. of benzene) extract of the crude reaction product was washed and dried as usual. Upon removal of most of the ether and some benzene, 1.17 g. (7%) of bis(*p*-nitrophenyl) dithiolcarbonate (XXIII) crystallized, m.p. 179.5–184°.

Attempted distillation of a similar reaction mixture at bath temperatures up to 120°, at which VIII usually distilled (1 mm.), had given no appreciable distillate. In the present experiment, distillation of 8.99 g. of the "red oil" (21.12 g.; obtained as usual after removal of the XXIII and concentration) did yield 0.70 g. (22%) of VIII, b.p. 44–151° (2–3 mm.), n_D^{25} 1.5363; however, the bath temperature required was 155–197° rather than the usual 125°.

Since this VIII might have been produced by thermal decomposition, another portion (5.04 g.) of the "red oil" was chromatographed directly. Hexane eluted 0.36 g. of oil; this, distilled, yielded material with an infrared spectrum much like that of VIII but this distillate probably contained little VIII since it lacked three infrared absorption bands of the VIII and had n_D^{25} 1.6250–1.6270.[41] Benzene (150 ml.) then eluted 2.44 g. (42%) of *p*-nitrophenyl ethylxanthate (XXIV), m.p. 34–56°; recrystallization (ethanol) gave 1.92 g. (33%), m.p. 47–51° and finally white XXIV with a constant m.p. 49.5–50°.

Anal. Calcd. for $C_9H_9NO_3S_2$: C, 44.43; H, 3.73. Found: C, 44.39; H, 3.80.

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(37) H. Rivier, *Bull. soc. chim. France*, (4) **1**, 738 (1907).

(38) Reported melting points usually have been in the range of 41–44° (*e.g.*, D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4463 (1954), but 63° has been reported (G. Daccomo; *cf. Beilstein's Handbuch*, **6**, 312).

(39) Includes XXI from a second chromatogram of a large end fraction; the second chromatogram also gave 0.97 g. of oil (n_D^{25} 1.6483–1.6495), which solidified, and 0.73 g. of a solid, neither of which were studied further.

(40) Ref. 3, p. 6.

(41) If VIII were formed in this Leuckart reaction, it should have been present in this fraction. Since its failure to form would be exceptional, this part of the experiment was repeated, but still with inconclusive results. Although distillation of the hexane effluent from the second reaction unquestionably gave VIII (17%; b.p. 47–60° (5–6 mm.), n_D^{25} 1.5348–1.5352) again high bath temperatures were required (152–225°). Accordingly, while VIII *seems* to be a genuine product of reaction, there is a definite possibility that it is produced instead by thermal decomposition. *p*-Nitrophenyl ethylxanthate (XXIV) was shown to be thermally stable: after 6 hr. under nitrogen at 133–135°, 96% was recovered, m.p. and mixture m.p. 46.5–48°.

Further elution with benzene gave an intermediate fraction (0.6 g.) and then 0.80 g. (20%) of presumed XXIII, m.p. *ca.* 150–178°, which upon recrystallization from benzene gave 0.68 g. (17%; m.p. 178.5–184°) and finally colorless XXIII with a constant m.p. 183.5–184.5°; reported,[42] 174.5°.

(42) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.*, 45, 2403 (1923).

Anal. Calcd. for $C_{15}H_8N_2O_5S_2$: C, 46.42; H, 2.40; S, 19.07. Found: C, 46.79; H, 2.69; S, 19.00.

Elution with ethyl acetate gave only gum (0.7 g.) and 0.13 g. of a solid (m.p. 160–173°, different from XXIII).

Acknowledgment. The authors are indebted to the Office of Ordnance Research, U. S. Army, for generous financial support of this investigation.

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

Orientation in Friedel-Crafts Acylations of 6-Substituted Chrysenes

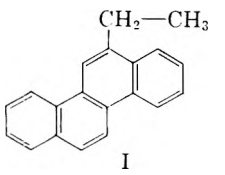
PHILIPPE MABILLE AND N. P. BUU-HOÏ

Received November 30, 1959

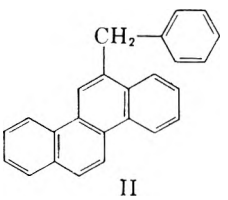
The Friedel-Crafts acylations of 6-ethyl- and 6-benzylchrysene are shown to take place in position 12; in the case of 6-benzylchrysene and acetyl chloride some disubstitution occurs, to give a diketone whose constitution is shown to be 6-(4′-acetylbenzyl)-12-acetylchrysene.

Whereas there is abundant proof[1] that Friedel-Crafts reactions with chrysene occur preferentially in position 6, the orientation in similar substitution reactions with 6-alkylchrysenes has hitherto not been investigated. In theory, such reactions should lead to 12-substituted derivatives, the positions 6 and 12 in the molecule of chrysene being the most reactive sites in view of their high free valence index.[2] Furthermore, we recently established that 6-ethylchrysene undergoes nitration to give 6-ethyl-12-nitrochrysene.[3]

The present work records the results of Friedel-Crafts acylations of 6-ethylchrysene (I) and 6-benzylchrysene (II). The aluminum chloride–catalyzed reaction of benzoyl chloride with (I), using carbon disulfide as the solvent, had been

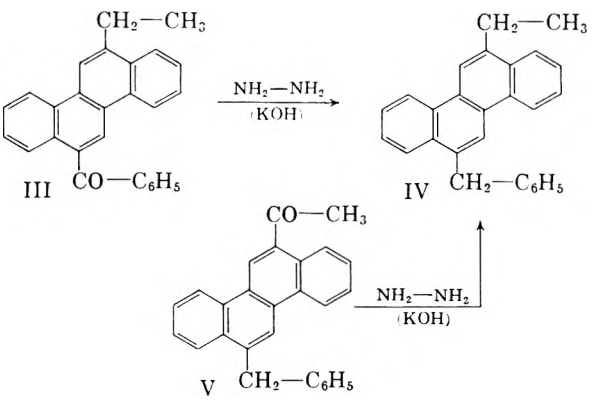


I



II

studied by Funke and Ristic,[4] who obtained a monoketone whose structure they did not investigate. We now found that this ketone readily underwent Wolff-Kishner reduction to give a 6-ethyl-x-benzylchrysene. The same hydrocarbon was obtained when 6-benzylchrysene was submitted to acetylation with acetyl chloride and aluminum chloride and the resulting ketone reduced by the Wolff-Kishner method. The fact that the same hydrocarbon was obtained in these two sets of reactions shows that it was 6-ethyl-12-benzylchrysene (IV), the starting ketones therefore being, respectively, 6-ethyl-12-benzoylchrysene



(III) and 6-benzyl-12-acetylchrysene (V). These experimental results confirm those obtained by π-electron density computations as regards the pronounced reactivity of both positions 6 and 12 in the molecule of chrysene.

It is of interest to note that in the Friedel-Crafts acetylation of 6-benzylchrysene, small amounts of a diketone were obtained along with the monoketone (V). This by-product was found to be 6-(4′-acetylbenzyl)-12-acetylchrysene (VI), as it underwent Wolff-Kishner reduction to a hydrocarbon, which could also be prepared in a different way, *viz.* Friedel-Crafts acylation of 6-ethylchrysene with *p*-ethylbenzoyl chloride followed by reduction of the ensuing ketone, which therefore must have been 6-ethyl-12-(4′-ethylbenzoyl) chrysene (VII). Hence, the hydrocarbon in ques-

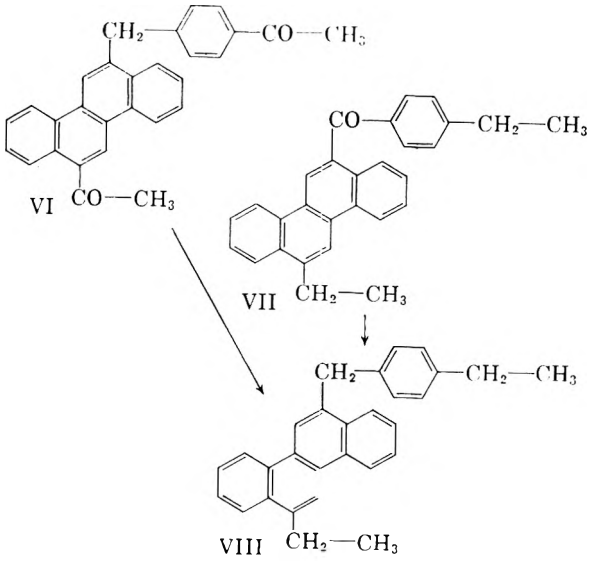
(1) See, for instance, F. Bergmann and H. E. Eschinazi, *J. Am. Chem. Soc.*, 65, 1413 (1943); N.P. Buu-Hoï, *J. Org. Chem.*, 19, 721 (1954).

(2) *Dictionary of Values of Molecular Constants (calculated theoretically by Wave Mechanical Methods)*, Vol. II, p. 29 (C. A. Coulson and R. Daudel, eds., Oxford and Paris).

(3) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, 25, 216 (1960).

(4) K. Funke and J. Ristic, *J. prakt. Chem.*, [2] 146, 151 (1936).

tion was 6-ethyl-12-(4′-ethylbenzyl)chrysene (VIII).



In the Friedel-Crafts benzoylation of chrysene, the main product obtained was 6-benzoylchrysene,[5] but two isomeric benzoylchrysenes were also formed in very small amounts. Because of the poor yields of these isomers, no structure determinations could be made, but, by analogy with Carruthers' findings in respect to the acetylation of chrysene[6] (he obtained small quantities of 2- and 3-acetylchrysene along with the 6-isomer), the two new benzoylchrysenes were most likely 2- and 3-benzoylchrysene.

EXPERIMENTAL

Benzoylation of chrysene. The following procedure was an improvement on the method described by Funke and Müller[5] for the preparation of 6-benzoylchrysene. To a suspension of 22.8 g. of pure chrysene in 1000 ml. of dry carbon disulfide containing 20 ml. of benzoyl chloride, 16 g. of finely-powdered aluminum chloride was added in small portions with stirring, during 10 min.; the mixture was left for 14 hr. at room temperature, then refluxed for 4 hr. After decomposition with ice and hydrochloric acid, and addition of *ca.* 1000 ml. of methylene chloride, the organic layer was washed with water and filtered. Evaporation of the solvents left a brownish semicrystalline mass, which was washed several times with hot water in order to dissolve the benzoic acid; this residue was recrystallized first from toluene, then from benzene-ethanol, to furnish 22.5 g. (62% yield) of *6-benzoylchrysene*, shiny cream-colored leaflets, m.p. 192° (lit.,[5] m.p. 191°), giving a blood red coloration in sulfuric acid.

Concentration of the mother liquors from the second crystallization yielded 5 g. of leaflets, m.p. 185–190°. Fractional crystallization of this portion from toluene afforded 2 to 3 g. of 6-benzoylchrysene, along with 0.1 to 0.2 g. of *x-benzoylchrysene*, which crystallized from acetic acid in almost colorless needles, m.p. 256° (sublimation above 240°), whose solutions in sulfuric acid were deep red, rapidly turning orange-brown.

Anal. Calcd. for $C_{25}H_{16}O$: C, 90.3; H, 4.9; O, 4.8. Found: C, 90.1; H, 5.0; O, 5.0.

The residue from evaporation of the first mother liquors was submitted to fractional recrystallization, first from acetone, then from acetic acid, to give 0.1 g. of *y-benzoylchrysene*, cream-colored leaflets, m.p. 224°, whose solutions in sulfuric acid were brown-yellow.

Anal. Calcd. for $C_{25}H_{16}O$: C, 90.3; H, 4.9. Found: C, 90.2; H, 4.7.

Preparation of 6-benzylchrysene (II). Reduction of 6-benzoylchrysene was effected more conveniently by the Wolff-Kishner than by the Clemmensen method.[6] A mixture of 9 g. of 6-benzoylchrysene, 9 g. of 98% hydrazine hydrate, and 350 ml. of diethylene glycol was refluxed for 7 hr. with 9 g. of potassium hydroxide; after cooling, dilute hydrochloric acid was added, and the precipitate was recrystallized from acetone, giving 5.2 g. (61% yield) of long colorless needles, m.p. 202–203°; lit.,[6] m.p. 200°.

Benzoylation of 6-ethylchrysene. 6-Ethylchrysene was prepared according to the literature.[3] To a solution of 5 g. of 6-ethylchrysene and 7.5 ml. of benzoyl chloride in 100 ml. of carbon disulfide, 5 g. of aluminum chloride was added with stirring, during 15 min. The mixture was left for 14 hr. at room temperature, then refluxed for 2 hr., and worked up as in the case of chrysene. The reaction product was crystallized, first from ethanol, then from ethanol-acetone, to yield 3.6 g. (50%) of *6-ethyl-12-benzoylchrysene* (III), fine yellow needles, which melted at 134°, then resolidified, to melt anew at 147–149° (lit.,[4] m.p. 130°); the coloration in sulfuric acid was cherry red.

Anal. Calcd. for $C_{27}H_{20}O$: C, 90.0; H, 5.6. Found: C, 89.8; H, 5.6.

6-Ethyl-12-benzylchrysene (IV). Reduction of 1.3 g. of the foregoing ketone was effected with 1.3 g. of hydrazine hydrate and 1.3 g. of potassium hydroxide in 50 ml. of diethylene glycol in the usual way. The yield was 0.8 g. of a *hydrocarbon*, crystallizing from ethanol-acetone in silky colorless needles, m.p. 169–170°.

Anal. Calcd. for $C_{27}H_{22}$: C, 93.6; H, 6.4. Found: C, 93.7; H, 6.4.

Acetylation of 6-benzylchrysene. To a solution of 15 g. of 6-benzylchrysene and 60 ml. of acetyl chloride in 600 ml. of carbon disulfide, 15 g. of aluminum chloride was added in small portions with stirring, during 20 min., and the mixture then treated as above. After decomposition with ice and hydrochloric acid, the solvent was distilled, and the residual brown crystalline mass (19 g.) was extracted with cyclohexane (2000 ml.). Concentration of the cyclohexane solution to 50 ml. yielded a precipitate which was recrystallized from ethanol, giving *6-benzyl-12-acetylchrysene* (V) (0.5 g.), pale yellow needles, m.p. 164–165°, whose solutions in sulfuric acid were orange-yellow.

Anal. Calcd. for $C_{27}H_{20}O$: C, 90.0; H, 5.6. Found: C, 89.9; H, 5.6.

The residue from the extraction with cyclohexane was taken up in acetone; evaporation of the acetone left a compound which was recrystallized several times from benzene and from benzene-acetone, to give *6-(4′-acetylbenzyl)-12-acetylchrysene* (VI) (4 g.), cream-colored needles, m.p. 226–227°, whose solutions in sulfuric acid were orange-yellow.

Anal. Calcd. for $C_{29}H_{22}O_2$: C, 86.5; H, 5.5; O, 8.0. Found: C, 86.3; H, 5.5; O, 8.0.

Reduction of 6-benzyl-12-acetylchrysene. Wolff-Kishner reduction of 0.3 g. of this ketone was effected in the usual way, giving a hydrocarbon (0.1 g.) which crystallized first from ethanol, then from acetone, in colorless needles, m.p. 169–170°, identical with compound IV (no depression in mixed melting point).

Reduction of 6-(4′-acetylbenzyl)-12-acetylchrysene. This reduction, performed with 0.8 g. of the diketone (VI), yielded *6-ethyl-12-(4′-ethylbenzyl)chrysene* (VIII), crystallizing from ethanol-acetone in silky colorless needles (0.6 g.), m.p. 179–180°.

(5) K. Funke and E. Müller, *J. prakt. Chem.*, [2] **144**, 242 (1936).

(6) W. Carruthers, *J. Chem. Soc.*, 3486 (1953).

Anal. Calcd. for $C_{29}H_{26}$: C, 93.0; H, 7.0. Found: C, 93.2; H, 6.8.

6-Ethyl-12-(4'-ethylbenzoyl)chrysene (VII). To a solution of 5.2 g. of 6-ethylchrysene and 5 g. of *p*-ethylbenzoyl chloride in 80 ml. of carbon disulfide, 4.5 g. of aluminum chloride was added, and the mixture treated in the usual way. The resinous mass obtained was taken up in cyclohexane, and concentration of the cyclohexane solution yielded crystals, which were recrystallized from ethanol-acetone to give 4.4 g. (56%) of colorless leaflets, m.p. 113–114°, whose solutions in sulfuric acid were raspberry red.

Anal. Calcd. for $C_{29}H_{24}O$: C, 89.7; H, 6.2; O, 4.1. Found: C, 89.6; H, 6.2; O, 4.4.

Wolff-Kishner reduction of this ketone (1.7 g.) afforded a hydrocarbon (1.2 g.), m.p. 179–180°, identical with compound VIII.

Acknowledgment. This work was conducted with the financial aid of The Anna Fuller Fund, New Haven, Conn.; the authors express their gratitude to Professor William U. Gardner and the Trustees of the Fund.

PARIS (VE) FRANCE

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

The Elbs Reaction of 6-(*o*-Toluoyl)chrysene and Similar Ketones

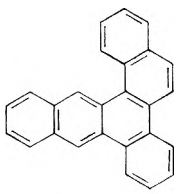
PHILIPPE MABILLE AND N. P. BUU-HOÏ

Received January 19, 1960

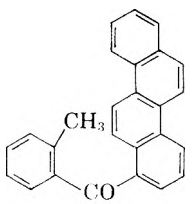
The Elbs reaction of 6-(*o*-toluoyl)chrysene has been investigated, and found to give rise predominantly to 15-oxatribenzo[a,e,jk]pyrene, with small amounts of benzo[a]naphtho[1,2-a]anthracene; similar compounds were obtained from the pyrolysis of 6-(2,4-dimethylbenzoyl)chrysene.

In view of the pronounced carcinogenic activity of many hexacyclic aromatic hydrocarbons,[1] a systematic investigation of other members of that group is being undertaken in this laboratory. Benzo[a]naphtho[1,2-a]anthracene (I), a hexacyclic derivative of chrysene, was included in this research, and a method for its preparation is reported here.

The most direct route to I was the cyclodehydration of 6-(*o*-toluoyl)chrysene (II). This ketone could



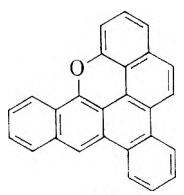
I



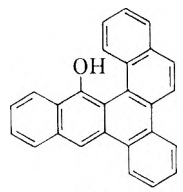
II

be readily obtained by Friedel-Crafts acylation of chrysene with *o*-toluoyl chloride, along with an isomeric ketone which, on grounds of analogy with the acetylation of chrysene,[2] could possibly be 2-(*o*-toluoyl)chrysene.

However, the pyrolysis of ketone II yielded only very small amounts of the expected hydrocarbon I, the main product of the reaction consisting of 15-oxatribenzo[a,e,jk]pyrene (III). This compound had previously been identified by Clar and Kelly[3] as one of the several products of an Elbs reaction performed on a crude noncrystalline mixture of ketones obtained from the Friedel-Crafts reaction of *o*-toluoyl chloride with chrysene. Those investigators attributed the formation of this oxygen heterocycle to the air-oxidation undergone by the hydrocarbon I during the pyrolysis. In view of the recent

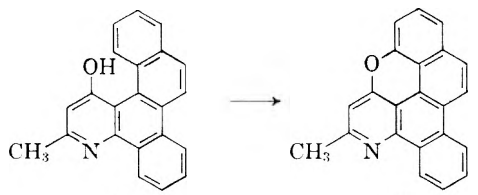


III



IV

observation of one of the present authors[4] on the ease with which compound V is converted into compound VI by zinc dust distillation, and of the stability of the hydrocarbon I toward heat and air, we prefer to consider that compound III is formed from the intermediary anthrol IV, this anthrol arising



V VI

from ketone II through rearrangement. Both the formation of anthrols and the occurrence of similar rearrangements have been reported in the literature.[5]

(1) A. Lacassagne, N. P. Buu-Hoï, and F. Zajdela, *Compt. rend.*, **245**, 876, 991 (1957); **246**, 1156 (1958).

(2) W. Carruthers, *J. Chem. Soc.*, 3486 (1953).

(3) E. Clar and W. Kelly, *J. Chem. Soc.*, 4163 (1957).

(4) G. C. Barrett and N. P. Buu-Hoï, *J. Chem. Soc.*, 2946 (1958).

(5) J. W. Cook, *J. Chem. Soc.*, 487 (1931); 1472 (1932); L. F. Fieser and E. Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

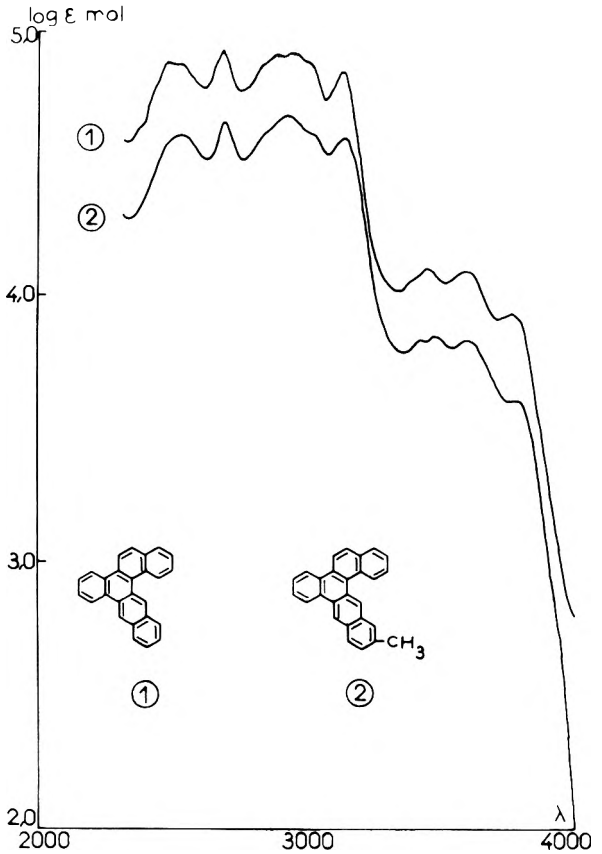
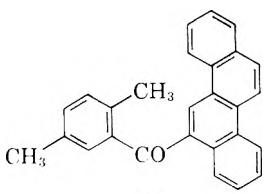


Fig. 1. Ultraviolet absorption spectra of methylated and non-methylated benzo[a]naphtho[1,2-a]anthracene

Support is given to this interpretation by the study of the Elbs reaction of 6-(2,4-dimethylbenzoyl)chrysene (VII). This ketone, readily obtained



VII

by a Friedel-Crafts acylation of chrysene with 2,4-dimethylbenzoyl chloride, likewise gave on pyrolysis mostly a methyl-15-oxatribenzo[a,e,jk]pyrene, and only small amounts of the expected 12-methylbenzo[a]naphtho[1,2-a]anthracene. If no rearrangement were to occur during the Elbs reaction, the methyl group in both compounds should be located in position 13, or, if rearrangement does occur, in position 12. The ultraviolet absorption spectra of these two methyl compounds closely resemble that of their nonmethylated counterparts, as is shown in Figs. 1 and 2.

In the Friedel-Crafts acylation of chrysene with *o*-toluoyl chloride, three isomeric diketones could be obtained when the proportion of the acid chloride was increased to two moles per mole of chrysene. A similar reaction using 2,4-dimethylbenzoyl chloride yielded two isomeric diacylation products,

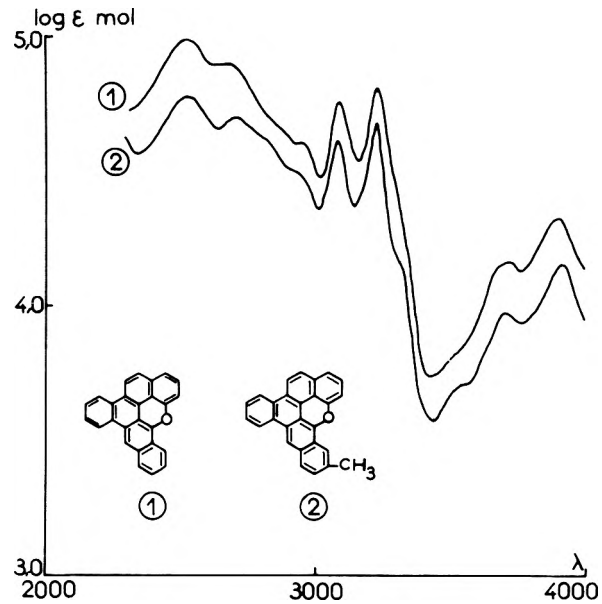


Fig. 2. Ultraviolet absorption spectra of methylated and non-methylated 15-oxatribenzo[a,e,jk]pyrene

one melting at 233°, the other at 282°; the Elbs reaction performed on the isomer, m.p. 233°, afforded a hydrocarbon, m.p. 372°, whose constitution could not be established.

EXPERIMENTAL

o-Toluoylation of chrysene. To a solution of 22.8 g. of pure chrysene and 35 g. of *o*-toluoyl chloride in 1000 ml. of dry carbon disulfide, 30 g. of finely powdered aluminum chloride was added during 10 min., with stirring. The brown-red mixture obtained was gradually brought to the boil and refluxed for 3 hr. After decomposition with ice and hydrochloric acid, 400 ml. of carbon disulfide was added, and the organic layer was washed with 3% aqueous sodium hydroxide, then with water, and dried over calcium chloride. The residue from evaporation of the solvent was taken up in 500 ml. of hot ethanol, and the insoluble fraction (26 g.) was added to the crystals obtained on cooling of the ethanolic phase and recrystallized several times from ethanol-benzene. The yield was 20 g. (58.8%) of *6-(o-toluoyl)chrysene* (II) as fine colorless needles, m.p. 194°, giving an orange-red coloration in sulfuric acid.

Anal. Calcd. for $C_{25}H_{18}O$: C, 90.1; H, 5.2; O, 4.6. Found: C, 90.1; H, 5.5; O, 4.6. From the mother-liquors, a very small quantity (0.1 g.) of an isomeric ketone, possibly 2-(*o*-toluoyl)chrysene, could be isolated, and was recrystallized from ethanol-benzene in colorless leaflets, m.p. 230°, giving a brown-yellow coloration in sulfuric acid.

Anal. Calcd. for $C_{25}H_{18}O$: C, 90.1; H, 5.2. Found: C, 89.8; H, 5.2.

Elbs reaction of ketone II. Eleven grams of the foregoing ketone was refluxed for 30 min., and the reaction product vacuum-fractionated, giving a pale yellow, low-boiling resin A (6.5 g.), and a brown-red, higher-boiling resin B (1.5 g.). Fractional crystallization of A from benzene furnished the less soluble compound III (1 g.), orange-yellow needles, m.p. 290–293°. Vacuum sublimation afforded the pure compound in the form of shiny yellow needles, m.p. 296°, giving a raspberry red coloration in sulfuric acid. Clar and Kelly[3] reported m.p. 288–289° for this compound.

Anal. Calcd. for $C_{25}H_{14}O$: C, 91.2; H, 4.1; O, 4.7. Found: C, 91.4; H, 4.3; O, 4.6. Crystallization of fraction B from toluene gave a further crop (0.4 g.) of this compound.

Concentration of the benzene mother-liquors gave (1) chrysene (1 g.), and (2) a resin which was recrystallized from methyl ethyl ketone to form *benzo[a]naphtho[1,2-a]anthracene* (I), colorless needles (50 mg.), m.p. 193°, giving no coloration in sulfuric acid. Beyer and Richter,[6] who prepared this hydrocarbon by a different method, reported m.p. 185–186°.

Di-o-toluoylation of chrysene. A solution of 22.8 g. of chrysene and 35 g. of *o*-toluoyl chloride in 1000 ml. of carbon disulfide was treated with 40 g. of aluminum chloride and the mixture left for 2 days at room temperature, then refluxed for 150 min. After decomposition with ice and hydrochloric acid, 1000 ml. of methylene chloride was added, and the organic layer treated in the usual way. The residue from evaporation of the solvent was a brown amorphous mass, which was treated with 100 ml. of hot acetone. The crystals that formed after cooling in the refrigerator were submitted to fractional recrystallization from methyl ethyl ketone, to yield first a portion (5 g.) melting at about 250°, which, after a second recrystallization, formed pale yellow prisms of a *di-o-toluoylchrysene*, m.p. 256°, giving a brown-red coloration in sulfuric acid.

Anal. Calcd. for $C_{33}H_{24}O_2$: C, 87.6; H, 5.4; O, 7.1. Found: C, 87.8; H, 5.3; O, 7.0.

A second, more soluble *di-o-toluoylchrysene* (1 g.), was recrystallized from methyl ethyl ketone, then from acetic acid, in fine, cream-colored needles, m.p. 231°, giving an orange-yellow coloration in sulfuric acid.

Anal. Calcd. for $C_{33}H_{24}O_2$: C, 87.6; H, 5.4; O, 7.1. Found: C, 87.7; H, 5.4; O, 6.9.

A third isomeric *di-o-toluoylchrysene* (5 g.), the most soluble of the three, was recrystallized from benzene to give colorless prisms, m.p. 213°, whose coloration in sulfuric acid was likewise orange-yellow.

Anal. Calcd. for $C_{33}H_{24}O_2$: C, 87.6; H, 5.4; O, 7.1. Found: C, 87.9; H, 5.3; O, 6.9.

Monoacylation of chrysene with 2,4-dimethylbenzoyl chloride. A mixture of 22.8 g. of chrysene, 33.7 g. of 2,4-dimethylbenzoyl chloride, and 760 ml. of carbon disulfide was treated with 26.7 g. of aluminum chloride; after a 22-hr. stand at room temperature, the mixture was refluxed for 1 hr., then treated in the usual way. A resinous product was obtained which on crystallization first from methyl ethyl ketone, and then from acetic acid yielded *6-(2,4-dimethylbenzoyl)chrysene* (VII), colorless needles (16.5 g.), m.p. 146°, whose coloration in sulfuric acid was crimson.

Anal. Calcd. for $C_{27}H_{20}O$: C, 89.9; H, 5.6. Found: C, 89.5; H, 5.6.

Pyrolysis of compound VII. This operation was performed on 9 g. of the ketone, as for ketone II, to furnish a lower-boiling portion (0.7 g.) which was identical with chrysene, and a higher-boiling, vitreous product (5.2 g.) which was recrystallized several times from toluene, giving 0.7 g. of *12- or 13-methyl-15-oxatribenzo[a,e,jk]pyrene*, stumpy yellow needles, m.p. 244°, whose coloration in sulfuric acid was chocolate brown.

Anal. Calcd. for $C_{27}H_{16}O$: C, 91.0; H, 4.5. Found: C, 91.0; H, 4.7.

From the mother-liquors, 0.13 g. of a *12- or 13-methylbenzo[a]naphtho[1,2-a]anthracene* was isolated; this hydrocarbon was recrystallized from hexane to afford fine colorless needles, m.p. 226°, giving no coloration in sulfuric acid.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.8; H, 5.1.

Diacylation of chrysene with 2,4-dimethylbenzoyl chloride. A mixture of 19 g. of chrysene, 23 g. of 2,4-dimethylbenzoyl chloride, and 650 ml. of carbon disulfide was treated with 22 g. of aluminum chloride; after a 2-day stand at room temperature, followed by 2 hr. refluxing, the reaction mixture was worked up in the usual way. The product was a viscous resin which crystallized on trituration with methyl ethyl ketone. The solid thus obtained (10.3 g.) was treated with 550 ml. of acetic acid, leaving an insoluble residue which was recrystallized from benzene, to give a first *di-(2,4-dimethylbenzoyl)chrysene* (1.9 g.), yellowish prisms, m.p. 282°, with a crimson coloration in sulfuric acid.

Anal. Calcd. for $C_{36}H_{28}O_2$: C, 87.8; H, 5.7. Found: C, 87.3; H, 5.8.

From the benzene mother-liquors, the more soluble isomeric *di-(2,4-dimethylbenzoyl)chrysene* was isolated, and recrystallized first from ethanol, then from acetic acid. The yield was 6 g. of fine yellowish prisms, m.p. 233°, with an orange-red coloration in sulfuric acid.

Anal. Calcd. for $C_{36}H_{28}O_2$: C, 87.8; H, 5.7. Found: C, 87.5; H, 5.8.

The Elbs reaction performed on this last diketone (4.5 g.) yielded an *octacyclic hydrocarbon* which crystallized from toluene in almost colorless leaflets (0.4 g.), m.p. 372°. That this hydrocarbon is almost colorless and gives no halochromism in sulfuric acid suggests that it does not contain a naphthacene arrangement in its molecule.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.6; H, 5.3.

Acknowledgment. The authors thank the Service d'Exploitation Industrielle des Tabacs et des Allumettes and its Director of Research, Dr. J. Cuzin, for financial support of this work, and Mrs. J. P. Mathieu for determination of the absorption spectra.

PARIS (VE), FRANCE

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Mannich Reaction on 7-Hydroxychromones and Flavones. Synthesis of Powerful Central Nervous System Stimulants

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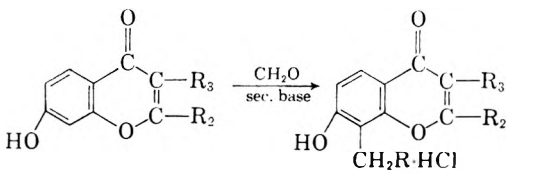
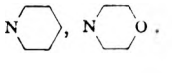
The application of the Mannich reaction to 7-hydroxychromones and flavones, which gives rise to the corresponding 8-aminomethyl derivatives, is described. Experimental proof of the position taken by the aminomethyl group is given. These derivatives act as powerful central nervous system stimulants, especially on the brain stem, and have a cardiokinetic and hypertensive action. The central nervous system stimulating activity of many of these compounds proved to be considerably greater than that of pentamethylentetrazol, which was taken as the standard.

Previous research[1,2] on the chromone and flavone groups led to the discovery of a new class of powerful central nervous system stimulants: the *N*-substituted 7-methoxy-8-aminomethyl derivatives. Pursuing this line of research, we prepared some Mannich bases starting from 7-hydroxychromones and flavones, substituted in the 2 and 3 positions, in order to extend the pharmacological investigation to derivatives with a free phenolic hydroxy group and to compounds not attainable by the procedure hitherto used.[2,3]

The application of the Mannich reaction to phenolic compounds is well known.[4,5] Wiley[6] tried it on the benz-substituted (including 7-methoxy) but 2,3-unsubstituted chromones; however, as far as we know, it has not been applied to 7-hydroxychromones and flavones. The conventional procedure was used, *i.e.*, condensation of the phenolic derivatives with formaldehyde and a secondary base such as dimethyl- or diethylamine, piperidine, or morpholine, in ethanol:



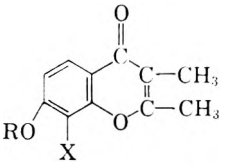
R_2 = CH_3, C_2H_5, C_6H_5
R_3 = H, CH_3, C_2H_5
R = $N(CH_3)_2$, $N(C_2H_5)_2$



The products were isolated as hydrochloride salts.

The position of the introduced aminomethyl group can be predicted on the basis of Rangaswami and Seshadri's work.[7] These authors, using the Claisen rearrangement on 7-allyloxyflavones, found that there was a peculiar distribution of aromatic double bonds in 7-hydroxyflavones, similar in every respect to that of β-hydroxynaphthalene, and such as to render the 8- position more reactive, as shown by the fact that they obtained 8-allyl derivatives.

Indeed, the Mannich reaction led to the 8-aminomethyl derivatives, as shown by the following series of reactions, limited to 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone (I). The same behavior was exhibited by the analogous flavone derivative (see Experimental).



I. R = H, X = $CH_2N(CH_3)_2$
II. R = H, X = CHO
III. R = H, X = H
IV. R = H, X = OH
V. R = CH_3CO, X = CH_2OOCCH_3
VI. R = H; X = CH_2OH
VII. R = H; X = CH_2N ⟨⟩ ; CH_2N ⟨O⟩
VIII. R = CH_3, X = CHO
IX. R = CH_3, X = CH_2OH
X. R = CH_3, X = CH_2OOCCH_3

Compound I, by boiling with acetic acid in the presence of hexamine, was converted into the 8-aldehydo-derivative (II), also obtainable by the Duff reaction from 7-hydroxy-2,3-dimethylchromone (III). The oxidation of II, following the Dakin modification of the Bayer-Williger procedure,[8] led to the corresponding 7,8-dihydroxy compound (IV), already described by Robertson *et al.*[9]

By boiling I with acetic anhydride using the Tiffeneau procedure[10] for *tert*-benzylamines, the dimethylamino group could be replaced by the ace-

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(2) P. Da Re, L. Verlicchi, and I. Setnikar, *Arzneimittel-Forsch.*, **10**, (1960), in press.
(3) P. Da Re, and L. Verlicchi, *Ann. Chim. (Rome)*, **46**, 904 (1956).
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toxy group, thereby yielding V, also obtainable by acetylating VI. The catalytic reduction of II (hydrogen on platinum at atmospheric pressure) led to the 8-hydroxymethyl derivative (VI) and the same course of the hydrogenolysis was observed with the 8-formyl-7-hydroxy-3-methylflavone (XI).

For an analogous compound, *i.e.*, the 8-formyl-7-hydroxy-3-methoxyflavone (XII), Rangaswami and Seshadri[7] obtained the 8-methyl derivative, as was to be expected if the reaction analogy between 7-hydroxyflavones and β-naphthol could be extended to the formyl derivatives; indeed, 1-formyl-2-hydroxynaphthalene is hydrogenolyzed to the 1-methyl-2-hydroxy derivative.[11]

The different behavior of II and XI as compared with XII could, perhaps, be attributed to the substituent in the 3-position, considering the influence exerted by a 2- or 3-substituent on the reactivity of the positions of the aromatic ring. Kelkar and Limaye[12] have shown that an acyl group in the 3-position of 7-benzoyloxy-2-methylchromone exerts an inhibitive influence on the Fries rearrangement, and one of us[13] has also noted that the nitration of some chromones takes a different course if an alkyl group is in the 2-position.

The reaction analogy, on the other hand, was observable between the products we have described and the β-naphthol Mannich bases: in both cases it was possible, with the amine exchange reaction, to substitute a secondary base such as piperidine or morpholine for the dimethylamino group (VII) using the Snyder and Brewster procedure.[14] The methylation of II gave the 7-methoxy derivative (VIII), the reduction of VIII yielded 8-hydroxymethyl-7-methoxy-2,3-dimethylchromone (IX), which was then acetylated to X. The mixture melting points of IX and X with authentic samples of the identical products obtained by another procedure as described earlier,[3] did not show depression.

As Rangaswami and Seshadri observed[7] in connection with the distribution of the aromatic double bonds in 7-hydroxyflavones, the 6-position also can become reactive. In fact, by carrying out the Mannich reaction on 7-hydroxy-2,3-dimethylchromone using two moles of piperidine and two moles of formaldehyde, the 6,8-dipiperidinomethyl derivative was obtained.

The compounds prepared and their pharmacological activity are summarized in Table I.

Pharmacological acknowledgment. The *N*-substituted 7-hydroxy-8-aminomethylchromones and flavones, like their 7-methoxy analogues, exert an intense stimulant action upon the central nervous system, probably at brain stem level. Administered in adequate doses by oral or parenteral route to mice, rats, rabbits, cats, or dogs, they cause clonic convulsions, followed by maximal tonic extension seizures. The general toxic picture is very similar to that induced by pentamethylentetrazol.

Although generally less active than their 7-methoxy analogues, some of the derivatives under examination were quite interesting. For example, the 3-methyl-7-hydroxy-8-dimethylaminomethylflavone (compound 21) is about nine times more active than pentamethylentetrazol, 2-ethyl-3-methyl-7-hydroxychromone (compound 9) about eight times more active, and the 2,3-dimethyl analogue (compound 1) is seven times more active than this well known bulbar stimulant. Furthermore, almost all these new derivatives, if administered intravenously in doses equivalent to a .1 to .05 of their intraperitoneal LD_{50}, exert pronounced and prolonged hypertensive and cardiokinetic effect. In addition, they have an intense respiratory stimulant action. This latter action together with the hypertensive and central nervous system stimulant actions should mean that these substances are indicated in cases of severe depression of the central nervous system, such as after barbiturate poisoning. In fact, mice intoxicated with lethal doses of pentobarbital survive if they are treated with these stimulants. A more detailed report on the pharmacology of these derivatives will be published elsewhere.[15]

EXPERIMENTAL

To exemplify the synthesis of the products of Table I, we shall describe the synthesis of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone hydrochloride.

8-Dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone-hydrochloride (I). To nine grams of 7-hydroxy-2,3-dimethylchromone in 300 ml. of ethyl alcohol, 5.5 ml. of 40% dimethylamine, and 5 ml. of formalin were added and the mixture was refluxed for 5 or 6 hr. After cooling, the mixture was acidified with alcoholic hydrochloric acid, concentrated, and again cooled until a precipitate formed. The solid was filtered and purified on crystallization from alcohol. The white crystalline product, so obtained, weighed 6.3 g. and melted at 213–214°.

8-Formyl-7-hydroxy-2,3-dimethylchromone (II). Two grams of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone and 2 g. of hexamine in 20 ml. of glacial acetic acid were refluxed for 1 hr. The reaction mixture was poured into ice water-hydrochloric acid mixture and left to stand overnight. The solid which separated was filtered, washed with water, and dried. The crude product on crystallizing from 40% acetic acid gave 0.3 g. of light yellow solid, m.p. 184–186°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.23; H, 4.77.

A mixture melting point with a sample of the same product, prepared by the Duff reaction on 7-hydroxy-2,3-dimethylchromone, was not depressed.

7,8-Dihydroxy-2,3-dimethylchromone (IV). 8-Formyl-7-hydroxy-2,3-dimethylchromone (II) (0.8 g.) and 40 ml. of 0.1*N* sodium hydroxide, were diluted with water to 100 ml. and 29.6 ml. of 4.9% hydrogen peroxide were added, while stirring, in the course of half an hour. The mixture, after

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(12) G. R. Kelkar and D. B. Limaye, *Rasayanam*, **1**, 183 (1939).

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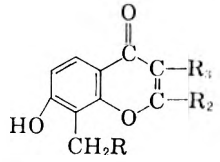
(14) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948).

(15) I. Setnikar, W. Murmann, M. J. Magistretti, and P. Da Re, *J. Pharmacol. exptl. Ther.*, **128**, 176 (1960).

TABLE I

N-SUBSTITUTED 7-HYDROXY-8-AMINOMETHYLCHROMONES AND FLAVONES[a]



Compound	R_2	R_3	R	Hydrochloride Salts M.P., °[b,c]	Yield, %	Formula	Analysis Chlorine % Calcd.	Chlorine % Found	Nitrogen % Calcd.	Nitrogen % Found	C.N.S.[d] stimulating activity[e]	Free Bases M.P., °[b,c]	Free Bases Nitrogen % Calcd.	Free Bases Nitrogen % Found
1	CH_3	CH_3	$N(CH_3)_2$	213–214	47	$C_{14}H_{18}ClNO_3$	12.50	12.38	4.94	4.93	7.1	178–179	5.66	5.60
2	CH_3	CH_3	$N(C_2H_5)_2$	196–198	55	$C_{16}H_{22}ClNO_3$	11.37	11.40	4.49	4.50	3.5	180–182	5.09	5.16
3	CH_3	CH_3	$N{=}C_5H_{10}$	246–247	26	$C_{17}H_{22}ClNO_3$	10.95	10.94	4.33	4.32	1.1	162–163	4.87	4.85
4	CH_3	CH_3	$N{=}C_4H_8O$	255–258	60	$C_{16}H_{20}ClNO_4$	10.88	10.87	4.30	4.28	1.3	209–210	4.84	4.89
5	CH_3	C_2H_5	$N(CH_3)_2$	226–228	41	$C_{15}H_{20}ClNO_3$	11.90	11.88	4.71	4.78	2.8	125–127	5.36	5.44
6	CH_3	C_2H_5	$N(C_2H_5)_2$	198–199	45	$C_{17}H_{24}ClNO_3$	10.88	10.83	4.30	4.32	0.7	119–120	4.84	4.76
7	CH_3	C_2H_5	$N{=}C_5H_{10}$	227–229	46	$C_{18}H_{24}ClNO_3$	10.50	10.47	4.15	4.17	0.9	147–148	4.64	4.57
8	CH_3	C_2H_5	$N{=}C_4H_8O$	225–226	53	$C_{17}H_{22}ClNO_4$	10.43	10.43	4.12	4.12	0.7	172–174	4.61	4.58
9	C_2H_5	CH_3	$N(CH_3)_2$	199–201	35	$C_{15}H_{20}ClNO_3$	11.90	11.88	4.81	4.83	7.9	139–141	5.36	5.46
10	C_2H_5	CH_3	$N(C_2H_5)_2$	188–190	42	$C_{17}H_{24}ClNO_3$	10.88	10.85	4.30	4.28	1.8	159–160	4.84	4.89
11	C_2H_5	CH_3	$N{=}C_5H_{10}$	246–247	75	$C_{18}H_{24}ClNO_3$	10.50	10.45	4.15	4.17	1.3	133–134	4.64	4.72
12	C_2H_5	CH_3	$N{=}C_4H_8O$	247–249	55	$C_{17}H_{22}ClNO_4$	10.43	10.44	4.12	4.12	1.4	177–178	4.61	4.64
13	C_2H_5	C_2H_5	$N(CH_3)_2$	219–220	38	$C_{16}H_{22}ClNO_3$	11.37	11.38	4.49	4.48	3.1	—[f]	5.09	5.11
14	C_2H_5	C_2H_5	$N(C_2H_5)_2$	182–183	44	$C_{18}H_{26}ClNO_3$	10.43	10.45	4.12	4.11	1.6	100–101.5	4.62	4.67
15	C_2H_5	C_2H_5	$N{=}C_5H_{10}$	210–212	48	$C_{19}H_{26}ClNO_3$	9.85	9.83	3.89	3.88	0.9	118–119	4.44	4.51
16	C_2H_5	C_2H_5	$N{=}C_4H_8O$	225–226	59	$C_{18}H_{24}ClNO_4$	10.02	10.00	3.96	3.93	0.3	145–146	4.41	4.47
17	C_6H_5	H	$N(CH_3)_2$	243–244	52	$C_{18}H_{18}ClNO_3$	10.68	10.65	4.22	4.23	5.4	169–170	4.74	4.74
18	C_6H_5	H	$N(C_2H_5)_2$	205–207	66	$C_{20}H_{22}ClNO_3$	9.85	9.85	3.89	3.90	7.1	112–113.5	4.33	4.28
19	C_6H_5	H	$N{=}C_5H_{10}$	202–205	62	$C_{21}H_{22}ClNO_3$	9.53	9.52	3.77	3.78	1.6	180–181	4.18	4.18
20	C_6H_5	H	$N{=}C_4H_8O$	256–259 dec.	88	$C_{20}H_{20}ClNO_4$	9.48	9.47	3.75	3.73	1.4	189–190.5	4.15	4.09
21	C_6H_5	CH_3	$N(CH_3)_2$	225–226	55	$C_{19}H_{20}ClNO_3$	10.25	10.21	4.05	4.00	8.9	168–169	4.53	4.35
22	C_6H_5	CH_3	$N(C_2H_5)_2$	205–207	40	$C_{21}H_{24}ClNO_3$	9.48	9.43	3.75	3.76	2.0	172–173	4.15	4.19
23	C_6H_5	CH_3	$N{=}C_5H_{10}$	229–231	87	$C_{22}H_{24}ClNO_3$	9.19	9.18	3.63	3.61	0.6	190–191	4.01	4.00
24	C_6H_5	CH_3	$N{=}C_4H_8O$	232–233	54	$C_{21}H_{22}ClNO_4$	9.14	9.17	3.61	3.59	—[g]	237–238	3.98	3.98
25	C_6H_5	C_2H_5	$N(CH_3)_2$	225–227	40	$C_{20}H_{22}ClNO_3$	9.85	9.81	3.89	3.88	2.0	180–181	4.33	4.41
26	C_6H_5	C_2H_5	$N(C_2H_5)_2$	207–209	51	$C_{22}H_{26}ClNO_3$	9.14	9.15	3.61	3.61	2.6	114.5–115.5	3.99	3.95
27	C_6H_5	C_2H_5	$N{=}C_5H_{10}$	236–237	55	$C_{23}H_{26}ClNO_3$	8.87	8.90	3.50	3.48	0.3	118–119	3.85	3.91
28	C_6H_5	C_2H_5	$N{=}C_4H_8O$	229–230	62	$C_{22}H_{24}ClNO_4$	8.82	8.80	3.48	3.50	0.03	199–200	3.83	3.74
Pentamethylenetetrazol			—	—	—	—	—	—	—	—	1	—	—	—

[a] Ethanol was used as solvent for the synthesis of the products reported. The reaction temperature and the reaction time are the same as in the example described in the Experimental. [b] Melting points are not corrected. [c] Crystallizing solvent was alcohol/ether for the hydrochloride salts and ligroin for the free bases. [d] Central nervous system. [e] Activity is expressed as the reciprocal of the intraperitoneal LD_{50} determined in mice with reference to the reciprocal LD_{50} of metrazol (LD_{50} = 71 mg/kg). [f] The product has no sharp melting point. [g] This compound was not assayed pharmacologically because in aqueous solution it decomposed.

stirring again for 1 hr., became dark and a solid separated. Acidification with dilute hydrochloric acid, completed the precipitation of the product, which was then filtered, washed with water, and dried. Crystallization of the crude product from 70% acetic acid afforded a white crystalline solid, m.p. 230–231°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.13; H, 4.89.

The *diacetate* was a white crystalline solid, m.p. 149–150°. A mixture melting point of (IV) with an authentic sample of 7,8-dihydroxy-2,3-dimethylchromone, prepared according to Robertson *et al.*,[9] was not depressed.

8-Acetoxymethyl-7-acetoxy-2,3-dimethylchromone (V). One gram of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone (I) and 1 g. of anhydrous sodium acetate in 15 ml. of acetic anhydride were refluxed for 2 hr. The reaction mixture was poured into ice water and left to stand overnight. The solid which separated was collected on filtration, washed with water, and dried. On crystallizing from ligroin the yield was 0.8 g. of white product, m.p. 127–129°.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.31. Found: C, 63.15; H, 5.10.

8-Hydroxymethyl-7-hydroxy-2,3-dimethylchromone (VI). A solution of 1.1 g. of 8-formyl-7-hydroxy-2,3-dimethylchromone (II) in 150 ml. of absolute ethanol, with 0.15 g. of platinum oxide, was hydrogenated at atmospheric pressure until absorption ceased. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The crude product (1.1 g.) on crystallizing from ethanol gave a white crystalline solid with no sharp melting point.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.66.

The *diacetate* was prepared from VI by boiling with acetic anhydride as a white crystalline solid, m.p. 127–129°. A mixture melting point of this diacetate with a sample of V was not depressed.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.31. Found: C, 63.16; H, 5.23.

8-Formyl-7-methoxy-2,3-dimethylchromone (VIII). A mixture of 2.18 g. of 8-formyl-7-hydroxy-2,3-dimethylchromone, 60 ml. of anhydrous acetone, 3 g. of anhydrous potassium carbonate, and 1.5 g. of methyl sulfate was boiled for 8 hr., cooled, filtered, and the solid washed with hot acetone. Removal of acetone left a residue which on crystallizing from ethanol, 95°, gave 0.8 g. of 7-methoxy derivative, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H 5.21. Found: C, 67.45; H, 5.44.

8-Hydroxymethyl-7-methoxy-2,3-dimethylchromone (IX). A solution of 1.16 g. of 8-formyl-7-methoxy-2,3-dimethylchromone (VIII) in 150 ml. of ethanol was hydrogenated, at atmospheric pressure, over 0.1 g. of platinum oxide catalyst until absorption ceased. After removal of the catalyst, the filtrate was concentrated to dryness and the crude product was crystallized from ethanol as a white crystalline powder, m.p. 188.5–189.5°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.64; H, 6.01. Found: C, 66.46; H, 5.80.

The *acetate* (X) was prepared from IX by boiling with acetic anhydride as white crystals from ligroin, m.p. 163–164°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.31; H, 5.57.

The mixture melting points of IX and X with the corresponding samples of the same products obtained by another procedure as described earlier,[3] were not depressed.

8-Acetoxymethyl-7-acetoxy-3-methylflavone. One gram of compound 21 (see Table I) with the same reactions as V, gave 0.8 g. (from ligroin) of diacetoxy derivative, m.p. 117–119°.

Anal. Calcd. for $C_{21}H_{18}O_6$: C, 68.83; H, 4.96. Found: C, 69.10; H, 5.24.

8-Hydroxymethyl-7-hydroxy-3-methylflavone (XII). A 1.4-g. sample of 7-hydroxy-8-formyl-3-methylflavone with the same reactions as VI, gave 1.1 g. (from ethanol) of XII, m.p. 183–185° dec.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.16; H, 5.31.

The *diacetate* was prepared as a white crystalline solid from ligroin, m.p. 118–119°. A mixture melting point with the same product obtained from compound 21 (see Table I) was not depressed.

8-Formyl-7-hydroxy-3-methylflavone (XI). Three grams of compound 21 (see Table I), with the same reactions as II, gave 1.5 g. (from dilute acetic acid) of the formyl derivative, m.p. 156–157°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.73; H, 4.39. Found: C, 72.49; H, 4.50.

A mixture melting point with a sample of the same product, prepared by the Duff reaction on 7-hydroxy-3-methylflavone, was not depressed.

8-Formyl-7-methoxy-3-methylflavone. Three grams of 8-formyl-7-hydroxy-3-methylflavone, methylated according to the procedure of VIII, gave 1.8 g. of the 7-methoxy derivative, m.p. 152–154°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.45; H, 4.80. Found: C, 73.23; H, 4.71.

8 Hydroxymethyl-7-methoxy-3-methylflavone. One gram of 8-formyl-7-methoxy-3-methylflavone hydrogenolyzed under the same conditions as IX gave 0.65 g. of the 8-hydroxymethyl derivative as a white crystalline solid with no sharp melting point.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.44. Found: C, 73.01; H, 5.34.

The *acetate* was prepared as a white solid from diluted ethanol, m.p. 168–169°.

Anal. Calcd. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.32. Found: C, 70.89; H, 5.20.

A mixture melting point with the same product obtained by another procedure,[3] was not depressed.

6,8-Dipiperidinomethyl-7-hydroxy-2,3-dimethylchromone-2-hydrochloride. To a solution of 1.9 g. of 7-hydroxy-2,3-dimethylchromone in 100 ml. of ethanol, 1.7 g. of piperidine, and 2 ml. of formalin were added, and then the mixture was refluxed for 8 hr. After cooling, alcoholic hydrochloric acid was added and the mixture was concentrated and again cooled until a precipitate formed. The crude product on crystallization from ethanol/ether gave 2.1 g. of white solid, m.p. 256–257°.

Anal. Calcd. for $C_{23}H_{34}Cl_2N_2O_3$: N, 6.12. Found: N, 6.04.

Amine exchange reaction of hydroxychromones Mannich bases. We employed the procedure of Snyder and Brewster[11] for β-naphthol Mannich bases. The product were identified by melting point and mixture melting point.

MILAN, ITALY

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

Condensed Cyclobutane Aromatic Compounds. XII. Some 5-Substituted Derivatives of Benzo[a]biphenylene

M. P. CAVA, K. W. RATTS, AND J. F. STUCKER

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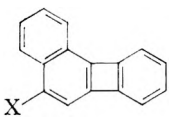
The dehydrohalogenation of *trans*-1,2-diiodobenzocyclobutene afforded 5-iodobenzo[a]biphenylene. The latter iodide served as starting material for the synthesis of the 5-carboxy-, 5-cyano- and 5-acetyl- derivatives of benzo[a]biphenylene.

The only reported substitution product of the hydrocarbon benzo[a]biphenylene (I)[1] is the 5-bromo derivative (II), obtained as the end product of the dehydrobromination[2] of *trans*-1,2-dibromobenzocyclobutene.[3]

As anticipated, the dehydrohalogenation of *trans*-1,2-diiodobenzocyclobutene[3,4] by potassium *t*-butoxide proceeded in a completely analogous manner to give 5-iodobenzo[a]biphenylene (III), m.p. 131–132°, in 71% yield. This readily available iodo compound was employed as the starting material for the synthesis of several other 5-substituted benzo[a]biphenylenes.

5-Iodobenzo[a]biphenylene underwent metal exchange with *n*-butyl lithium. The resulting lithium derivative (IV) was treated with carbon dioxide to give, in 57% yield, benzo[a]biphenylene-5-carboxylic acid (V), m.p. 257°. The same acid was obtained in lower yield, by carbonation of the lithio derivative prepared from the bromide II, as well as by carbonation of the Grignard derivative (VI) of the iodide II. Benzo[a]biphenylene-5-carboxylic acid is scarlet in color as the free acid, although the corresponding anion has the lemon yellow color characteristic of the parent hydrocarbon benzo[a]biphenylene.[2] The acid V was converted *via* the acid chloride (VII), into the orange methyl ester (VIII), m.p. 126–127°, and also into the yellow amide (IX), m.p. 271–272°. Dehydration of the amide with thionyl chloride afforded the orange 5-cyanobenzo[a]biphenylene (X), which was obtained directly from iodide III by reaction with cuprous cyanide.

Treatment of 5-cyanobenzo[a]biphenylene with methylmagnesium iodide gave, after hydrolysis of the intermediate imine, 5-acetylbenzo[a]biphenylene (XI). The bright red ketone XI, m.p. 85–86°, was isolated in pure form only in low yield (11%) after initial separation as a crude 2,4,7-trinitrofluorenone complex. It was prepared, however, in excellent yield (93%) by an alternate synthesis from dimethylcadmium and the acid chloride VII. An attempt was made to effect the direct Friedel-Crafts acetylation of benzo[a]biphenylene under conditions employed successfully for the conversion of biphenylene to 2-acetylbiphenylene.[5] Although partial reaction of the hydrocarbon occurred, none of the 5-acetyl derivative (XI) was found after careful chromatographic examination of the oily reaction mixture.



I. X = H
II. X = Br
III. X = I
IV. X = Li
V. X = COOH
VI. X = MgI
VII. X = COCl
VIII. X = $COOCH_3$
IX. X = $CONH_2$
X. X = CN
XI. X = $COCH_3$

EXPERIMENTAL[6]

5-Iodobenzo[a]*biphenylene* (III). Finely ground *trans*-1,2-diiodobenzocyclobutene[3,4] (2.50 g.) was added slowly to a hot solution of potassium *t*-butoxide prepared by dissolving potassium (1.60 g.) in *t*-butanol (32 ml.). The orange solution was refluxed for 30 min. Water (20 ml.) was then added, followed by sufficient acetic acid to neutralize the excess base. The mixture was cooled and the orange crystalline precipitate (1.00 g.) was filtered, washed with water, and dried. The crude product was purified by continuous extraction with petroleum ether (30–60°) in a Soxhlet apparatus, evaporation of the extract and crystallization from aqueous ethanol to give, in two crops, orange needles of iodide III (0.82 g., 71%). The first crop (0.69 g.), m.p. 131–132°, was of analytical purity.

Anal. Calcd. for $C_{16}H_9I$: C, 58.56; H, 2.76; I, 38.68. Found C, 58.56; H, 2.75; I, 38.55. Ultraviolet spectrum (ethanol): λ_{max} 226 (log ϵ 4.23); λ_{max} 266 (log ϵ 4.31).

Benzo[a]*biphenylene-5-carboxylic acid* (V). *A. By carbonation of Grignard reagent* VI. To an excess of magnesium turnings in dry ether (25 ml.) was added 5-iodobenzo[a]biphenylene (0.100 g.), followed by a few drops of methyl iodide. After refluxing for 30 min., the yellow ether solution was pipetted from the residual magnesium and gaseous carbon dioxide was passed through it slowly for 5 min. Dilute hydrochloric acid was added and the ether solution was shaken with 5% sodium hydroxide until no further color passed into the aqueous phase. The lemon yellow solution of the sodium salt of V was acidified and the orange flocculent precipitate was extracted into ether. Evaporation of the

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(6) Analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and by Schwarzkopf Laboratories, Woodside, N. Y. All melting points are uncorrected.

dried extract and crystallization of the residue from benzene–methanol–petroleum ether (30–60°) mixture afforded small bright red needles of V (0.029 g., 39%), m.p. 257°.

Anal. Calcd. for $C_{17}H_{10}O_2$: C, 82.92; H, 4.07. Found: C, 82.90; H, 4.23. Ultraviolet spectrum (ethanol): λ_{max} 264 (log ϵ 4.69); λ_{max} 287.5 (log ϵ 4.30); λ_{max} 297 (log ϵ 4.42).

B. By carbonation of lithio derivative IV. A solution of *n*-butyllithium in dry ether was prepared from 1-bromobutane (2 ml.), lithium (0.25 g.), and ether (25 ml.). A 5 ml. aliquot of this solution was added to a solution of 5-iodobenzo[a]biphenylene (0.500 g.) in dry ether (10 ml.). After 2 min. the red solution of the lithio derivative IV was saturated with gaseous carbon dioxide and worked up as described above for the product of the Grignard carbonation. The yield of recrystallized acid V was 0.212 g. (56.5%).

When this same preparation was carried out using 5-bromobenzo[a]biphenylene instead of the iodide III the acid V was obtained in 37% yield.

5-Carbomethoxybenzo[a]*biphenylene* (VIII). A mixture of benzo[a]biphenylene 5-carboxylic acid (0.100 g.), thionyl chloride (1.3 ml.) and a trace of pyridine was refluxed for 30 min., then allowed to stand for an additional 15 min. Removal of excess thionyl chloride under vacuum left a dark red residue of the crystalline acid chloride VII. Absolute methanol (6 ml.) was added and the mixture refluxed for 10 min., then evaporated to dryness under reduced pressure. Chromatography of the residue on neutral alumina in benzene afforded the pure ester VIII as orange needles (0.099 g., 94%), m.p. 126–127°, on evaporation of the benzene eluate.

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.08; H, 4.61. Found: C, 83.10; H, 4.67.

Benzo[a]*biphenylene-5-carboxamide* (IX). The crude acid chloride VII was prepared from benzo[a]biphenylene-5-carboxylic acid (0.100 g.) as described in the preparation of the methyl ester VIII. A solution of the chloride VII in benzene (5 ml.) was saturated with gaseous dry ammonia. The yellow precipitate was filtered, dried, washed with cold water, and dried once more. Crystallization of the yellow powder from benzene-methanol gave fine yellow needles of amide IX (0.076 g., 76%), m.p. 271–272°. Recrystallization from ethanol afforded the analytical sample, m.p. 273°.

Anal. Calcd. for $C_{17}H_{11}NO$: C, 83.24; H, 4.52; N, 5.71. Found: C, 83.42; H, 4.74; N, 5.83.

5-Cyanobenzo[a]*biphenylene* (X). *A. From Iodide* III. A mixture of cuprous cyanide (0.50 g.), 5-iodobenzo[a]biphenylene (0.50 g.) and dimethylformamide (11 ml.) was refluxed for 3 hr. The cooled solution was diluted with saturated aqueous ferric chloride (5 ml.) followed by sufficient cold water to effect complete precipitation of the product. The orange precipitate was filtered, dried, dissolved in benzene and chromatographed on alumina. The nitrile X moved down the column as a strong orange band, which was eluted with benzene. Concentration of the eluate yielded, in two crops, fine orange needles of 5-cyanobenzo[a]biphenylene (0.29 g., 84%). The first crop (0.21 g.), m.p. 154–155°, was of analytical purity.

Anal. Calcd. for $C_{17}H_9N$: C, 89.84; H, 3.99; N, 6.17. Found: C, 89.60; H, 3.83; N, 6.03. Ultraviolet spectrum (ethanol): λ_{max} 239 (log ϵ 4.43); λ_{max} 270 (log ϵ 4.73); λ_{max} 290 (log ϵ 4.42); λ_{max} 299.5 (log ϵ 4.42).

B. From benzo[a]*biphenylene-5-carboxamide* (IX). A solution of amide IX (0.143 g.) in thionyl chloride (3.0 ml.) was refluxed for 5 min. Excess thionyl chloride was removed under vacuum and the red residue was dissolved in ether. The ethereal solution was washed successively with water, dilute sodium hydroxide, and again with water. The solution was dried over magnesium sulfate, evaporated, and the residue dissolved in benzene and chromatographed on alumina. Elution of the orange band and evaporation of the eluate afforded 5-cyanobenzo[a]biphenylene (0.097 g., 70%), m.p. 153–154°. Recrystallization from benzene gave small orange needles, m.p. 154–155°. The melting point was not depressed by a sample of nitrile prepared by the cuprous cyanide method, and the infrared spectra of both samples were identical.

5-Acetylbenzo[a]*biphenylene* (XI). *A. From 5-cyanobenzo*[a]*biphenylene* (X). A solution of the nitrile X (0.200 g.) in benzene (2 ml.) was added to 4 *M* ethereal methylmagnesium bromide (4 ml.) and the mixture was refluxed for 5 hr. The cooled red solution was diluted with ether and shaken with cold aqueous ammonium chloride. The organic layer was then extracted with cold dilute sulfuric acid and the aqueous acidic extract, which contained the intermediary ketimine as the sulfate, was allowed to stand overnight at room temperature to effect hydrolysis of the imine to the ketone. Extraction of the cloudy yellow solution with ether and evaporation of the dried ether phase gave a red oil which resisted crystallization. 2,4,7-Trinitrofluorenone (0.040 g.) was added to a solution of this oil in a small volume of benzene and the mixture was heated to effect complete solution. Addition of excess methanol to the hot benzene solution caused the separation of the crude 2,4,7-trinitrofluorenone derivative of XI as a deep purple precipitate, which was filtered, dried, and dissolved in benzene. Chromatography on alumina and elution of the principal orange-red band afforded, after concentration of the benzene eluate and addition of 30–60° petroleum ether, red needles (0.024 g., 11%) of 5-acetylbenzo[a]biphenylene, m.p. 85–86°.

Anal. Calcd. for $C_{18}H_{12}O$: C, 88.50; H, 4.95. Found: C, 88.34; H, 4.89. Ultraviolet spectrum (ethanol): λ_{max} 246 (log ϵ 4.18); λ_{max} 267 (log ϵ 4.61); λ_{max} 297 (log ϵ 4.35).

B. From Benzo[a]*biphenylene-5-carboxylic acid* (V). The acid V (0.100 g.) was converted into the acid chloride VII as described in the preparation of the methyl ester VIII. The crude chloride VII, dissolved in dry benzene (25 ml.) was added at room temperature to an ethereal solution (10 ml.) of dimethylcadmium containing an excess (*ca.* 1 g.) of cadmium reagent. After 5 min. the red turbid solution was diluted with ether and shaken with cold 10% hydrochloric acid. The organic layer was washed with water and dilute sodium carbonate, dried, and evaporated to dryness to yield the almost pure red crystalline ketone XI (0.092 g., 93%), m.p. 80–84°. Chromatography of this material in benzene on alumina afforded completely pure ketone, m.p. 85.5–86.5°. This material was identical with that prepared from nitrile X, as evidenced from mixed melting point and infrared comparisons.

Attempted acetylation of benzo[a]*biphenylene* (I). Benzo[a]biphenylene (0.400 g.) was dissolved in carbon disulfide (40 ml.) and aluminum chloride (0.300 g.) and acetyl chloride (2.1 ml.) were added. The purple mixture was refluxed for 45 min. and then treated with dilute hydrochloric acid to decompose the aluminum chloride complex formed. Extraction with ether afforded, after usual workup conditions, a red oil which was dissolved in benzene and chromatographed on Woelm neutral alumina (activity grade II) to yield unchanged hydrocarbon I (0.150 g.) and two orange bands containing red oils (0.147 g. and 0.089 g., respectively). Neither red oil could be seeded by authentic 5-acetylbenzo[a]biphenylene (XI) and both oils had ultraviolet and infrared spectra quite different from those of authentic ketone XI.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

2-Sulfonylbiphenyls and 6,7-Dihydro-2,3,4,5-dibenzothiapin-6-one-1-dioxide; a Seven-Membered Ring β-Ketosulfone[1]

DONALD D. EMRICK[2] AND WILLIAM E. TRUCE

Received December 23, 1959

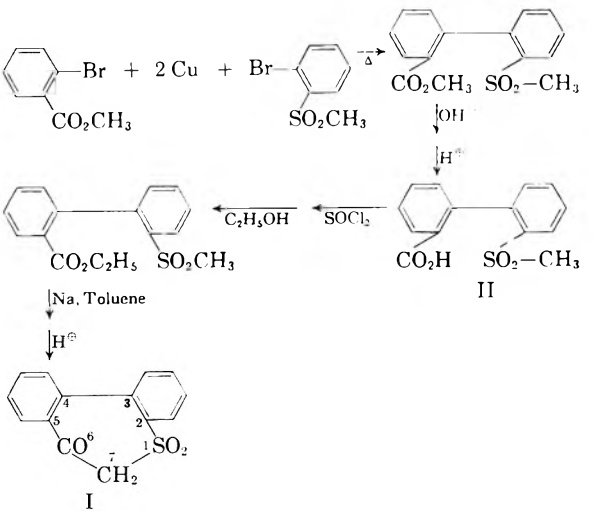
A new seven-membered ring β-ketosulfone has been synthesized in good yield by the Claisen condensation of ethyl 2′-methylsulfonylbiphenyl-2-carboxylate with sodium metal. The material resembles ω-phenylsulfonylacetophenone in its chemistry and appears to be nonplanar with respect to the seven-membered ring flanked by phenyl groups.

The synthesis of a β-ketosulfone structure of type I was of interest in view of its potential similarity to dibenzotropones. Numerous examples of the ease of formation of seven-membered ring O,O′-bridged biphenyls are noted in the literature. Among these examples are the thioketal compounds of Barber and Smiles.[3]

Also, 2,2′-diacetobiphenyl and 2′-acetobiphenyl-2-carboxaldehyde undergo aldol-type cyclizations to form seven-membered rings[4] with ease, while similar condensations in the aliphatic series produce only five- and six-membered rings.[5]

Several examples of cyclizations involving methylene hydrogens activated by sulfone groups are known.[6] These cyclizations are mixed Claisen-type condensations between alkyl sulfonyl and carbalkoxyl groups to produce β-ketosulfones. Thus, esters of *o*-carboxyphenyl benzyl sulfone readily undergo internal cyclizations in the presence of sodium ethoxide to form cyclic β-ketosulfones.[6] Such Claisen condensations have been used to prepare several cyclic β-ketosulfones in the aliphatic series.[7]

6,7-Dihydro-2,3-4,5-dibenzothiapin-6-one-1-dioxide (I) is readily prepared in good yield by such a Dieckmann type of ring closure employing the action of sodium metal upon the ethyl ester of 2′-methylsulfonylbiphenyl-2-carboxylic acid in refluxing toluene. The parent (2′-methylsulfonyl)biphenyl-2-carboxylic acid (II) is most conveniently obtained by saponifying the high boiling fraction of the products of a mixed Ullmann reaction employing methyl *o*-bromobenzoate, methyl *o*-bromophenyl



sulfone and copper powder, the yield of acid after extensive purification being only 12%. Conversion of the acid to the acid chloride by means of thionyl chloride followed by treatment with ethanol gave the ethyl ester in high yield.

The Dieckmann product (I) is somewhat acidic, being readily soluble in dilute ammonia and sodium carbonate solution, but is not acidic enough to react readily with cold bicarbonate or to form stable salts with alkaloids having an ionization constant of about 1×10^{-6} or less. Like ω-phenylsulfonylacetophenone,[8] I readily reacts with phenylhydrazine. It likewise does not form a coloration with either ferric chloride or ceric sulfate nor does it react with acetyl chloride. Bright yellow or orange dyes are produced on coupling I with aromatic diazonium compounds similar to corresponding bright orange or red dyes produced from ω-phenylsulfonylacetophenone. As with the latter, bromine reacts with I to produce a colorless bromide which liberates free iodine from potassium iodide solution.

Buchanan[9] has confirmed the earlier suggestion of Sakan and Nakazaki[10] that the presence of

(1) Abstracted from a portion of the Ph.D. thesis of Donald D. Emrick, Purdue University, 1956.

(2) Present address: Research Department, The Standard Oil Company (Ohio), Cleveland 28, Ohio.

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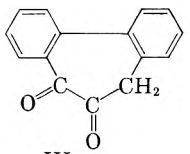
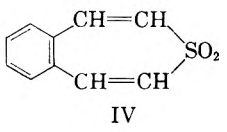
two flanking benzo groups suppresses the aromatic character of the central seven-membered ring even when highly conjugated as in the enol of the dibenzocycloheptadienedione (III).



III



IV

Truce and Lotspeich[11] prepared 3-benzothiepin-3-dioxide (IV), the sulfone analog of benzotropone. Many lines of recent evidence[12,13] indicate that the sulfone group, like the carbonyl group, is capable of conjugation by electron acceptance. However, the properties of IV were best explained by assuming more unsaturated character for the ethylenic bonds than quasi-aromatic character.[11] The inference of this essential lack of quasi-aromatic character is that the seven-membered ring is not appreciably resonance stabilized and is probably nonplanar. Although not so fully conjugated as IV, the optical resolution of 2,7-dihydro-3,4,5,6-dibenzothiepin-1-dioxide-2′,3′′-dicarboxylic acid and a wealth of ultraviolet absorption spectra have been presented to indicate that such seven-membered sulfones flanked by biphenylic benzenes are definitely not coplanar.[14]

During the course of this work several 2-sulfonylbiphenyls were prepared. These 2-sulfonylbiphenyls show very characteristic maxima at 270–272 μ and 276–278 μ which are rather analogous to the maxima observed at 264–265 μ and 271–272 μ in alkyl phenyl sulfones (alkylsulfonylbenzenes).[15] This information is summarized in Table I. The interpretation of ultraviolet absorption spectrum of I is complicated by the presence of the carbonyl function adjacent to one of the aromatic nuclei (consult work of Hedden and Brown[16] dealing with the ultraviolet spectra of hindered ketones). A conjugative interaction, through the sulfone function, of the carbonyl group with *both* benzene rings of the bridged biphenyl may be possible. However, such interaction probably would occur *only* with the β-ketosulfone anion.[15] Support of this viewpoint may possibly

TABLE I

ULTRAVIOLET ABSORPTION OF SULFONYLBENZENES AND 2-SULFONYLBIPHENYLS

Compound (in 95% ethanol)	λ_{max}, μ[a]	ϵ
2-Biphenylylmercaptoacetic acid	232	ca. 15,000
Methylsulfonylbenzene[b]	264	980
	271	890
2-Methylsulfonylbiphenyl	270	2,240
	276	2,490
Ethyl phenylsulfonylacetate[b]	266	1,050
	272	890
2-Biphenylylsulfonylacetic acid	(271)	2,330
	276	2,570
2′-Methylsulfonylbiphenyl-2-carboxylic acid (II)	272	—
	277	—
Ethyl 2′-methylsulfonylbiphenyl-2-carboxylate	271	—
	277	—
2,6-Dihydro-2,3,4,5-dibenzothiapin-6-one-1-dioxide (I)	240	—
	(271)	—
Phenylsulfonylacetone[b]	219	8,700
	265	1,120
	272	1,000
α-Phenylsulfonylisopropyl methyl ketone[b]	218	10,000
	266	1,150
	273	1,000

[a] Secondary maxima in all cases, primary maxima being in region 210–217 μ. [b] See ref. 15.

be indicated by the existence of the remnant of the 271 μ peak in I which is present in all the *unbridged* 2-sulfonylbiphenyls discussed in Table I.

Papanastassiou[17] has observed that nonplanar dibenzo[a,c][1,3]cycloheptadiene - 5 - one (carbonyl adjacent to aromatic nucleus) shows a principal absorption peak at 233 μ. If the sulfone function adjacent to a benzene ring produces a bathochromic and hyperchromic displacement of the benzenoid absorption[15] towards longer wave lengths, the principal absorption maximum at 240 μ for 6,7-dihydro-2,3,4,5-dibenzothiapin-6-one-1-dioxide (I) would seem in accord with the value observed by Papanastassiou for dibenzo-[a,c][1,3]cycloheptadiene - 5 - one.[17] Admittedly, the situation may be more complex, however.

In view of the work of Bergmann,[18] the infrared spectrum of I also indicates nonplanarity of the seven-membered ring. Thus, both I and nonplanar nonaromatic dibenzotropones[18] display carbonyl absorption bands at 6.0 μ while planar aromatic tropone displays a carbonyl band at 6.1 μ.

In summary, the chemistry and properties of I are in accord with a nonplanar configuration, the material resembling ω-phenylsulfonylacetophenone more than a fully conjugated coplanar biphenyl. The much greater chemical stability of I as contrasted to its β-diketone analog dibenzo-

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(14) W. E. Truce and D. D. Emrick, *J. Am. Chem. Soc.*, **78**, 6130–6137 (1956).

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(16) G. D. Hedden and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 3744–3748 (1953).

(17) Z. B. Papanastassiou, Ph.D. Thesis, University of West Virginia, Morgantown, West Virginia, June 1954.

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[a,e][1,3]cycloheptadiene-5,7-dione[19] is also noteworthy.

EXPERIMENTAL

Biphenylthiol. The general procedure for converting Grignard reagents to magnesium mercaptides was that of Taboury.[20]

A solution of 60 g. (0.214 mole) of 2-iodobiphenyl in 150 ml. of anhydrous ether was added slowly, with refluxing, to a well stirred suspension of 5.21 g. (0.214 g.-atom) of fine magnesium turnings in 100 ml. of anhydrous ether, employing a crystal of iodine to initiate the reaction. The resulting mixture was refluxed for an additional hour. Eight grams of powdered rhombic sulfur was added to the Grignard solution causing a vigorous reaction to take place. Refluxing was continued for 45 more min. and the mixture was then cautiously acidified with 15% sulfuric acid. The ethereal layer was separated and extracted with two 200-ml. portions of cold 15% sodium hydroxide. The combined sodium hydroxide solutions were then extracted with 100 ml. ether. The sodium hydroxide layer was then acidified with a mixture of ice and concd. hydrochloric acid to precipitate a thick light-greenish oil which was taken up in 200 ml. ether. The ethereal solution was shaken with 60 ml. water and evaporated to give nearly white crystals, m.p. 32–37°. Distillation gave 22.1 g. (56%) of product, b.p. 143° (4 mm.), m.p. 39–40.

Anal. Calcd. for $C_{12}H_{10}S$: C, 77.4; H, 5.38. Found: C, 77.12; H, 5.37.

2-Biphenylyl methyl sulfone. A solution of sodium ethoxide was prepared by dissolving 1.24 g. (0.054 g.-atom) of sodium metal in 25 ml. of absolute ethanol. To this solution was added 5.0 g. (0.027 mole) of 2-biphenylthiol and then a solution of 11.5 g. (0.081 mole) of methyl iodide in 10 ml. of ethanol was run in with vigorous stirring. The mixture was refluxed with stirring for 2 hr. and then the excess alcohol (and methyl iodide) was distilled at 100°. The residue was taken up with 50 ml. water and the oily 2-methylmercaptobiphenyl was separated from the aqueous phase. All of the oily sulfide was oxidized by refluxing for 1 hr. with a mixture of 30 ml. of 30% hydrogen peroxide (about 0.27 mole) and 60 ml. of glacial acetic acid. Upon pouring the resulting solution into excess sodium hydroxide solution and allowing to stand at 0° overnight, crude crystals of sulfone were obtained. Recrystallization from 70% ethanol gave pure white flat platelets of the desired 2-biphenylyl methyl sulfone; yield 5.4 g. (87%), m.p. 100–101°.

Anal. Calcd. for $C_{13}H_{12}SO_2$: C, 67.2; H, 5.17. Found: C, 67.46; H, 5.06.

2-Biphenylylmercaptoacetic acid. A solution of sodium ethoxide was prepared by dissolving 1.92 g. (0.083 g.-atoms) of sodium metal in 150 ml. of absolute ethanol. To this solution was added 15.5 g. (0.083 mole) of 2-biphenylthiol to form the sodium mercaptide. Twenty milliliters (0.19 mole) of ethyl chloroacetate was added slowly with vigorous stirring. After refluxing for 6 hr., most of the ethanol was distilled and the residue was extracted with chloroform. After drying overnight with 10 g. of anhydrous calcium sulfate, the chloroform was removed by distillation and the residue distilled to yield 16.4 g. of pale yellow-oil (70%), b.p. 205–208° (16 mm.), n_D^{20} 1.5952.

Anal. Calcd. for $C_{16}H_{16}SO_2$: C, 70.6; H, 5.88. Found: C, 68.51; H, 6.16.

A mixture of 14 g. (0.0514 mole) of the above ethyl 2-biphenylylmercaptoacetate, 18 ml. of water, 18 ml. of ethanol, and 6 g. (0.15 mole) of sodium hydroxide were refluxed for 5 hr. The resulting solution was poured into 50 g. of ice and was acidified with excess hydrochloric acid. After standing 15 min., the precipitated acid was filtered and washed with cold water. The yield of white crystals was 12.4 g. (98%), m.p. 169–170°.

Anal. Calcd. for $C_{14}H_{12}SO_2$: C, 68.8; H, 4.92; neut. eq. 244. Found: C, 68.50; H, 5.25; neut. eq. 249.

2-Biphenylylsulfonylacetic acid. A mixture of 6.0 g. (0.025 mole) of 2-biphenylylmercaptoacetic acid, 17 ml. of glacial acetic acid, and 7.6 ml. (about 0.07 mole) of 30% hydrogen peroxide were refluxed for 1 hr. and then poured into a cold solution of 15 g. of sodium hydroxide dissolved in 60 ml. of water. After standing at 0° for 1 hr., the solution was filtered and the filtrate was acidified to congo red with concd. hydrochloric acid. The resulting paste was allowed to stand at 0° for 10–12 hr. to complete the precipitation of the white crystalline acid which was filtered and washed with ice water. The yield of glistening white needles was 5.7 g. (84%), m.p. 117–119°. Recrystallization from a minimum of a mixture of benzene and petroleum ether (b.p. 70–90°) gave a product melting at 119–120° (the melted material evolved carbon dioxide at about 185° and turned black at 230°); experimental equivalent weight, 277 (calcd. 276).

Anal. Calcd. for $C_{14}H_{12}SO_4$: C, 60.90; H, 4.37. Found: C, 61.21; H, 4.29.

All attempts to prepare the seven-membered ring *O,O'*-bridged biphenyl, 6,7-dihydro-2,3-4,5-dibenzothiapin-6-one-1-dioxide, (XXIX) by treatment of 2-biphenylylsulfonylacetic acid with concd. sulfuric acid or polyphosphoric acid failed, 2-biphenylyl methyl sulfone being produced with loss of carbon dioxide. The preparation of 2-biphenylylsulfonylacetyl chloride from the free acid under mild conditions (with low boiling oxalyl chloride) and attempted Friedel Crafts cyclization of this material with aluminum chloride or stannic chloride under very mild conditions gave extensive degradation, the only product isolated being impure 2-biphenylyl methyl sulfone.

2'-Methylsulfonylbiphenyl-2-carboxylic acid. (II) *o*-Bromophenylmethyl sulfone[21] was prepared by alkylating sodium *O*-bromobenzenesulfinate[22] with methyl iodide by the general method of Todd and Shriner;[23] 92% yield, m.p. 108–108.5°; Martin[21] reports m.p. 108–108.5°.

Forty-four grams (0.20 mole) of methyl *O*-bromobenzoate and 32 g. (0.136 mole) of *O*-bromophenyl methyl sulfone were heated to 180°, with stirring, by means of an external oil bath. In four portions, 50 g. (0.785 g.-atom) of #445 copper bronze powder was added, maintaining the temperature at 220–230° after each addition for 20 min. and then cooling to 180–190° before adding more copper powder. The resulting mixture was then stirred at 230–240° for 1 hr. and then cooled. The residue was extracted with several portions of refluxing chloroform; the combined extracts were filtered and evaporated on a steam cone to give a brown oil. The resulting oily residue was distilled at 2 mm. until a pot temperature of 200° was achieved, unchanged starting materials and dimethyl diphenate, b.p. 158° (2 mm.), being collected in the distillate to this point. The residue, which was essentially a mixture of 2,2'bis(methylsulfonyl)biphenyl and the desired methyl 2'-methyl-sulfonylbiphenyl-2-carboxylate, was then refluxed with 200 ml. of 15% aqueous potassium hydroxide. The resulting solution was cooled to 0° for 24 hr., filtered, decolorized by boiling with 2 g. of activated charcoal, refiltered, and acidified to give a crude acid. The product was grossly impure but was easily purified by extraction with hot benzene, the desired 2-methylsulfonylbiphenyl-2-carboxylic acid (II) being nearly insoluble in boiling benzene while the other acidic materials were very soluble in benzene. The purified sulfone carboxylic acid was recrystallized from a large volume of a mixture of ben-

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(21) G. A. Martin, *Iowa State Coll. J. Sci.*, **21**, 38–40 (1946); *Chem. Abstr.*, **41**, 952 (1947).

(22) M. E. Hanke, *J. Am. Chem. Soc.*, **45**, 1321–1323 (1923).

(23) H. R. Todd and R. L. Shriner, *J. Am. Chem. Soc.*, **56**, 1383 (1934).

zene and petroleum ether to give pure white crystals, m.p. 187–188°. Two more recrystallizations from 65% ethanol gave beautiful golden-flecked crystals m.p. 194–195°. The crystals showed moderate yellow fluorescence and in strong ethanol solutions showed moderate green fluorescence. The yield of highly purified acid was 4.5 g. (12%); experimental equivalent weight 274 (calcd. 276).

Anal. Calcd. for $C_{14}H_{12}SO_4$: C, 60.90; H, 4.35. Found: C, 60.97; H, 4.49.

The structure of the 2′-methylsulfonylbiphenyl-2-carboxylic acid (II) was confirmed as follows. 2′-Methyl-2-nitrobiphenyl was prepared[24] and reduced to 2-amino-2′-methylbiphenyl.[24] The latter was diazotized and upon treatment with potassium iodide produced 2-iodo-2′-methylbiphenyl[24] in fair yield. The Grignard of 2-iodo-2′-methylbiphenyl upon treatment with sulfur and subsequent acidification (see above preparation of 2-biphenylthiol) produced 2′-methylbiphenyl-2-thiol in 51% yield, b.p. 110–113° (1 mm.), n_D^{29} 1.6272.

2′-Methylbiphenyl-2-thiol treated with sodium ethoxide in ethanol and then methyl iodide produced 2′-methyl-2-methylmercaptobiphenyl as a noncrystallizable oil. Oxidation of the latter sulfide with 30% hydrogen peroxide in glacial acetic acid produced waxy low melting 2′-methyl-2-methylsulfonylbiphenyl which could not be readily recrystallized for analysis. Oxidation with strong sodium dichromate and sulfuric acid in aqueous acetic acid produced fair yields of the desired 2′-methylsulfonylbiphenyl-2-carboxylic acid upon diluting with water and standing for 10 days at 0°. From about 3 g. of starting 2′-methylbiphenol-2-thiol about 0.6 g. of crude acid was obtained. After recrystallization from benzene-petroleum ether mixture and then from 56% ethanol, the material melted at 192–194°; the material failed to depress the melting point of the acid obtained from the mixed Ullman reaction, confirming the structure of the latter.

Two grams of the above highly purified 2′-methylsulfonylbiphenyl-2-carboxylic acid were refluxed for 16 hr. with 5 ml. of thionyl chloride to convert it to the acid chloride. The excess thionyl chloride was distilled *in vacuo* at 100° and the cooled residual acid chloride was then cautiously treated with 6 ml. of ethanol under reflux. After refluxing for 15 min., the resulting solution was poured into ice and the oil shaken first with 5% sodium bicarbonate solution and then water. The oil spontaneously crystallized to form white crystals of ethyl 2′-methylsulfonylbiphenyl-2-carboxylate which was recrystallized from petroleum ether (b.p. 70–90°); yield was 2.0 g. (91%), m.p. 70.5–72°.

Anal. Calcd. for $C_{16}H_{16}SO_4$: C, 63.1; H, 5.26. Found: C, 62.96; H, 5.23.

6,7-Dihydro-2,3-4,5-dibenzothiapin-6-one-1-dioxide (I). Two grams (0.0066 mole) of ethyl 2′-methylsulfonyl-biphenyl-2-carboxylate, 11 ml. of toluene, and 0.30 g. (0.0132 g.-atom) of sodium metal were refluxed with stirring for 18 hr. After cooling, the toluene layer was decanted cautiously into 4*N* aqueous ammonia and shaken. The ammoniacal layer, containing the desired compound, was decolorized by boiling with 0.3 g. of activated charcoal, filtered, and acidified with hydrochloric acid. After standing at 0° for 24 hr., the resulting 6,7-dihydro-2,3-4,5-dibenzothiapin-6-one-1-dioxide was filtered and recrystallized from a minimum of 70% ethanol to give white crystals; yield 1.3 g. (76%), m.p. 167–168°.

The material was stable to hot hydrochloric acid and was reprecipitated unchanged upon acidifying a hot sodium hydroxide solution of the material.

Anal. Calcd. for $C_{14}H_{10}SO_3$: C, 65.1; H, 3.88. Found: C, 65.27; H, 3.86.

The infrared absorption spectrum shows characteristic bands at 5.95μ (6.26μ) (benzoyl type aryl ketone bands); 7.57μ, 8.66μ, and 8.85μ (sulfone bands); and 12.88μ, 13.16μ, and 13.81μ (apparently, substituted phenyl bands). Compare with significant bands in ethyl 2′-methylsulfonylbiphenyl-2-carboxylate at 5.88μ, (aryl ester band), 7.68–7.76μ, 8.69μ (8.79 and 8.86μ) (12.63–12.74μ), 13.09μ, and 13.24μ: and also the significant bands in 2-methylsulfonylbiphenyl at 7.71μ, 8.71μ, 8.90μ, 12.77μ, 13.19μ, and 13.33μ. Planar, aromatic, seven-membered ring, tropone displays carbonyl band at *ca.* 6.1μ while dibenzotropones (believed to contain nonplanar, nonaromatic seven-membered rings) have bands at *ca.* 6.0μ.

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

Derivatives of Fluorene. IX. 4-Hydroxy-2-fluorenamine; New 3,4-Benzocoumarin Derivatives[1]

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Synthesis of 4-hydroxy-2-fluorenamine, 4-hydroxyfluorene, and related compounds is described. New 7- and 6-substituted 3,4-benzocoumarins were synthesized; the first series was obtained in an alternate attempt to synthesize 4-hydroxy-2-fluorenamine. Ultraviolet and infrared spectral data for several of these new compounds are reported.

Although several ring-hydroxylated metabolites of the carcinogen, *N*-2-fluorenylacetamide have been identified,[3] *N*-2-(4-hydroxyfluorenyl)acetamide has not been reported, nor is there any recorded synthesis. The following describes the preparation of this substance and of 4-hydroxyfluorene, also new to the literature, and of several related derivatives. One approach failed to give the fluorene nucleus when facile splitting of the methoxyl group

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(3) E. K. Weisburger and J. H. Weisburger in J. P. Greenstein and A. Haddow (eds.), *Advances in Cancer Research, Vol. V*, Academic Press, Inc., New York, N.Y., 1958, pp. 409–418.

in 2-carboxy-2′-methoxy-4′-nitrobiphenyl, led to lactonization giving a new 3,4-benzocoumarin derivative.

Selective monoacetylation of 2,4-fluorenediamine had given us excellent yields[4] of the 2-acetylated derivative. Diazotization of the latter in fluoboric acid followed by treatment with acetic anhydride gave *N*-2-(4-acetoxyfluorenyl)acetamide. Mild and more drastic hydrolysis led respectively to *N*-2-(4-hydroxyfluorenyl)acetamide and 4-hydroxy-2-fluorenamine. Treatment of the phenolic amine with 100% formic acid yielded *N*-2-(4-hydroxyfluorenyl)formamide which was acetylated giving the *O*-acetyl derivative.

Deamination of 4-hydroxy-2-fluorenamine was not successful. The expected product, 4-hydroxyfluorene, was obtained by diazotization and hydrolysis of 4-aminofluorene.

Reaction of *N*-2-(4-acetoxyfluorenyl)acetamide and dimethyl sulfate in the presence of potassium hydroxide gave *N*-2-(4-methoxyfluorenyl)acetamide, which, upon hydrolysis and deamination gave 4-methoxyfluorene. The latter compound was also obtained from reduction of the known 4-methoxyfluorene.

Ullmann coupling, with methyl *o*-bromobenzoate, of 2-iodo-5-nitroanisole and of 2-iodo-4-nitroanisole followed by hydrolysis of the reaction product in a mixture of acetic acid and 64% sulfuric acid gave, respectively 7-nitro-3,4-benzocoumarin and 6-nitro-3,4-benzocoumarin. Raney nickel and hydrazine hydrate reduction[5] of the nitro compounds followed by deamination gave 3,4-benzocoumarin. Methylation of 7-nitro-3,4-benzocoumarin with dimethyl sulfate in an excess of alkali led to the formation of 2-methoxy-4-nitrodiphenyl-2′-carboxylic acid. The latter was also obtained by mild alkaline hydrolysis (to avoid ether-splitting and lactonization) of methyl 2-methoxy-4-nitrodiphenyl-2-carboxylate in the Ullmann reaction mixture. Attempted cyclization of 2-methoxy-4-nitrodiphenyl-2′-carboxylic acid to a fluorenone in polyphosphoric acid gave, instead, the lactone which had been obtained from acid hydrolysis.

Table I gives data from the ultraviolet spectra[6] of some of these compounds. Infrared spectral data[6] for some of the 3,4-benzocoumarin derivatives are included in Table II.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound (molarity)	λ max, mμ	Log ε
4-Hydroxyfluorene (2.67×10^{-5})	258	4.37
	268	4.42
	287	4.02
	294	4.06
	306	3.83
4-Hydroxyfluorenone (2.5×10^{-5})	249	4.42
4-Hydroxy-2-fluorenamine	297	3.96
(5×10^{-5})	213[b]	
	283[b]	
N-2-(4-Hydroxyfluorenyl)formamide	217	4.56
(2.35×10^{-5})	281	4.41
	294	4.39
	300[b]	
	318[b]	
N-2-(4-Acetoxyfluorenyl)formamide	281	4.51
(2.5×10^{-5})	289	4.55
	303	4.45
N-2-(4-Acetoxyfluorenyl)acetamide	282	4.47
(1.86×10^{-5})	290	4.52
	303	4.43
	220[b]	
2-Methoxy-4-nitrodiphenyl-2′-carboxylic acid (8×10^{-5})	293	3.96
	338	3.81
7-Nitro-3,4-benzocoumarin	261	4.57
(2.5×10^{-5})	278	4.57
	325[b]	
7-Amino-3,4-benzocoumarin	229	4.38
(2.5×10^{-5})	296	4.18
	317	4.19
6-Nitro-3,4-benzocoumarin	226	4.41
(2.5×10^{-5})	243	4.35
	258	4.38
6-Amino-3,4-benzocoumarin	232	4.53
(2.5×10^{-5})	238	4.52
	271[b]	

[a] Determined in absolute ethanol. [b] Shoulder.

EXPERIMENTAL[6]

N-2-(4-Acetoxyfluorenyl)acetamide. *N*-2-(4-Aminofluorenyl)acetamide[4] (2.1 g., 0.009 mole) was stirred in a mixture of 48% fluoboric acid (25 ml.) and water (10 ml.). To the suspension sodium nitrite (0.62 g., 0.009 mole) in water (3 ml.) was added dropwise at 0° (10 min.). The reaction mixture was stirred at −10–0° for 30 min., then filtered, washed successively with cold 5% fluoboric acid, methanol and ether, and dried over phosphorus pentoxide giving 2.9 g. of 4-(2-acetamidofluorenyl)diazonium fluoborate.

The fluoborate was suspended in acetic anhydride (15 ml.) and heated under reflux at 90–95° (bath) until evolution of gas ceased. The mixture was then distilled under reduced pressure and the residue treated with dilute sodium acetate solution, and the residual acetic anhydride destroyed with sodium carbonate solution. The solid was filtered, washed with water, and recrystallized twice from ethanol-water and once from acetone-methanol giving glistening crystals, 1.1 g. (44% from the amine), m.p. 230.5–231.5°. One more crystallization from acetone-methanol gave an analytical sample, m.p. 231–232°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.74; H, 5.42; N, 5.09.

4-Hydroxy-2-fluorenamine. *N*-2-(4-Acetoxyfluorenyl)acetamide (0.3 g.) was dissolved in boiling absolute ethanol (50 ml.). To the solution, concd. hydrochloric acid (10 ml.) was added. The mixture was refluxed for 16.5 hr. with occasional agitation. The alcohol was distilled and the precipitate filtered (0.25 g.) and refluxed for 15 min. in 2*N* sodium hy-

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(6) All melting points were taken on a Fisher-Johns apparatus and were corrected to standards. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The ultraviolet absorptions were measured with a Beckman model DK-1 Recording Spectrophotometer and the infrared spectra were run on a Beckman IR-5 (potassium bromide disks).

TABLE II

SELECTED INFRARED ABSORPTION BANDS OF SOME 3,4-BENZOCOUMARINS[a]

Compound	$\lambda_{C=O}$,μ	λ_{C-O},μ	λ_{NH_2},μ	$\lambda_{C_6H_5-N}$,μ	$\lambda_{C_6H_5-NO_2}$,μ
3,4-Benzocoumarin	5.80	7.90 8.29(?)			
6-Amino-3,4-benzocoumarin	5.88	7.85 8.27(?)	2.91[b] 2.98[b] 3.09[c]	7.59	
6-Nitro-3,4-benzocoumarin	5.75	7.92 8.20(?)			7.42
7-Amino-3,4-benzocoumarin	5.89	7.88 8.44(?)	2.90[b] 2.97[b] 3.07[c]	7.62	
7-Nitro-3,4-benzocoumarin	5.75	7.91 8.29(?)			7.43

[a] Potassium bromide disk. [b] Free. [c] Bonded.

droxide (10 ml.). After cooling to room temperature, the *p*H was adjusted to 6 and the precipitate collected by filtration, 0.2 g. Recrystallization from methanol-water (Darco) gave white bars which started blackening at 225° and melting at 230–234° dec., 0.15 g. (76%). Two crystallizations from methanol-water gave an analytical sample, m.p. 234.5–236.5° dec.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.98; H, 5.74; N, 7.06.

N-2-(4-Hydroxyfluorenyl)acetamide. *N*-2-(4-Acetoxyfluorenyl)acetamide (0.1 g.) was refluxed for 1 hr. in a mixture of ethanol (10 ml.) and 10% sodium carbonate solution (10 ml.). The mixture was distilled to 50% of the original volume and acidified with dilute hydrochloric acid to *p*H 5. The precipitate was filtered, washed with water, and dried. The material started darkening at 255° and melted at 265° dec., 0.07 g. (83%). Two crystallizations from methanol-water gave an analytical sample, m.p. 270–272.5° dec.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.13; H, 5.70; N, 6.14.

N-2-(4-Hydroxyfluorenyl)formamide. 4-Hydroxy-2-fluorenamine (0.1 g.) was dissolved in 98–100% formic acid (1 ml.) and the solution heated on a steam bath for 30 min. and then cooled. The precipitate was filtered, washed with water, and dried giving shiny flakes, 0.11 g., m.p. 250–253° dec. Recrystallization from ethanol-water raised the m.p. to 256.5–258° dec.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.46; H, 4.83; N, 6.33.

N-2-(4-Acetoxyfluorenyl)formamide. *N*-2-(4-Hydroxyfluorenyl)formamide (0.06 g.) was mixed with acetic anhydride (0.5 ml.) and warmed. Pyridine was added dropwise until a solution was obtained which was heated in a water bath at 70–80° for 20 min. and the volatile material removed in a vacuum. The crystalline solid was stirred in 10% sodium acetate solution, which was then made alkaline to *p*H 8 with sodium bicarbonate, and the solid was filtered off, washed with water, and dried. Crystallization from ethanol-water and then from benzene–carbon tetrachloride gave lustrous prisms (0.04 g.), m.p. 189.5–191°. Recrystallization from benzene–carbon tetrachloride gave an analytical sample, m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.76; H, 5.05; N, 5.12.

N-2-(4-Methoxyfluorenyl)acetamide. *N*-2-(4-Acetoxyfluorenyl)acetamide (1.5 g.) was suspended in boiling acetone (25 ml.) and 66% potassium hydroxide (1.5 ml.) was added, (a modification of a reported method[7]). The mixture was shaken, boiled briefly and shaken at room temperature for 10 min. Dimethyl sulfate (1.5 ml.) was then added dropwise over a period of 25 min. with occasional heating and constant agitation, which was continued for another hour. The mixture was then cooled and diluted with 5% sodium acetate solution (200 ml.), and the precipitate filtered, washed with water, and dried (1.3 g.). Chromatographic separation on neutral alumina gave 0.6 g. (45%), m.p. 192.5–194.5°. Crystallization from benzene-ligroin gave an analytical sample, m.p. 195.5–196.5°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.90; H, 6.12; N, 5.77.

4-Methoxy-2-fluorenamine. *N*-2-(4-Methoxyfluorenyl)acetamide (0.67 g.) was dissolved in hot absolute ethanol (25 ml.) and concd. hydrochloric acid (10 ml.) was added. This solution was refluxed for 7 hr. and then distilled. The residue (0.55 g.) was filtered, washed with absolute ethanol, and dried.

The amine hydrochloride (0.25 g.) was treated with dilute ammonium hydroxide (1:3) and the free amine was collected and crystallized from methanol-water, 0.2 g. (95%), m.p. 148.5–149.5°.

Anal. Calcd. for $C_{14}H_{13}NO$: N, 6.63; —OCH_3, 14.69. Found: N, 6.56; —OCH_3, 15.02.

4-Methoxyfluorene. (a) 4-Methoxy-2-fluorenamine hydrochloride (0.3 g., 0.0012 mole) was diazotized in dilute hydrochloric acid (2:3) with sodium nitrite (0.1 g., 0.0015 mole) at 0°. The solution was then treated at 0–3° with 50% hypophosphorous acid (6 ml.) for 16 hr. and the product isolated and purified, 0.08 g. (30%), m.p. 72.5–76°; mixture melting point of this material with the analytical sample obtained below, 74–77°. Infrared spectra of these two compounds are identical.

(b) 4-Aminofluorenone was converted to 4-hydroxyfluorenone by a standard procedure, m.p. 250–251.5° (reported[8] m.p. 250–251°), and methylated with dimethyl sulfate to give 4-methoxyfluorenone, m.p. 114–115° (reported[8] m.p. 114.5–115.5°). The methoxy ketone (4.2 g., 0.02 mole) was mixed with 85% hydrazine hydrate (15 ml.) and a solution of sodium hydroxide (4 g., 0.1 mole) in 2,2′-oxydiethanol (80 ml.). The mixture was refluxed at 170–180° (bath) for 2.5 hr. then at 200° (bath) for another 2.5 hr. and cooled. The reaction solution was diluted with water and extracted with ether. By evaporation of the ether there was obtained 2.6 g. of an oil which crystallized upon refrigeration. The crystalline solid was extracted with ligroin (*d.* 0.67–0.69), and recrystallized from methanol giving 1.4 g. of the product, m.p. 73.5–76°. A second crop was obtained from the ligroin extract (0.4 g.). The combined crops were recrystallized again from methanol giving 1.5 g. (39%), m.p. 76.5–77.5°.

Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.38; H, 6.01.

4-Hydroxyfluorene. This hydroxy compound was prepared from 4-aminofluorene by hydrolyzing the diazonium salt (35% from the amine), m.p. 108–109°.

(7) H. M. Duvall and E. Mosettig, *J. Am. Chem. Soc.*, 60, 2409 (1938).

(8) R. Huisgen and H. Rist, *Ann.*, 594, 137 (1955).

Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.51; H, 5.64.

7-Nitro-3,4-benzocoumarin. To a stirred mixture of 2-iodo-5-nitroanisole[9] (21 g.), activated copper powder[10] (10 g.), and methyl *o*-bromobenzoate (32.3 g., 2 equiv.), activated copper powder (60 g.) was added in small portions over a period of 1 hr. while the mixture was heated at 210–215° (bath) then at 220° for 30 min. with occasional addition of activated copper powder (10 g.). The reaction mixture was cooled, extracted with boiling chloroform, and the residual oil from the chloroform extract was hydrolyzed by refluxing for 6 hr. in a mixture of acetic acid (300 ml.), concd. sulfuric acid (200 ml.) and water (100 ml.).[11] After water dilution of the hydrolysis solution the precipitate was filtered and extracted with hot 20% sodium carbonate solution. The insoluble solid was recrystallized from toluene giving 3.5 g. (18.5%), m.p. 203–205°. Thinking at first that the carbonate extract contained the desired carboxylic acid, it was acidified and the precipitate filtered, dried (15 g.) and heated in polyphosphoric acid (150 g.) at 150–160° (oven) for 2 hr. Upon water dilution and extraction of the solid with hot 20% sodium carbonate solution there was obtained 8.5 g. of the crude carbonate insoluble product, which, after recrystallization from benzene gave 3.9 g. (20%) of the pure substance supposedly a fluorenone, m.p. 203.5–204.5°.

This, however, was identical with the carbonate insoluble product and did not appear to be a fluorenone (infrared spectrum) and is described in the following procedure.

Anal. Calcd. for $C_{13}H_7NO_4$: C, 64.73; H, 2.93; N, 5.81. Found: C, 64.61; H, 3.07; N, 6.07.

2-Methoxy-4-nitrodiphenyl-2'-carboxylic acid. The above product (2 g.) was refluxed in a solution of sodium hydroxide (1 g.) in water (20 ml.) until all the solid had gone into solution. It was cooled in an ice bath and dimethyl sulfate (1 g., 2 equiv.) were added dropwise with rapid stirring (10 min.). The ice bath was removed and the reaction mixture was stirred at room temperature for 30 min., then refluxed for 10 hr. The mixture was filtered and the filtrate carefully neutralized with concd. hydrochloric acid with rapid stirring. The solid was removed by filtration and the filtrate acidified. The precipitate was separated, recrystallized from glacial acetic acid (rhombic crystals, 0.75 g.), m.p. 225–227.5°. Two crystallizations from acetic acid–water gave an analytical sample, m.p. 229.5–230.5°.

(9) W. E. Hanford and R. Adams, *J. Am. Chem. Soc.*, **57**, 1592 (1935).

(10) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

(11) When the oil was hydrolyzed by refluxing for 7 hr. in an equal mixture of ethanol and 20% sodium carbonate solution, there was obtained a compound melting at 228–229°. A mixture melting point with 2-methoxy-4-nitrodiphenyl-2'-carboxylic acid was not depressed.

Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13; $-OCH_3$, 11.36. Found: C, 61.59; H, 4.33; N, 4.91; $-OCH_3$ 11.17.

Heating this compound in polyphosphoric acid at 150° for 2 hr. gave the compound obtained previously, 7-nitro-3,4-benzocoumarin, m.p. and mixture m.p. 203–204°.

7-Amino-3,4-benzocoumarin. 7-Nitro-3,4-benzocoumarin (5 g.) was dissolved in a boiling mixture of toluene (200 ml.) and 95% ethanol (200 ml.) and reduced in the usual way[5] with Raney nickel and hydrazine hydrate. The product amounted to 3.8 g. (86%), m.p. 239.5–240.5°. Recrystallization from chloroform gave the analytical sample.

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63. Found: C, 74.11; H, 4.35; N, 6.47.

7-Acetamido-3,4-benzocoumarin. Acetylation of the above amine with acetic anhydride in glacial acetic acid gave a quantitative yield of the acetamido compound, m.p. 298–299°.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.13; H, 4.46; N, 5.76.

3,4-Benzocoumarin. Deamination of 1 g. of 7-amino-3,4-benzocoumarin was effected with hypophosphorous acid giving 0.9 g. of the crude product which was extracted with ligroin (d. 0.67–0.69). After evaporation of the ligroin the residue was recrystallized from methanol-water yielding 0.7 g. This melted at approximately 85°, resolidified and remelted at 91.5–92.5°. A mixture with the authentic material[12] showed no melting point depression and the infrared spectrum of the product is identical with that of 3,4-benzocoumarin.

6-Nitro-3,4-benzocoumarin. Ullmann reaction of 2-iodo-4-nitroanisole[13] and methyl *o*-bromobenzoate at 210–220° (bath) for 2 hr. gave an oil which was hydrolyzed in a mixture of acetic acid and 64% sulfuric acid. The solid obtained from the hydrolysis was extracted with sodium carbonate solution, giving 9.5% of the product as insoluble solid. The carbonate extract was acidified and the precipitate heated in polyphosphoric acid at 150–160° (oven) for 2 hr. giving another 16% of the benzocoumarin, m.p. 261.5–262.5°.

Anal. Calcd. for $C_{13}H_7NO_4$: C, 64.73; H, 2.93; N, 5.81. Found: C, 64.78; H, 3.13; N, 5.89.

6-Amino-3,4-benzocoumarin. Raney nickel and hydrazine hydrate reduction[5] of the nitro compound gave a 94% yield of the amine, m.p. 190–191°.

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63. Found: C, 74.09; H, 4.05; N, 6.56.

Deamination of the amine gave 3,4-benzocoumarin,[12] as shown by melting point, mixture melting point, and infrared spectrum.

SEATTLE 5, WASH.

(12) C. Graebe and P. Schestakow, *Ann.*, **284**, 306 (1895).

(13) G. M. Robinson, *J. Chem. Soc.*, **109**, 1083 (1916).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Certain Condensations at the Terminal Methyl Group of 3-Phenylpentane-2,4-dione through Its Dipotassio Derivative Cyclizations[1]

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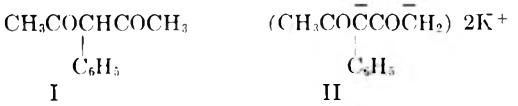
3-Phenylpentane-2,4-dione was benzylated, benzoylated, and carbonated at one of its terminal methyl groups through its dipotassio derivative, which was prepared by means of two molecular equivalents of potassium amide in liquid ammonia. The benzylation and benzoylation were best effected in the presence of pyridine, and the carbonation in ether. When the benzoylation was carried out in liquid ammonia, ether, or tetrahydrofuran, phenylacetone was obtained as by-product. This ketone evidently arose by cleavage of the original β-diketone. The benzoylation and carbonation products of the β-diketone were cyclized by means of acid to form the corresponding γ-pyrone and δ-lactone respectively. None of the possible cyclization products involving the aromatic ring was isolated.

Recently[2] acetylacetone was benzylated and benzoylated at one of its terminal methyl groups through the intermediate formation of its dipotassio derivative,[3] which was prepared by means of two molecular equivalents of potassium amide in liquid ammonia (Equation 1).

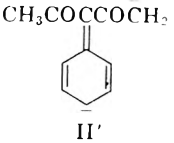
$$CH_3COCH_2COCH_3 \xrightarrow[\text{liq. } NH_3]{2KNH_2} (CH_3\bar{C}OCH\bar{C}OCH_2)2K^+ \quad (1)$$

In the present investigation a similar study was made of 3-phenylpentane-2,4-dione (I), which was converted to its dipotassio derivative II[3] in the usual manner.



I II

Like the dipotassio derivative of acetylacetone, II was obtained as a suspension in liquid ammonia. At least in this medium the latter salt was found to be less reactive than the former. This relative sluggishness of II might be due to a lower solubility in liquid ammonia and/or a lower nucleophilicity of its dicarbanion because of contributions of ring resonance structures such as II'.



II'

First, a study was made of the benzylation of II with benzyl chloride. Whereas the dipotassio salt of acetylacetone has been benzylated in 60% yield in liquid ammonia within one hour,[2] II failed to undergo appreciable benzylation under similar conditions even within two hours. However, the benzylation of the latter salt was realized under appropriate conditions, the product being the expected terminal methyl derivative III. Thus, this product was obtained in 16% yield on refluxing the reactants in ether for five hours, and in 50–62% yields on carrying out the reaction in pyridine containing a small amount of liquid ammonia (Equation 2).

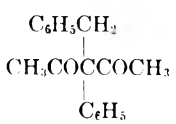
$$II \xrightarrow[\substack{\text{pyridine,}\\ \text{liq. } NH_3}]{C_6H_5CH_2Cl} CH_3COC(C_6H_5)COCH_2CH_2C_6H_5 \xrightarrow{\text{acid}} CH_3COCH(C_6H_5)COCH_2CH_2C_6H_5 \quad (2)$$

III

Although the 62% yield of III was obtained on stirring the reaction mixture for two hours at room temperature, almost as good a yield (52%) was realized when the cold reaction mixture was stopped after three minutes, during which time the suspension of II had dissolved.

Evidently the benzyl chloride did not first react with the pyridine to form the benzylpyridinium ion to serve as the alkylating agent, since, on first preparing the quaternary ammonium salt and then adding it to II in pyridine containing a small amount of liquid ammonia, none of the product III was isolated. In a blank experiment in which II was stirred with pyridine for two hours, I was recovered in 87% yield.

That the product was III and not the possible methinyl derivative IV was shown by the fact that it formed a copper chelate. IV, which has no readily



IV

enolizable hydrogen, could not yield the chelate. Moreover, the infrared spectrum of this chelate was similar to that of the starting β-diketone I, both giving a peak at 6.35 μ and no peaks in the region of 6.52–6.60 μ. This result is characteristic

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, 80, 6360 (1958).

(3) For the present purpose only dicarbanion resonance forms are considered, although other resonance forms may contribute more to the structure of the molecule.

of the chelates of such β-diketones having a 3-substituent.[4]

The structure of the product was confirmed as III by an independent synthesis involving the acylation of phenylacetone with hydrocinnamic anhydride by means of boron trifluoride (Equation 3).

$$CH_3COCH_2C_6H_5 \xrightarrow[BF_3]{(C_6H_5CH_2CH_2CO)_2O} III \qquad (3)$$

Next a study was made of the benzoylation of II with methyl benzoate. Whereas the dipotassio salt of acetylacetone has been benzoylated in 60% yield in liquid ammonia (half an hour) followed by ether (one hour), II gave only a 14% yield of triketone V in liquid ammonia (five hours) and only an 11% yield in refluxing ether (five hours). However, the reaction was realized in 47% yield in pyridine containing a small amount of liquid ammonia (Equation 4).

$$II \xrightarrow[\text{pyridine, liq. } NH_3]{C_6H_5COOCH_3} CH_3COCCOCH_2COC_6H_5 \xrightarrow{II} CH_3COCCOCHCOC_6H_5 \xrightarrow{\text{acid}} CH_3COCHCOCH_2COC_6H_5 \qquad (4)$$

(with C_6H_5 substituents; V)

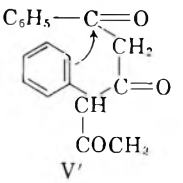
In these experiments II was treated with only one half of a molecular equivalent of methyl benzoate, since half of the dicarbanion II was involved in converting the triketone to its dicarbanion (see Equation 4). Therefore the yield of V was based on the ester.[5]

The structure of the product was established as triketone V by cyclization by means of concentrated sulfuric acid, hydrobromic acid, or polyphosphoric acid (PPA) to form the γ-pyrone VI in good yields (Equation 5).

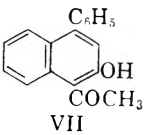
$$V \xrightarrow[HBr, \text{ or PPA}]{H_2SO_4,} \text{(CO; } C_6H_5CH; CH_2C{=}O; CH; CC_6H_5; OH\text{)} \longrightarrow \text{(H, O; } C_6H_5, CH_3, C_6H_5, OH\text{)} \xrightarrow{-H_2O} VI \qquad (5)$$

The ultraviolet absorption spectrum of the cyclic product had a maximum at 270 mμ and a log ε value of 4.33, which are in close agreement with such values for certain related γ-pyrones.[6]

There was a possibility that aromatic cyclodehydration occurred as indicated in V′ to form VII, since this type of cyclization is also known to be acid catalyzed[7] especially by polyphosphoric acid.[8] However, the γ-pyrone structure of the



V′



VII

product is supported not only by the ultraviolet spectrum mentioned above but also by the fact that it failed to give a positive enol test with ethanolic ferric chloride as should be expected if it had been a naphthol such as VII.

When the benzoylation of II with methyl benzoate was effected in refluxing tetrahydrofuran for five hours, the γ-pyrone VI was obtained directly in 39% yield. This accompanying cyclization under these conditions was unexpected, since the cyclization of 1,3,5-triketones have generally been considered to be catalyzed by acids but not by bases.[5] In fact certain bases have been employed to effect ring opening of γ-pyrones.[5] In the present experiment the γ-pyrone was apparently obtained first as a hemihydrate (based on analysis) which readily underwent dehydration on treatment with sulfuric acid. The possibility that the supposed hemihydrate was the intermediate cyclic hemiacetal shown in equation 5 was not supported by analysis.

It should be mentioned that, in the benzoylations of II in liquid ammonia, ether, and tetrahydrofuran described above, there was obtained phenylacetone in yields of 20–30%, 52%, and 30% respectively. This product evidently arose at least partly from the cleavage of the β-diketone I, since it was produced in 25% yield in a blank experiment, in which I was treated with two equivalents of potassium amide in liquid ammonia for five hours. By analogy with similar cleavages of β-diketones by aqueous alkali,[9] this cleavage would be considered to be initiated by the attack of the amide ion on one of the carbonyl groups of the free β-diketone, a low concentration of which would presumably be in

(4) See R. P. Dryden and A. Winston, *J. Phys. Chem.*, **62**, 635 (1958).

(5) See R. J. Light and C. R. Hauser, *J. Org. Chem.*, in press.

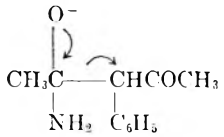
(6) See ref. 5 and P. Franzosini, G. Traverso, and M. Sanesi, *Ann. chim. (Rome)*, **45**, 128 (1955).

(7) See C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946).

(8) See C. R. Hauser and J. G. Murray, *J. Am. Chem. Soc.*, **77**, 3858 (1955); C. K. Bradsher, L. E. Beavers, and N. Tokura, *J. Am. Chem. Soc.*, **78**, 3196 (1956).

(9) See J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, 1956, p. 295.

equilibrium with the mono and dicarbanion. The resulting intermediate (VIII) would then decom-

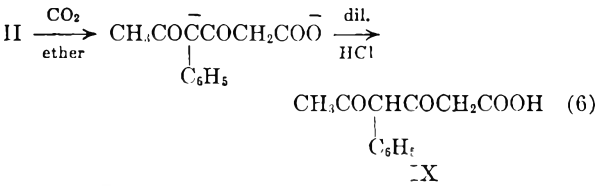


VIII

pose as indicated. Because of the presence of the phenyl group, however, it appears possible that the mono or dicarbanion might also undergo some cleavage.

Although the preferred agent for the benzoylation of II was methyl benzoate, benzoyl chloride was found to produce a 22% yield of triketone V on treating II in pyridine with benzoyl chloride in the ratio of two to one. No dibenzoylation product was isolated, and 64% of the original β-diketone I was recovered. In a previous study[10] of certain acylations of monosodio ketones with acid chlorides a three to one ratio of the reactants was preferred to the two to one ratio because of the tendency to form the diacylation product.

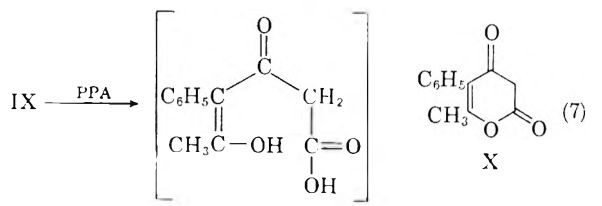
Finally II was carbonated in ether (six hours) to form the diketoacid IX in 26% yield (Equation 6).



(6)

IX

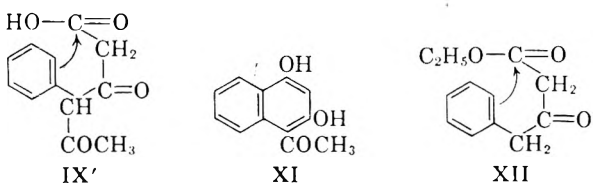
The structure of the product was established as IX by cyclization by means of polyphosphoric acid (PPA) to give the δ-lactone X in 96% yield (Equation 7).



(7)

X

It is of interest that the diketo acid IX evidently did not undergo aromatic cyclization as indicated in IX′ to form the dihydroxynaphthalene derivative XI, a type of cyclization that also is known to be acid catalyzed. For example, β-keto ester XII has been cyclized by means of sulfuric acid to form the corresponding dihydroxynaphthalene.[11]



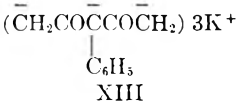
IX′ XI XII

(10) B. O. Linn and C. R. Hauser, *J. Am. Chem. Soc.*, **78**, 6066 (1956).

(11) G. Soliman and R. W. West, *J. Chem. Soc.*, 54 (1944).

Evidence that the cyclic product was the lactone X and not the dihydroxynaphthalene derivative XI was provided by the fact that the product gave a negative enol test with ferric chloride, which result would be expected for a lactone such as X but not for a dihydroxynaphthalene.[11] The infrared spectrum of the product did not have a hydroxyl peak which is further evidence that its structure is lactone X rather than dihydroxynaphthalene XI.

An attempt to prepare the tripotassio salt XIII by treating I with three molecular equivalents of potassium amide in liquid ammonia was evidently unsuccessful.



XIII

Thus, on treating the reaction mixture with one equivalent of benzyl chloride for five hours, none of the possible dibenzylation product was isolated and only a 2% yield of the monobenzylation product III was realized. Instead there were obtained a 45% yield of stilbene based on the benzyl chloride and a 25% yield of phenylacetone based on the β-diketone I, 20% of I being recovered. The purple color associated with the formation of stilbene through the self-condensation of benzyl chloride by amide ion was observed.[12] It is possible that the self-condensation of the benzyl chloride was effected by tripotassio salt XIII but it seems more likely that this reaction was brought about by the extra equivalent of amide ion over the two equivalents involved in the formation of II.

EXPERIMENTAL[13]

Preparation of dipotassio derivative II. 3-Phenylpentane-2,4-dione[14] was synthesized from phenylacetone and acetic anhydride by the boron trifluoride method.

To a stirred solution of 0.2 mole of potassium amide in 300 ml. of commercial, anhydrous liquid ammonia was added 17.6 g. (0.1 mole) of solid β-diketone I in small portions. The resulting white suspension was stirred for 15–30 min. after which the formation of 0.1 mole of the dipotassio derivative II was assumed to be complete.

Benzylation of dipotassio derivative II. A. *In ether.* To a stirred suspension containing 0.0284 mole of the dipotassio derivative II in 300 ml. of liquid ammonia was added 3.566 g. (0.0284 mole) of benzyl chloride. The liquid ammonia was

(12) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(13) Melting points (uncorrected) were taken on a Fisher-Johns melting point apparatus. Infrared spectra were produced with a Perkin-Elmer Model 21 Spectrophotometer by the potassium bromide method. Ultraviolet spectra were taken on a Warren Spectracord. Elemental analyses were by Galbraith Microchemical Laboratories, Knoxville, Tenn.

(14) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 133.

evaporated (steam bath) as an equal volume of dry ether was added. The resulting ethereal suspension was stirred for 6 hr., and then cooled. The reaction mixture was shaken with dilute hydrochloric acid, and the two layers were separated. After washing with water, the ethereal layer was dried over Drierite, and the solvent removed. The residual oil was heated *in vacuo* until low boiling material (containing some benzyl chloride and β-diketone I) was removed, and the residue was dissolved in ether. The ethereal solution was shaken with excess saturated aqueous copper acetate solution, and the resulting copper chelate was collected on a funnel. After recrystallization from ethanol there was obtained 13 g. (16%) of gray-green platelets of the copper chelate of 1,4-diphenylhexane-3,5-dione, m.p. 190–192°.

Anal. Calcd. for $C_{36}H_{34}O_4Cu$: C, 72.76; H, 5.78; Cu, 10.70. Found: C, 72.92; H, 5.57; Cu, 10.73.

Its infrared spectrum showed the following peaks: 3.3, 6.3, 3.18, 7.0, 7.2, 7.45, 7.55, 7.75, 9.35, 9.9, 9.13, 13.0, 13.2, 14.25 μ.

B. *In pyridine and liquid ammonia.* A 0.05-mole suspension of II was prepared in 100 ml. of liquid ammonia. When most of the liquid ammonia had evaporated 6.33 g. (0.05 mole) of benzyl chloride was added to the stirred suspension followed immediately by the addition of 50 ml. of dry pyridine. The dipotassio salt dissolved within 1–2 min. giving a very light red colored solution. The reaction mixture was heated gently on the steam bath until it reached room temperature and stirring was continued at this temperature for 2 hr. It was then neutralized by addition to a mixture of concd. hydrochloric acid and crushed ice to precipitate the product which was dissolved in ether. The ethereal solution was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and the solvent removed. The residual oil was distilled *in vacuo* to give 1,4-diphenylhexane-3,5-dione, collected at 136–138°, 0.25 mm., which was dissolved in ether. The ethereal solution was shaken with a saturated aqueous solution of copper acetate to precipitate 8.64 g. (62%) of the copper chelate of III, m.p. 188–190°. A mixed melting-point determination with an authentic sample of the copper chelate of III (prepared above) showed no depression. Some (1.7 g.) of the starting diketone was recovered (collected at 60–63°, 0.25 mm.), m.p. 54–57°. A mixed melting-point determination with an authentic sample of 3-phenylpentane-2,4-dione showed no depression.

The reaction was repeated, first adding the pyridine to the dipotassio derivative in a small quantity of liquid ammonia. Some of the dipotassio derivative dissolved giving a light green colored solution, the rest of the derivative remaining in suspension. On addition of the benzyl chloride all the dipotassio derivative dissolved within 1–2 min. giving a light red colored solution which was brought to room temperature and stirred for 2 hr. The product was worked up as in the previous reaction to give 3.8 g. (51%) of the copper chelate of III, m.p. 183–185° and to recover 0.8 g. (18%) of the starting diketone, m.p. 54–56°.

The above reaction was repeated except that it was neutralized 3 min. after the benzyl chloride had been added to the suspension of the dipotassio derivative in pyridine. The product was worked up as before to give 3.45 g. (52%) of diketone III collected mostly at 155–158°, 3.0 mm. The copper chelate melted at 190–192° (ethanol). Some (0.65 g.; 15%) of the starting diketone, m.p. 53–57° was recovered.

In a blank experiment 0.05 mole of II (suspension) in pyridine containing a small quantity of liquid ammonia was stirred at room temperature for 2 hr. The reaction mixture was then neutralized by addition to a mixture of concd. hydrochloric acid and ice to precipitate 3.8 g. (87%) of the starting diketone, m.p. 52–54°. A mixed melting-point determination with an authentic sample of 3-phenylpentane-2,4-dione showed no depression.

An unsuccessful attempt was made to benzylate II with benzylpyridinium chloride, prepared by heating an equimolecular mixture of benzyl chloride and pyridine to 100° for 5 min. Solid benzylpyridinium chloride (0.025 mole) was added to a 0.025 mole suspension of II in 50 ml. of pyridine containing a small amount of liquid ammonia. An immediate blood red color appeared in the reaction mixture. After stirring for 3 min. the reaction mixture was neutralized with acid to give 2 g. (45%) of the starting diketone, m.p. 54–56°.

An attempt to benzylate II in liquid ammonia was unsuccessful. After 2 hr. none of the benzylated product was isolated and a considerable amount of starting material was recovered.

Independent synthesis of β-diketone III. A mixture of 13.4 g. (0.1 mole) of phenylpropane-2-one, 56.5 g. (0.2 mole) of hydrocinnamic anhydride, and 5.15 g. (0.03 mole) of *p*-toluenesulfonic acid was saturated at 0–10° with boron trifluoride according to the method of Hauser and Manyik.[15] The product was heated *in vacuo* until low boiling material was removed. The residue was dissolved in ether and the ethereal solution was shaken with a saturated aqueous copper acetate solution to precipitate 6.7 g. (23%) of the copper chelate of 1,4-diphenyl-3,5-dione, m.p. 188–190°. A mixed melting point determination with the copper chelate of III (obtained in a previous reaction described above) showed no depression. The infrared spectra of the copper chelates of both products were identical.

The copper chelate of III was decomposed with 10% sulfuric acid, and the free diketone was dissolved in ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, the solvent removed, and the residual oil distilled *in vacuo*. 1,4-Diphenylhexane-3,5-dione was collected at 127° at 0.1 mm. and redistilled at 147–148° at 0.3 mm., $n_D^{26} = 1.5769$.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.81. Found: C, 80.96; H, 6.82.

The compound gave a cherry-red enol test with alcoholic ferric chloride.

Benzoylation of II *to form triketone* V. A. *In liquid ammonia.* To a stirred suspension of 0.1 mole of II in 300 ml. of liquid ammonia was added 6.8 g. (0.05 mole) of methyl benzoate in an equal volume of ether, and stirring was continued for 5 hr. The reaction mixture was then neutralized with an excess of ammonium chloride and the liquid ammonia was replaced with an equal volume of ether. Water was added to dissolve the salts present and the resulting aqueous and ethereal layers were separated. The ethereal layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. The residual oil was distilled *in vacuo* to give 1.3 g. of phenylacetone, n_D^{29} 1.5165, and 7.3 g. of oil, collected at 52–58°, 0.6 mm. The oil was dissolved in ether and the ethereal solution was shaken with a saturated aqueous solution of copper acetate to precipitate 4 g. (18%) of the copper chelate of the starting diketone II, identified by its infrared spectrum. The residue in the distilling flask was washed with a small quantity of ethanol and recrystallized from the same solvent to give 2 g. (14%) of yellow crystals of 1,4-diphenylhexane-1,3,5-trione, m.p. 80–82°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.11; H, 5.75. Found: C, 76.97; H, 5.58.

The compound gave a green enol test with alcoholic ferric chloride.

Its infrared spectrum showed the peaks: 6.24, 6.35–6.5 (broad), 6.7, 6.85, 7.0, 7.25, 7.8, 8.4, 8.65, 9.1, 9.2, 9.3, 9.7, 9.8, 10.1, 10.6, 11.0, 12.3, 12.9, 13.25, 13.45, 14.15, 14.5, 14.95 μ.

B. *In ether.* The experiment was repeated in ether, the procedure being essentially the same as in the previous reaction except that the liquid ammonia was replaced by an equal volume of dry ether and the reaction mixture was stirred at reflux for 5 hr. It was then cooled and neutralized with dilute hydrochloric acid. On distillation of the product *in vacuo*, 7.6 g. of phenylacetone was collected at 61°, 0.95 mm.

(15) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, 18, 588 (1953).

($n_D^{26.5}$ 1.5142; 6.7 g.) and 51°, 0.6 mm. ($n_D^{26.5}$ 1.5145; 0.9 g.), identified by infrared spectra. The residue in the distilling flask was dissolved in ether and the ethereal solution was shaken with a saturated aqueous solution of copper acetate to precipitate 4.8 g. of copper chelate which after washing with boiling ethanol had a melting point of 200–240°. The copper chelate was decomposed with 15% sulfuric acid to give, after recrystallization from ethanol 1.0 g. of 1,4-diphenylhexane-1,3,5-trione, m.p. 79–83° which did not depress the melting point of an authentic sample of the triketone (obtained in the previous reaction). A second crop of 0.5 g. of the triketone (total yield, 18%) was obtained from the filtrate.

C. *In tetrahydrofuran.* To a stirred solution of 0.9 mole of II in 400 ml. of liquid ammonia was added 6.12 g. (0.045 mole) of methyl benzoate. The liquid ammonia was replaced by an equal volume of tetrahydrofuran and the resulting suspension was boiled under reflux for 5 hr. About 300 ml. of water was added to the cooled reaction mixture which was then acidified with dilute sulfuric acid and extracted several times with ether. The combined ethereal extracts were washed with water and dried over Drierite and the solvent removed. On distillation of the residual oil *in vacuo*, 2.25 g. of oil was obtained at 36°, 0.26 mm., n_D^{25} 1.5154, which was identified by its infrared spectrum as phenylacetone. The residue in the distilling flask was washed with ether and collected on a funnel to give 4.82 g. solid, m.p. 121–125°, which on recrystallization twice from *n*-hexane (using Norit once) and finally from ethanol gave colorless prisms of 2,5-diphenyl-6-methyl-γ-pyrone (hydrated), m.p. 120–122°.

Anal. Calcd. for $C_{18}H_{14}O_2 \cdot {}^1/_2H_2O$: C, 79.66; H, 5.57. Found: C, 79.86; H, 5.77.

The compound did not give an enol test with an ethanolic solution of ferric chloride. A concd. sulfuric acid solution of the compound exhibited a bright blue fluorescence in ultraviolet light. The ultraviolet spectrum of the compound had a maximum at 270 mμ and a log ε value 4.295.

A sample of the compound was dissolved in concd. sulfuric acid, kept at 0° for 10 min. and poured onto ice water to give 2,5-diphenyl-6-methyl-γ-pyrone. It was recrystallized several times from ethanol from which it was obtained in white needles, m.p. 147–148°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.41; H, 5.38. Found: C, 82.26; H, 5.31.

The ultraviolet spectrum of the pyrone had a maximum at 270 mμ and a log ε value of 4.327. It did not give a positive enol test with alcoholic ferric chloride.

D. *In pyridine and liquid ammonia.* A 0.05-mole suspension of II was prepared in 100 ml. of liquid ammonia. When most of the liquid ammonia had evaporated, 3.4 g. (0.025 mole) of methyl benzoate was added followed immediately by the addition of 50 ml. of dry pyridine. Some of II appeared to dissolve but most of it remained in suspension. The reaction mixture was stirred at room temperature for 2 hr. and then neutralized by pouring onto a mixture of excess of concd. hydrochloric acid and crushed ice to precipitate the product which was dissolved in ether. The ethereal solution was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and the solvent removed. The residual oil was distilled *in vacuo* to give 5.8 g. (66%) of the starting diketone collected mostly at 67–68°, 0.3 mm., m.p. 45–51°. Mixed melting point determination with 3-phenylpentane-2,4-dione gave m.p. 45–54°. The distillation was stopped at 70° and the residue was recrystallized from ethanol to give 2.65 g. of yellow crystals of 1,4-diphenylhexane-1,3,5-trione, m.p. 76–80°, a sample of which did not depress the melting point of an authentic sample of the compound. A second crop, 0.6 g. of the triketone (total yield, 47%) was obtained from the ethanolic filtrate.

In another experiment 0.05 mole of II was prepared in liquid ammonia. The liquid ammonia was evaporated completely (steam bath), sweeping out the last traces of it with ether. Pyridine (50 ml.) was added to II in a small amount of ether, followed immediately by the addition of 3.51 g. (0.025 mole) of benzoyl chloride. Most of the dipotassio derivative appeared to dissolve in the pyridine, and the solution assumed a deep red color. The reaction mixture was stirred for 2 hr., then neutralized by acidification and worked up as in the previous reaction to give 5.66 g. (64%) of starting diketone collected at 60–70° at 0.22 mm., m.p. 48–53°, and 2.8 g. of copper chelate of triketone V, obtained on shaking an ethereal solution of the residue (from the distillation of the product) with a saturated aqueous solution of copper acetate. The free triketone, m.p. 81–85°, was obtained on decomposition of the copper chelate with 15% sulfuric acid. A mixed melting point determination with 1,4-diphenylhexane-1,3,5-trione showed no depression. A further 0.7 g. of the copper chelate was obtained from an intermediate fraction collected at 69–70° at 0.22 mm.

Formation of 2,5-diphenyl-6-methyl-γ-pyrone. A sample of 0.25 g. of the triketone was dissolved in 5 ml. of cold concd. sulfuric acid and cooled to 0°–10° for 10 min. and then poured on to ice water to precipitate 0.2 g. (85%) of the pyrone V, m.p. 143–144°. A mixed melting point determination with an authentic sample of the pyrone obtained above showed no depression.

Samples of the triketone were also cyclized to the pyrone, in good yields, by refluxing for 2 hr. in 45% hydrobromic acid and by heating (steam bath) in polyphosphoric acid for 1.5 hr.

Carbonation of II. A 0.0284 mole suspension of II was prepared in 300 ml. of liquid ammonia. The liquid ammonia was evaporated rapidly (steam bath) as an equal volume of dry ether was added. The resulting slurry of II was poured on to a large excess of pulverized Dry Ice. The mixture was agitated at intervals and more Dry Ice was added as needed. After 6 hr. the ether slurry was extracted twice with water and the aqueous extracts combined. The aqueous solution was cooled in an ice bath, acidified, and the resulting precipitate was collected and redissolved in aqueous sodium bicarbonate solution. After washing with ether, the cooled bicarbonate solution was acidified and the resulting precipitate was collected on a funnel, washed with water, and dried to give 1.6 g. (26%) of 4-phenyl-3,5-dioxohexanoic acid which recrystallized from hexane in white prisms, m.p. 110–112°. It gave a cherry-red enol test with ethanolic ferric chloride.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.41, H, 5.67.

Its infrared spectrum showed the following peaks: 3.3 (broad), 5.8, 6.2 (broad), 6.7, 7.15, 7.55, 8.55, 9.35, 9.95, 10.2, 10.8 (broad), 13.15 μ.

Formation of lactone. A 0.5-g. sample of the β-keto acid was dissolved in 5 ml. of polyphosphoric acid and heated on a steam bath for 1.5 hr. The solution was then poured onto crushed ice and the resulting precipitate was collected, washed with water, and dried, yielding 0.44 g. (96%) crude 4-hydroxy-6-methyl-5-phenyl-α-pyrone which was recrystallized from ethanol (Norit) to give 0.35 g. of the pure lactone, m.p. 227–229°. It did not give a positive enol test with alcoholic ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99. Found: C, 71.15; H, 4.96.

Its infrared spectrum showed the peaks: 3.4, 3.9, (broad), 6.0, 6.2, 6.5, (broad), 6.7, 7.95, 7.7, 7.8, 8.0, 8.5, 9.25, 9.35, 9.65, 9.9, 10.3, 10.8, 11.1, 12.05, 12.3, 13.0, 14.2 μ.

A sample of the β-keto acid was heated at 135° for 5 min. during which time carbon dioxide was evolved. The residue was recrystallized from petroleum ether (Dry Ice cooling) to give white crystals, m.p. 53–55°. A mixed melting point determination with 3-phenylpentane-2,4-dione showed no depression.

DURHAM, N. C.

[CONTRIBUTION OF THE CHEMISTRY RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE LABORATORY]

Metal Halide Catalyzed Hydrolysis of Trichloromethyl Compounds

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Ferric chloride, gallium chloride, and antimony pentachloride catalyze the hydrolysis of carbon tetrachloride to phosgene in high yield under mild conditions. The catalysts are dehydrated by the hydrolysis reaction, affording a convenient means of preparing anhydrous ferric and gallium chlorides. The hydrolysis of other halomethanes, trichloromethylaryl compounds, and trichloroethane is also easily accomplished with ferric chloride catalysis. A complex of the metal halide with the chlorocarbon which readily reacts with water is proposed as a highly reactive intermediate in the hydrolysis reaction.

Carbon tetrachloride and other chlorinated hydrocarbons have produced phosgene under oxidative conditions by passing the vapor mixed with air over heated metals, metal oxides and chlorides at elevated tmperatures[1b-3] and by irradiation with light of wave length 2537 Å in the presence of oxygen.[4] Phosgene from wet carbon tetrachloride in the presence of metals such as copper and iron has been observed qualitatively, but little information of the nature of the reaction was reported.[5] Recently we detected a small amount of phosgene in the reaction vessel after conducting a Friedel-Crafts type reaction involving ferric chloride as catalyst in carbon tetrachloride solvent. In subsequent experiments to determine the source of the phosgene we found that ordinary commercial pure sublimed ferric chloride and carbon tetrachloride would evolve phosgene. The apparent hydrolysis of the solvent by small amounts of water in the anhydrous ferric chloride was confirmed by the preparation of phosgene by adding water to a mixture of carbon tetrachloride and catalyst at reflux temperature. These observations prompted us to study the heretofore unreported easily catalyzed hydrolysis of carbon tetrachloride and other trichloromethyl compounds by iron, gallium, and antimony chlorides under very mild conditions.

RESULTS

The hydrolysis of carbon tetrachloride in the presence of ferric chloride was a convenient method for the preparation of phosgene, one mole of phosgene being produced for each mole of water added. In the general study comparing catalysts and their hydrates in the hydrolysis reaction, phosgene was not isolated but was swept out of the system by nitrogen into an ether solution of aniline which reacted with phosgene and hydrogen chloride. The diphenylurea which precipitated was isolated and the phosgene yields calculated. Aniline hydrochloride also precipitated in the correct ratio for the overall reaction

$$CCl_4 + H_2O \xrightarrow{FeCl_3} COCl_2 + 2HCl$$

$$COCl_2 + 2HCl + 6\,C_6H_5NH_2 \longrightarrow C_6H_5NHCONHC_6H_5 + 4C_6H_5NH_2\cdot HCl.$$

When phosgene was desired, the effluent gases were swept into cold traps and the phosgene recovered from the condensate by redistillation.

Although water may be added directly to the heterogeneous catalyst-carbon tetrachloride mixture, water in the form of the tetrahydrate of ferric chloride and lesser hydrates readily reacted. The phosgene began evolving slowly at 60°, increasing in evolution rate up to reflux temperature. The hexahydrate of ferric chloride did not undergo reaction. Antimony pentachloride and gallium chloride were also efficient in promoting carbon tetrachloride hydrolysis. With antimony pentachloride it was difficult to prevent the formation of its oxychlorides by reaction with water. Gallium chloride was easily made inactive by the addition of water in excess of the dihydrate equivalent. Neither the hydrate of aluminum chloride nor a mixture of anhydrous aluminum chloride with a small amount of hydrated catalyst would react with carbon tetrachloride.

In the course of the hydrolysis reaction the catalysts were dehydrated. For example, ferric chloride tetrahydrate, which initially was an orange oil, was observed to become crystalline, eventually having the particulate blue green anhydrous ferric chloride form. Iron oxide formation, which usually occurs when ferric chloride hydrates are heated, was not observed. Therefore, this procedure provided a simple way of preparing anhydrous ferric chloride without employing the inconvenient high temperature sublimation procedure. Gallium chloride was also dried by the hydrolytic action without formation of oxide and has been obtained in good purity.[6] Although aluminum chloride hydrate

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(1b) E. Bielsalski, *Z. angew. Chem.*, **37**, 314 (1924).

(2) B. Sjoberg, *Svensk. Kem. Tidskr.*, **64**, 63 (1952).

(3) W. B. Crummett, and V. A. Stenger, *Ind. Eng. Chem.*, **48**, 434 (1956).

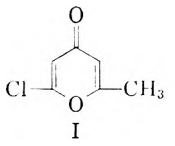
(4) E. H. Lyons, and R. G. Dickinson, *J. Am. Chem. Soc.*, **57**, 443 (1935).

(5) A. W. Doughty, *J. Am. Chem. Soc.*, **39**, 2685 (1917).

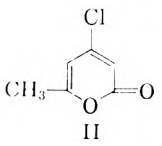
(6) W. F. Sager, George Washington University, private communication; using the procedure as described by us for ferric chloride, crude gallium chloride was dried and redistilled to give pure gallium chloride crystals.

would not react with carbon tetrachloride, its anhydrous state could be restored by refluxing its mixture with anhydrous ferric chloride until phosgene evolution stopped, yielding a reactive mixed metal halide catalyst.

Other halomethanes such as dichlorodibromomethane and bromotrichloromethane reacted with water and ferric chloride, producing low yields of phosgene and molecular bromine by-product. Chloroform was almost completely unaffected even after prolonged reaction periods, and was subsequently used as a convenient solvent for other trichloromethyl compounds which were being hydrolyzed. 1,1,1-Trichloroethane reacted very vigorously at room temperature with hydrated ferric chloride, giving acetic acid as the hydrolysis product. However, as the catalyst become anhydrous, dehydrohalogenation became predominant and vinylidene chloride was formed. In addition a small amount of a solid side reaction product was isolated. Elemental analysis indicated that it had an empirical formula $C_6H_5O_2Cl$. Infrared analysis showed a strong carbonyl, double bond, and some ring absorption. This spectrum plus qualitative organic analytical tests and melting point indicated that the compound was the same as the $C_6H_5O_2Cl$ compound isolated by Wichterle and Vogel[7] as a side product from the acetylation of vinylidene chloride by acetyl chloride in the presence of aluminum chloride. This seemed reasonable as both vinylidene chloride from dehydrohalogenation and acetyl chloride as an intermediate in the hydrolysis of the methylchloroform were present. Additionally, in a separate experiment, ferric chloride did catalyze the condensation of vinylidene chloride and acetyl chloride to the C_6 compound. Wichterle and Vogel[7] proposed that the compound was either 2-methyl-6-chloro-4H-pyran-4-one, I, or 6-methyl-4-chloro-2H-pyran-2-one, II.



I



II

From physical data obtained on the compound we prefer to consider the product to be the α-pyrone, II. The ultraviolet absorption curve in methanol gave a single peak at 300 mμ, log ϵ = 3.38, which is not consistent with the absorptions found for γ-pyrones of log ϵ 4.08–4.23 at 250–260 mμ, and corresponds to the observations of Berson[8] that the α-compounds absorb at pronouncedly longer wave lengths and lower intensities than the γ-compounds. Furthermore, it is difficult to correlate the structure of I with the fact that catalytic hydrogenation of the product in methanol[7] gave methyl caproate. Prior published work has consistently reported that only the double bonds of γ-pyrones have been reduced by catalytic hydrogenation without ring cleavage.[9]

Although previous catalytic hydrolysis reactions of aryl trichloromethyl compounds have been reported,[10] we reinvestigated the hydrolysis of these compounds because of the unusually high temperature of 150° employed to hydrolyze them by prior investigators. We found that benzotrichloride in chloroform solution reacted very vigorously with hydrated ferric chloride, cooling to 0° being necessary to moderate the reaction. Similarly, *m*- and *p*-hexachloroxylene reacted extremely vigorously at room temperature, producing nearly quantitative yields of isophthalic and terephthalic acids respectively.

DISCUSSION

In considering a mechanism for this reaction, the simplicity of the procedure indicates that an unexpected activation of the chlorinated hydrocarbons by the weak Lewis acids is a principal factor influencing the reaction. Such consideration should be consistent with the observed activity of iron, gallium, and antimony chlorides in anhydrous and hydrated states in contrast to the lack of activity by aluminum chloride. The reaction must proceed by a nucleophilic attack by water on a reactive trichloromethyl complex with the metal halide-, the overall reaction being

$$R{-}CCl_3 + HOH \xrightarrow{FeCl_3} \left[\begin{array}{c} OH \\ | \\ RCCl_2 \end{array}\right] + HCl \longrightarrow \begin{array}{c} O \\ \| \\ RC{-}Cl \end{array} + HCl.$$

Such a mechanism is not inconsistent with the lack of reaction with chloroform because in its hydrolysis the intermediate, $HOCHCl_2$, would have to split out hydrogen to form phosgene, or alternatively to split out hydrogen chloride to form the very unstable formyl chloride. No evidence of either course of reaction was found.

There remains then the question of the form of the complex and why it apparently exists in the presence of water. Consideration of its possible structure is aided by two recent explanations which were used to account for the results of kinetic measurements on Friedel-Crafts reactions. The effectiveness of ferric chloride, gallium chloride, and antimony pentachloride in promoting the hydrolysis of carbon tetrachloride is similar to the observations of Jensen and Brown,[11] who found that in benzoyl chloride solvent these chlorides catalyzed the benzoylation of toluene more effectively than did aluminum chloride. They ex-

(7) O. Wichterle and J. Vogel, *Collection Czechoslovak Chem. Commun.*, **19**, 1197 (1954).

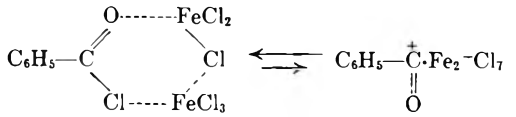
(8) (a) J. A. Berson, *J. Am. Chem. Soc.*, **75**, 3521 (1953). (b) E. R. Riegl and M. C. Reinhard, *J. Am. Chem. Soc.*, **48**, 1334 (1926).

(9) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).

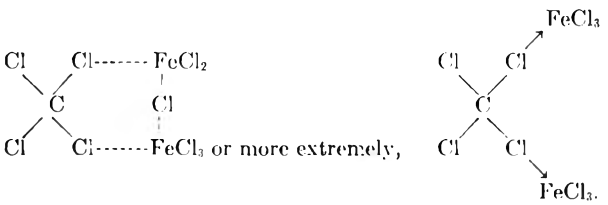
(10) W. Griehl, *Faserforsch. u. Textiltech.*, **4**, 464 (1953).

(11) F. R. Jensen and H. C. Brown, *J. Am. Chem. Soc.*, **80**, 3039 (1958).

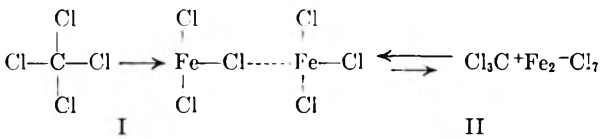
plained the observed third order kinetics by proposing the existence of a kinetically significant amount of a 1:2 compound of acyl halide with the metal halide dimer, $C_6H_5COCl:M_2X_{2n}$. Ahmad[12] has suggested that the same results could be accounted for by a cyclic intermediate or transition state in which the iron atom or gallium atom of the



second molecule of MX_n has more than eight valency electrons. More specifically in the hydrolysis reaction it seems reasonable that the halogen bridge of the metal halide dimer is opened and replaced by coordination with the chlorocarbon, forming by analogy



In essence the complex may have at least the form of I in equilibrium with a very small amount of the



very reactive carbonium ion–metal halide pair, II. That weak Lewis acids must very easily form such complexes is strongly indicated by the ability of the ferric chloride hydrate to react with the trichloromethyl compounds. Such complexes can similarly be formed by the gallium and antimony chlorides, the latter chloride having been observed by Meyer[13] to exist in a stable complex as a dimer with acetophenone. It is not presumed that a complex does not form with aluminum chloride, as many Friedel Crafts condensations involving aluminum chloride and carbon tetrachloride can be explained by proposing reactive intermediate carbonium ion complexes with the catalyst. However, in this system the affinity of aluminum chloride for water as the hydrate must be greater than its affinity for chlorine in a similar manner proposed for aluminum chloride in acylation[11] and cannot enter into reaction with carbon tetrachloride. The ability of the added anhydrous ferric chloride to dry the hydrated aluminum chloride can be explained by considering that the ferric chloride–carbon tetrachloride complex simply reacts with the water of the aluminum chloride hydrate lattice.

(12) M. S. Ahmad, G. Baddeley, and R. M. Topping, *Chem. Ind.*, 1958, 1327.

(13) K. H. Meyer, *Ber.*, 41, 2568 (1908).

EXPERIMENTAL

Hydrolysis of carbon tetrachloride. (A) Water, 4.0 g., 0.22 mole, was added dropwise to a mixture of 60 ml. of carbon tetrachloride and 8.1 g. (0.05 mole) of commercial anhydrous ferric chloride over a period of 4 hr. at reflux temperature. The gases evolved were swept by nitrogen into a spiral Dry Ice condenser equipped with a round bottom flask as receiver and then into an aqueous methanol trap. After the water addition, the catalyst-carbon tetrachloride mixture was heated an additional 2 hr. and then cooled. The Dry Ice condenser spirals contained a small amount of ice from entrained water. The product collected in the Dry Ice trap receivers was then redistilled, passing the vapor through mossy zinc to remove small amounts of hydrogen chloride. The phosgene obtained, 90% yield based on added water, b.p. 8.0, was partially distilled into 100 ml. of an ether solution containing 12 g. of aniline. The precipitate formed was collected, washed with water, and recrystallized from alcohol. The derivative, *sym*-diphenylurea, m.p. 240°, was identical with known diphenylurea as determined by mixed melting point and infrared traces.

(B) A mixture of 2.34 g. of ferric chloride tetrahydrate, m.p. 73°, (0.023 mole water) was heated with 35 ml. of carbon tetrachloride at reflux temperature for 3 hr., the efflux gases being swept into a solution of 0.1 mole of aniline in 250 ml. of ether. The precipitate was collected and dried, 12.55 g., and then slurried with water to recover the diphenylurea. This plus a small amount obtained by concentration of the ether weighed 4.00 g., 0.019 mole, 82%. The weight of aniline hydrochloride, 9.95 g., 0.077 mole, gave a ratio of the hydrochloride to diphenylurea of 4.05 *vs.* 4.00 required by theory.

In 10 hr. the same system gave 94% of phosgene as determined by diphenylurea, and about 24 hr. were required before phosgene detection was virtually nil.

Table I summarizes the results obtained by using the general procedure of (A). Where applicable, phosgene yields were determined by formation of diphenylurea derivative; otherwise the reaction products were isolated.

TABLE I

CATALYZED HYDROLYSIS OF Cl_3C— COMPOUNDS

$RCCl_3$ Compound	Solvent	Moles Catalyst	% Yield, Product[a]
CCl_4	—	0.1 $SbCl_5$	90, $COCl_2$
CCl_4	—	0.01 $GaCl_3$	89, $COCl_2$
CCl_4	—	0.01 $AlCl_3$	nil
CCl_4	—	0.01 $ZnCl_2$	nil
Cl_2CBr_2	—	0.013 $FeCl_3$	30, $COCl_2$
p-$(CCl_3)_2C_6H_4$	$CHCl_3$	$FeCl_3$	98,[b] p-$(COOH)_2C_6H_4$
m-$(CCl_3)_2C_6H_4$	$CHCl_3$	$FeCl_3$	98,[b] m-$(COOH)_2C_6H_4$
$C_6H_5CCl_3$	$CHCl_3$	$FeCl_3$	88,[c] C_6H_5COOH
CH_3CCl_3	—	$FeCl_3$	70,[b] CH_3COOH

[a] Based on water added. [b] Stoichiometric amount of water added; reaction temperature, 25°. [c] Reaction temperature, 0°.

Catalyst drying. (A) A mixture of 16.25 g. (0.1 mole) of commercial anhydrous ferric chloride and 75 ml. of carbon tetrachloride was held at reflux temperature for 24 hr. while sweeping the efflux gases from the system with nitrogen. The catalyst after this period was finely divided dark blue green to reflected light. A reddish deposit was identified as ferric chloride and not iron oxide. Similarly, gallium chloride (0.01 mole) was dried in carbon tetrachloride with nitrogen sweep until phosgene evolution was virtually nil.

(B) A mixture of 2.14 g. (0.01 mole) of aluminum chloride hexahydrate, 0.82 g. of anhydrous ferric chloride, and 40 ml. of carbon tetrachloride was heated with stirring at reflux

temperature for 24 hr. The solvent was decanted from the dried mixed catalyst, which readily catalyzed the acylation of toluene (in excess) with benzoyl chloride, 4.20 g., 0.03 mole, giving *p*-methylbenzophenone in 60% yield.

Hydrolysis of 1,1,1-trichloroethane. A mixture of 21 g. of ferric chloride (0.13 mole) containing 3 g. (0.028 mole) of water and 72 g. (0.54 mole) of 1,1,1-trichloroethane was warmed gently until hydrogen chloride began to evolve. As reaction progressed, 3.0 g. of water was added over a period of 4 hr. while maintaining a temperature of 30° by water bath. When gas evolution had ceased, the reaction mixture consisted of an organic layer and a heavier layer containing the catalyst as a black oil. The organic layer was combined with several milliliters of product distilled under reduced pressure from the catalyst oil, and then fractionated, giving 6.3 g. of acetic acid (70% yield based on water added), 5.5 g. of vinylidene chloride, and 22 g. of methylchloroform. The inorganic residue was triturated with water which turned a deep violet color, leaving out of solution a tarry oil which eventually partially crystallized. The mixture was extracted with ether, decolorized and dried. Evaporation of the ether left a crystalline deposit which when recrystallized from hexane yielded 4.9 g. of white needlelike crystals, m.p. 85–6.

Anal. Calcd. for $C_6H_5ClO_2$: C, 49.84; H, 3.49; Cl, 24.53. Found: C, 50.10; H, 3.63; Cl, 24.36.

Infrared analysis in carbon tetrachloride gave an extremely intense absorption at 1744 cm.$^{-1}$ In methanol solution, maximum absorption occurred at 300 mμ, log ε = 3.38. Qualitative organic analytical tests for carbonyl and active chlorine were negative; bromine would not add; hydrolysis by acid solution was negative.

SILVER SPRING, MD.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF RESOURCES UTILIZATION, TOKYO INSTITUTE OF TECHNOLOGY]

O-Alkyl- and Aryl-*N*,*N*-ethyleneurethanes. I. Preparation and Reaction with Amines[1]

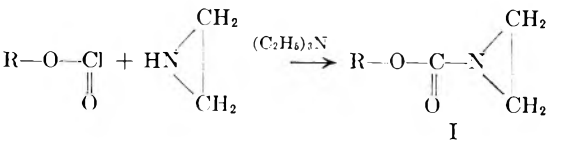
YOSHIO IWAKURA AND AIKO NABEYA

Received December 1, 1959

Several *O*-alkyl- or aryl-*N*,*N*-ethyleneurethanes were prepared, and the reactions of these urethanes with some aromatic amines were investigated. *O*-Alkyl-*N*,*N*-ethyleneurethanes gave only O-alkyl-*N*-(β-substituted ethyl)urethanes as the reaction products with amines. In the case of *O*-phenyl-*N*,*N*-ethyleneurethane, however, 1-substituted imidazolidinones-2 were obtained in addition to *O*-phenyl-*N*-(β-substituted ethyl)urethanes. This unexpected result was also observed in the reaction of other *O*-aryl-*N*,*N*-ethyleneurethanes with amines.

In our previous paper,[2] we reported the reaction of *N*-thiocarbamyl- and carbamyl derivatives of ethylenimine with several nucleophilic reagents. The results obtained there are summarized as follows: (1) *N*-phenyl- or cyclohexyl-*N'*,*N'*-ethylenethiourea is isomerized to thiazoline derivatives by heating in a high boiling solvent such as decalin or more smoothly in acids such as hydrochloric[3] or acetic. (2) The derivatives react with thiophenol giving *N*-phenyl- or cyclohexyl-*N'*-(β-phenylthioethyl)thiourea in good yields, and (3) in all cases, they show a strong tendency to polymerize by ring opening. In the case of *N*-phenyl-*N'*,*N'*-ethyleneurea, however, (1) the tendency to polymerize is not marked, and (2) isomerization to the oxazoline derivative is only observed in the reaction with picric acid, but (3) it reacts with thiophenol, hydrochloric acid, benzoic acid, and *p*-nitrobenzoic acid to give *N*-phenyl-*N'*-(β-substituted ethyl)-urea. Summarizing these results, it may be said that the substituent groups on the nitrogen of ethylenimine exert a strong influence upon the ring opening reaction of ethylenimine compounds.

We have extended the study to *N* - alkoxycarbonyl- or aryloxycarbonylethylenimine. The preparation of *O*-ethyl-*N*,*N*-ethyleneurethane (Ia) was described by Bestian.[4] In the same manner, we prepared several *O*-alkyl- and aryl-*N*,*N*-ethyleneurethanes from chloroformic acid esters and ethylenimine.



I

R = alkyl or aryl

O-Alkyl-*N*,*N*-ethyleneurethanes of lower molecular weight, in general, can be isolated by distillation and stored in a sealed tube for years without any appreciable change. But, the *O*-phenyl derivative (Id) seemed to be very unstable, especially on heating, and our attempts to isolate it by distillation under high vacuum were unsuccessful. Moreover, Id could not be crystallized by strong cooling in a Dry Ice–acetone bath. Accordingly, the purification of Id was only performed by extracting impurities with petroleum ether. *O*-*p*-substituted phenyl derivatives (Ie–Ih) were re-

(1) Presented at the annual meetings of the Chemical Society of Japan, April 1957 and April 1958, and at the symposium of Organic Synthetic Chemistry of Japan, November 1958.

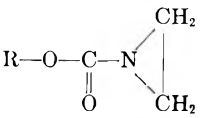
(2) Y. Iwakura and A. Nabeya, in part in the paper, *J. Chem. Soc. Japan, Pure Chem. Sect*, **77**, 773 (1956), and in part presented at the symposium of Organic Synthetic Chemistry of Japan, November 1958.

(3) Reported by S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(4) H. Bestian, *Ann.*, **566**, 210 (1950).

TABLE I

O-ALKYL- OR ARYL-N,N-ETHYLENEURETHANES (I)

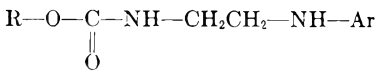


	R	B.P.,°	Mm.	M.P.,°	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	Ethyl	67–68[a]	27		$C_5H_9NO_2$						
Ib	*n*-Butyl	49–51.5	2		$C_7H_{13}NO_2$	58.72	9.15		58.81	9.31	
Ic	Cyclohexyl	80–82	2.5		$C_9H_{15}NO_2$	63.88	8.94		63.68	8.99	
Id	Phenyl				$C_9H_9NO_2$	66.24	5.56		65.80	5.77	
Ie	*p*-Tolyl			46–48	$C_{10}H_{11}NO_2$			7.91			8.00
If	*p*-Ethoxyphenyl			47–49	$C_{11}H_{13}NO_3$			6.76			6.97
Ig	*p*-Nitrophenyl			125	$C_9H_8N_4O_2$	51.92	3.87	13.46	51.52	4.06	13.66
Ih	*p*-Chlorophenyl			50–51.5	$C_9H_8ClNO_2$			7.10			7.32

[a] Lit.,[4] b.p. 60–63°/21 mm.

TABLE II

REACTION PRODUCTS OBTAINED BY THE REACTION OF O-ALKYL-N,N-ETHYLENEURETHANES WITH AROMATIC AMINES



II

	R	Ar	M.P.,°	Yield, %	Formula	N Analyses Calcd.	N Analyses Found
IIc	Cyclohexyl	Phenyl[a]	74–75	30	$C_{15}H_{22}N_2O_2$	10.68	10.82[b]
IIa′	Ethyl	*p*-Ethoxyphenyl	80–81.5	40	$C_{13}H_{20}N_2O_3$	11.10	11.10[b]
IIb′	*n*-Butyl	*p*-Ethoxyphenyl	68–69.5	30	$C_{15}H_{24}N_2O_3$	9.99	10.14
IIc′	Cyclohexyl	*p*-Ethoxyphenyl	82.5–83.5	55[c]	$C_{17}H_{26}N_2O_3$	9.14	9.36

[a] When the reaction was carried out at 75°, a small amount of higher melting compound (IVc), m.p. 127–128°, was obtained in addition to IIc. *Anal.* Calcd. for $C_{24}H_{37}N_3O_4$: C, 66.74; H, 8.64; N, 9.79. Found: C, 67.02; H, 8.58; N, 9.82. From the analytical data, IVc is considered to be *N,N*-bis(β-cyclohexyloxycarbonylamino)ethylaniline. [b] Phenyl isocyanate adducts were made as a proof of existence of amino group. From IIc: R = cyclohexyl and Ar = phenyl, m.p. 142–143°.

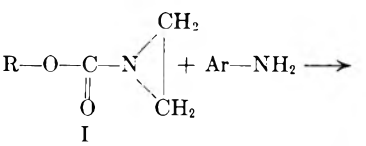
$$R{-}O_2C{-}NH{-}CH_2CH_2{-}N(Ar)CONHC_6H_5$$

Anal. Calcd. for $C_{22}H_{27}N_3O_3$: N, 11.02. Found: 10.90. From IIa′: R = ethyl and Ar = *p*-ethoxyphenyl, m.p. 129–130°. *Anal.* Calcd. for $C_{20}H_{25}N_3O_4$: N, 11.31. Found: 11.72. [c] By reaction at 75° the yield was 36% after 24 hr.

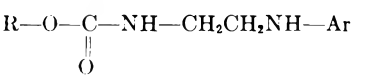
crystallized from ether or alcohol (in the case of Ig).

It was said that amines did not add to ethylenimine in an anhydrous state and without a catalyst,[5] while thiophenol[6] and phenol[7] did, giving β-substituted ethylamines. In our previous study,[2] no addition reactions of amines to the ethylenimine ring of ethylenethicurea or urea were observed.

O-Cyclohexyl-*N,N*-ethyleneurethane (Ic) gave, after standing two months with aniline at room temperature, *O*-cyclohexyl-*N*-(β-anilinoethyl)urethane (IIc) in 30% yield, while the other two *O*-alkyl urethanes (Ia and Ib) failed to give such a product under the same conditions even after one year. *p*-Phenetidine reacted with all of the three *O*-alkyl derivatives (Ia–Ic) giving *O*-alkyl-*N*-(β-*p*-phenetidinoethyl)urethanes (IIa′–IIc′) after standing one week at room temperature.



I



II

where R = alkyl and Ar = aryl

In the case of *O*-phenyl-*N,N*-ethyleneurethane (Id), the reaction proceeded rather differently. A few hours after Id was mixed with aniline at room temperature, white crystals began to separate, and soon the whole contents grew to a white mass. The melting point of the crude product ranged from 90° to 160° showing that it was a mixture. Recrystallization from alcohol gave 1-phenylimidazolidinone-2 (III), m.p. 163–164° (lit.,[3]

(5) G. I. Braz and V. A. Skorodumov, *Compt. rend. acad. sci. U.R.S.S.* **55**, 315 (1947); *Chem. Abstr.*, **41**, 6527 (1947).

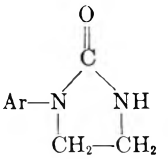
(6) G. Meguerian and L. B. Clapp, *J. Am. Chem. Soc.*, **73**, 2121 (1951).

(7) L. B. Clapp, *J. Am. Chem. Soc.*, **73**, 2584 (1951).

TABLE III

RESULTS OBTAINED BY THE REACTION OF *O*-ARYL-*N*,*N*-ETHYLENEURETHANES WITH AROMATIC AMINES

$ArNHCH_2CH_2NHCO_2Ar$ (II)

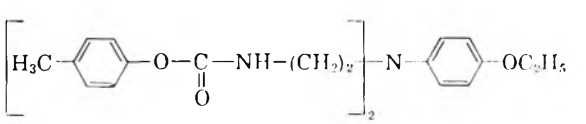

(III)

I	Ar′	Ar	React. Temp.,°	Product	M.P.,°	Yield, %	Formula	N Analyses, % Calcd.	Found
Id	Phenyl	Phenyl	0	(IId)[a]					
				III	163–164		$C_9H_{10}N_2O$	17.27	17.17
		p-Ethoxyphenyl	0	IId′	89–91	17	$C_{17}H_{20}N_2O_3$	9.33	9.39[b]
				III′	210–211	15	$C_{11}H_{14}N_2O_2$	13.58	13.42
Ie	*p*-Tolyl	*p*-Ethoxyphenyl	0	IIe′	120–122	80	$C_{18}H_{22}N_2O_3$	8.91	9.27[b]
			35	IIe′		56			
				IVe′[c]	141–142	16	$C_{28}H_{33}N_3O_5$	8.55	8.43[d]
			75	IIe′		10			
				III′		19			
				IVe′		6			
If	*p*-Ethoxyphenyl	*p*-Ethoxyphenyl	0		120–140[e]				
Ih	*p*-Chlorophenyl	*p*-Ethoxyphenyl	0	IIh′	118–120	30	$C_{17}H_{19}ClN_2O_3$	8.37	8.70
				III′		20			
			35	IIh′		20			
				III′		30			
			75	III′		73			
Ig	*p*-Nitrophenyl[f]	Phenyl	0	IIg	107–109	40	$C_{15}H_{15}N_3O_4$	13.95	13.95[b]
			35	IIg		7			
				III		>0			
		p-Tolyl	0	IIg″	108–110	20	$C_{16}H_{17}N_3O_4$	13.33	13.65[b]
			35	IIg″		6			
				III″	193–194	17	$C_{10}H_{12}N_2O$	15.90	15.91
		p-Ethoxyphenyl	0	IIg′	115–117	18	$C_{17}H_{19}N_3O_5$	12.17	12.56
			35	III′		39			

[a] II or III refers to aniline, II′ or III′ to *p*-phenetidine, and II″ or III″ refers to *p*-toluidine. [b] Phenyl isocyanate adducts were prepared. Ar—O—C(=O)—NH—CH_2CH_2—N(Ar)C(=O)NHC_6H_5.

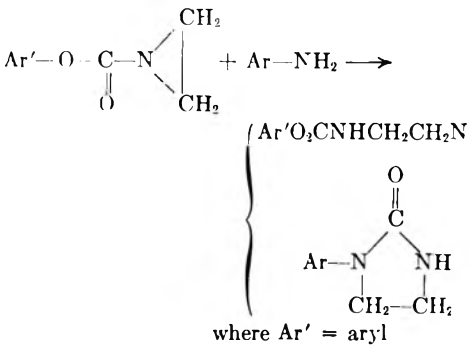
Ar′	Ar	M.P., °	Formula	N Analyses, % Calcd.	Found
Phenyl	*p*-Ethoxyphenyl	101–102	$C_{24}H_{25}N_3O_4$	10.02	9.98
p-Tolyl	*p*-Ethoxyphenyl	106–108	$C_{25}H_{27}N_3O_4$	9.69	9.81
p-Nitrophenyl	Phenyl	122–124	$C_{22}H_{20}N_4O_5$	13.33	13.52
p-Nitrophenyl	*p*-Tolyl	110 *ca.*	$C_{23}H_{22}N_4O_5$	12.90	12.86

[c] In the presence of 1% of triethylaminehydrochloride, III′ was produced in 24% yield along with IIe′ and IVe′. From this fact it may be said that a small amount of triethylaminehydrochloride which might be contained in Id as an impurity has a catalytic action on the formation of type III compounds. Accordingly, further study on the reaction of Id was abandoned. [d] IVe is considered to be *N*,*N*-bis(*β*-*p*-methylphenoxycarbonylamino)ethyl-*p*-phenetidine,



It will be discussed in the Experimental. [e] The separation was unsuccessful. [f] Toluene was used as a solvent.

m.p. 160–161°), which was identified with an authentic sample prepared from *N*-phenyl-*N'*-(β-chloroethyl)urea and alcoholic potassium hydroxide. We failed, after some efforts, to isolate another compound, presumably *O*-phenyl-*N*-(β-anilinoethyl)urethane (IId). By the reaction of Id with *p*-phenetidine at 0°, 1-*p*-ethoxyphenylimidazolidinone-2 (III'), m.p. 210–211° (lit.,[8] m.p. 211–212°), and *O*-phenyl-*N*-(β-*p*-phenetidinoethyl)-urethane (IId'), m.p. 89–91°, were obtained in 15% and 17% yield respectively.



where Ar' = aryl

To confirm these unexpected results encountered in the case of Id, we tried the same reaction using crystalline *O*-arylurethanes such as Ie–Ih, at various temperatures. The results are summarized in Table III.

These results support the general observation that the higher the reaction temperature and the greater the basicity of amine, the more type III compounds are formed (from the results of Ig, >0% for aniline, 17% for *p*-toluidine, and 39% for *p*-phenetidine at 35°), and that the greater the electron-attracting power of the substituent on the phenyl group of the urethanes the more type III compounds produced. It is a matter of interest by what mechanism type III compounds are formed under the experimental conditions. First, it may be considered that type II compounds once formed will be converted to III by the condensation reaction initiated by the intramolecular attack of nitrogen on the carbonyl carbon.

To confirm this hypothetical mechanism, we investigated the conversion of II to III. First, we heated the former in pyridine for one hour and compared the percentages of conversion with the yields of III by the reaction of ethyleneurethanes and amines in dioxane at 55°. The results are summarized in Table IV.

It is noted from Table IV that the order of conversion percentages from II to III is the same as the order of yields of III by the reaction of ethyleneurethanes and amines (NO_2 > Cl > CH_3, with respect to *p*-phenetidine).

We next investigated the conversion of II to III under nearly the same experimental conditions (of Table III). The results are summarized in Table V.

These results suggest that in some cases, type III compounds might be formed *via* type II (from Ig and aniline and from Ig and *p*-phenetidine at 35°, and from Ih and *p*-phenetidine at 75°). But this fact does not entirely support the previous mechanism. (At 75°, Ie and *p*-phenetidine gave III' in 19% yield, but IIe' did not give III' at 75° in the presence of excess *p*-phenetidine. At 0°, Ih and *p*-phenetidine gave III' in 20% yield, but IIh' did not give III' at a temperature lower than 35° in the presence of excess *p*-phenetidine.)

The second hypothetical mechanism in which *N*-aryl-*N'*,*N'*-ethyleneurea is taken as an intermediate of the reaction, must be discarded, be-

TABLE IV

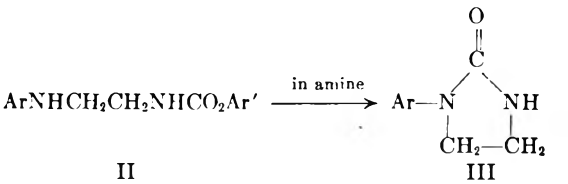
COMPARISON OF THE PERCENTAGES OF CONVERSION FROM II TO III WITH THE YIELDS OF TYPE III COMPOUNDS FROM ETHYLENEURETHANES AND AMINES

	Yield of III from I and Amine[a]		Conversion from II to III[d]	
I	Amine	Yield of III(II), %	II	Conversion, %
Ic	Aniline	0(34)[b]	IIc	0
Ic	*p*-Phenetidine	0(26)	IIc'	0
Ie	*p*-Phenetidine	18(17)	IIe'	0
Ih	*p*-Phenetidine	31(32)	IIh'	32
Ig	Aniline[c]	10	IIg	74
Ig	*p*-Phenetidine[c]	43	IIg'	83

[a] A 0.005-mole sample of I and 0.005 mole of amine in 10 ml. of dioxane (in the case of Ic, dioxane was not added) were allowed to stand at 55° for 48 hr. [b] A small amount of IVc, m.p. 127–128°, was obtained. [c] An appreciable amount of Ig was polymerized. [d] II was heated in pyridine at reflux temperature for 1 hr.

TABLE V

CONVERSION OF TYPE II COMPOUNDS TO TYPE III COMPOUNDS

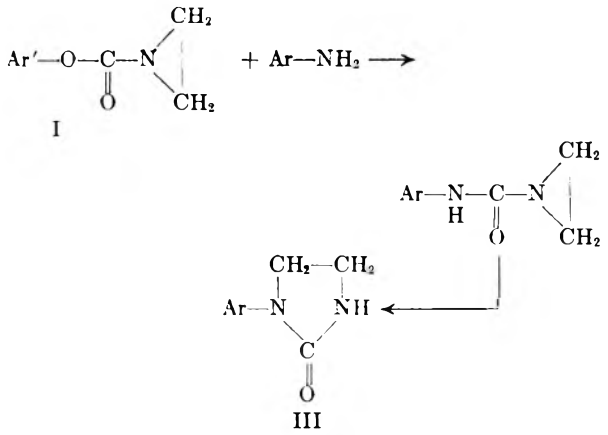


II III

Ar'	Ar	Amine	React. Temp., °	Conversion
Phenyl	*p*-Ethoxyphenyl	*p*-Phenetidine	35	0
p-Tolyl	*p*-Ethoxyphenyl	*p*-Phenetidine	35	0
p-Tolyl	*p*-Ethoxyphenyl	*p*-Phenetidine	75	0
p-Chlorophenyl	*p*-Ethoxyphenyl	*p*-Phenetidine	35	0
p-Chlorophenyl	*p*-Ethoxyphenyl	*p*-Phenetidine	75	76
p-Nitrophenyl	Phenyl	Aniline[a]	35	>0
p-Nitrophenyl	*p*-Ethoxyphenyl	*p*-Phenetidine[a]	35	83

[a] Toluene was used as a solvent.

(8) A. F. McKay, W. R. R. Park, and S. J. Viron, *J. Am. Chem. Soc.*, 72, 3660 (1950).



cause *N*-phenyl-*N'*,*N'*-ethyleneurea and *p*-phenetidine gave *N*-phenyl-*N'*-*p*-ethoxyphenylurea at 35°.

EXPERIMENTAL

All boiling points and melting points are uncorrected. Microanalyses were done by Mr. A. Kondo of Tokyo Institute of Technology. Infrared absorption spectra were determined by Miss Y. Kada of Tokyo Institute of Technology, using a Perkin-Elmer Spectrometer Model 112.

Chloroformic acid esters. Chloroformic acid esters were prepared by the usual method[9] from phosgene and alcohols or phenols. (Commercially available ethyl chloroformate was distilled; b.p. 92–93°.) The following esters, ROCOCl, were prepared: R = *n*-Butyl, b.p. 50°/32 mm., yield: 80% (lit.,[10] b.p. 137.8°/734.5 mm.; lit.,[11] b.p. 142°, yield: 35%; lit.,[12] b.p. 40–47°/16 mm., 138°/756 mm.); R = Cyclohexyl, b.p. 46–47°/2–3 mm., yield: 82% (lit.,[13] b.p. 78–83°/12 mm.; lit.,[14] b.p. 38–44°/2 mm., yield: 73%); R = phenyl, b.p. 80°/22 mm., yield: 70% (lit.,[15] b.p. 95°/20 mm.); R = *p*-tolyl, b.p. 55–56°/4 mm., yield: 82% (lit.,[16] b.p. 108°/30 mm., yield: 78–80%); R = *p*-ethoxyphenyl, b.p. 99°/5 mm., yield: 65%; R = *p*-Nitrophenyl, m.p. 80–81°, yield: 80% (lit.,[17] m.p. 81–82°); R = *p*-Chlorophenyl, b.p. 79–80°/5 mm., yield: 82% (lit.,[9a] b.p. 114°/20 mm.).

An example of the preparation of N-alkoxycarbonylethylenimine. O-Cyclohexyl-N,N-ethyleneurethane (Ic). To a solution of 10.7 g. (0.250 mole) of ethylenimine and 24.4 g. (0.241 mole) of triethylamine in 100 ml. of ether, a solution of 37.7 g. (0.232 mole) of cyclohexyl chloroformate in 20 ml. of ether was added dropwise under cooling in an ice-salt bath and with vigorous stirring. After the addition was complete, stirring was continued for 1 hr., then triethylamine hydrochloride was removed by filtration. After the ether was evaporated, the residual liquid was distilled under vacuum. The yield was 72% (28 g.).

The yield of Ia was 74%, of Ib 78%. Ib and Ic were almost unchanged after storage in a sealed tube for 2.5 years at room temperature.

Examples of the preparation of N-aryloxycarbonylethylenimine. (a) *O-Phenyl-N,N-ethyleneurethane* (Id). A 23.5-g. sample (0.150 mole) of phenyl chloroformate, 6.6 g. (0.153 mole) of ethylenimine and 15.5 g. (0.153 mole) of triethylamine were mixed by the above method keeping the temperature below −5°. After removing triethylamine hydrochloride by filtration and ether by distillation under reduced pressure, the residual liquid was submitted to distillation at 0.06 mm. When the temperature of the bath reached 60°, the liquid became very viscous. Even by strong cooling in a Dry Ice–acetone bath, it failed to crystallize. Thus the isolation of Id was unsuccessful. Washing the above liquid twice with petroleum ether, followed by distillation of the low boiling substances under reduced pressure left 13.5 g. of viscous liquid, which on standing at room temperature, solidified to a polymer-like mass.

(b) *O-p-Tolyl-N,N-ethyleneurethane* (Ie). An 8.5-g. sample (0.050 mole) of *p*-tolyl chloroformate 2.2 g. (0.051 mole) of ethylenimine, and 5.2 g. (0.051 mole) of triethylamine were brought to reaction in the preceding way. After removal of the triethylamine hydrochloride, the ethereal solution was immersed in a Dry Ice–acetone bath. White crystals precipitated. Thus 6.4 g. (72%) of Ie, melting at 45–47°, was obtained. After washing with cold water and recrystallization from ether, it melted at 46–48°. Infrared absorption spectra showed a strong absorption band at 1743 cm.$^{-1}$ (C=O).

If (yield 69%) and Ih (yield 70%) were prepared in the same manner.

(c) *O-p-Nitrophenyl-N,N-ethyleneurethane* (Ig). When a solution of *p*-nitrophenyl chloroformate was added to a solution of ethylenimine and triethylamine, in the same method mentioned in the preparation of Ic, *p,p'*-dinitrophenyl carbonate was obtained instead of ethyleneurethane, (m.p. 138–140°,[18] after recrystallization from chloroform and petroleum ether).

Anal. Calcd. for $C_{13}H_8N_2O_7$: N, 9.21. Found: N, 9.37. As the same substance was obtained by the reaction of *p*-nitrophenyl chloroformate with triethylamine, the preceding method of mixing was considered to be inadequate to the preparation of ethyleneurethane. (At the beginning of the reaction, *p*-nitrophenyl chloroformate was surrounded by a large amount of amine). Therefore, a solution of amines was slowly added to a solution of chloroformate.

To a solution of 15.0 g. (0.075 mole) of *p*-nitrophenyl chloroformate in 200 ml. of ether was added a solution of 3.3 g. (0.075 mole) of ethylenimine and 7.6 g. (0.075 mole) of triethylamine in 50 ml. of ether, keeping the temperature at about −10°. The precipitate was filtered and extracted with 200 ml. of acetone. By cooling the acetone solution in a Dry Ice–acetone bath, colorless crystals were obtained. Additional yield was obtained by treating the above residue with ice water. The combined product after being washed several times with ice water and dried, weighed 10 g. (65%), and melted at about 125°. Recrystallization from alcohol did not raise the melting point. Infrared absorption spectra of Ig showed a strong carbonyl absorption band at 1737 cm.$^{-1}$

Examples of reaction of ethyleneurethane with aromatic amines. (a) *Reaction of O-ethyl-N,N-ethyleneurethane* (Ia) *with p-phenetidine.* A 1.2-g. sample (0.01 mole) of Ia and 1.4 g. (0.01 mole) of *p*-phenetidine were allowed to stand at room temperature. After a week, crystals began separating. By adding petroleum ether (b.p. 40°–65°), the crude product was obtained. After recrystallization from ether and petroleum ether (b.p. 40°–65°) 1.0 g. (40%) of IIa' was obtained.

IIb' and IIc' were obtained in the similar way.

(9) (a) R. E. Oesper, W. Broker, and W. A. Cook, *J. Am. Chem. Soc.*, **47**, 2609 (1925); (b) F. Strain, W. E. Bissinger, W. R. Dial, H. Rudoff, B. J. DeWitt, H. C. Stevens, and J. H. Langston. *J. Am. Chem. Soc.*, **72**, 1254 (1950).

(10) F. D. Chattaway and E. Saerens, *J. Chem. Soc.*, **1920**, 708.

(11) C. S. Hamilton and C. Sly, *J. Am. Chem. Soc.*, **47**, 437 (1925).

(12) A. N. Kost, *Uchenye Zapiski, Moskovi Gosudarst. Univ. im. M. V. Lomosova*, No. **131**, 39–97 (1950); *Chem. Abstr.*, **47**, 9907 (1953).

(13) M. E. Fourneau, M. Montaigne, and J. Puyal, *Anales soc. españ. fís. y quím.*, **18**, 323 (1920); *Chem. Abstr.*, **16**, 240 (1922).

(14) J. H. Saunders, R. J. Slocombe, and E. E. Hardy, *J. Am. Chem. Soc.*, **73**, 3797 (1951).

(15) E. Barral and A. Morel, *Compt. rend.*, **128**, 1579 (1899).

(16) M. Copisarow, *J. Chem. Soc.*, 253 (1929).

(17) *Beilstein*, **6**, I, 120.

(18) J. M. A. Hoeflake, *Rec. trav. chim.*, **36**, 24 (1916).

By refluxing IIa′ with phenyl isocyanate in benzene for 2 hr. the adduct was obtained.

(b) *Reaction of O-p-tolyl-N,N-ethyleneurethane* (Ie) *with p-phenetidine at 0°.* A 1.77-g. sample (0.010 mole) of Ie and 1.37 g. (0.010 mole) of *p*-phenetidine were mixed together at 0°, and stored in a refrigerator for a week. By recrystallization of the product from ether and alcohol, 2.5 g. (80%) of IIe′, melting at 120–122°, was obtained. Infrared absorption spectra of IIe′ showed a strong carbonyl absorption band at 1701 cm.$^{-1}$, and NH band at 3349 cm.$^{-1}$.

At 35°. A 1.77-g. sample of Ie and 1.37 g. of *p*-phenetidine were mixed at 35° and stored in a thermostat kept at 35°. After 4 days, the crude product was recrystallized from alcohol. Fine needles, melting at about 140° (IVe′), were obtained, weighing 0.8 g. From the alcoholic filtrate, 1.8 g. (56%) of IIe′, melting at about 120°, was obtained.

IVe′ was recrystallized from alcohol and melted at 141–142°. Infrared absorption spectra of IVe′ showed a strong absorption band at 1695 cm.$^{-1}$, (C=O), and of NH at 3311 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.79. Found: C, 67.71; H, 6.70. Molecular weight determined by Akiya's method[19] was nearly 490. (Calcd. 491.)

By the reaction of 220 mg. of Ie and 400 mg. of IIe′ in toluene at 35°, 450 mg. of IVe′ was obtained. IVe′ reacted with diethylamine to give presumably *N,N*-bis(β-diethylureido)ethyl-*p*-phenetidine, m.p. 124–125°.

Anal. Calcd. for $C_{22}H_{39}N_5O_3$: C, 62.68; H, 9.33; N, 16.61. Found: C, 62.50; H, 9.39; N, 17.06.

At 75°. A 1.77-g. sample of Ie and 1.37 g. of *p*-phenetidine were mixed at 75°, and stored in a thermostat kept at 75°. After an hour, crystals began separating. After 24 hr., the sticky crude product (presumably polymerization of Ie took place in part) was recrystallized from alcohol. Glittering flakes, melting at 210° (III′), were obtained first. After filtration of III′, the alcoholic solution was concentrated gradually, and an additional crop of III′ was filtered, and the filtrate was again concentrated. As soon as fine needle crystals began separating, the solution was cooled gradually. IVe′ was thus obtained. After removing IVe′ and evaporating the alcohol, the residue was recrystallized from ether. Thus IIe′ was obtained.

III′ weighed 0.4 g. (19%) and melted at 210°. IVe′ weighed 0.3 g. (6%) and melted at 140°. IIe′ weighed 0.3 g. (10%) and melted at 120°.

(c) *Reaction of O-p-nitrophenyl-N,N-ethyleneurethane* (Ig) *with p-toluidine, at 0°.* To a solution of 0.54 g. (0.005 mole) of *p*-toluidine in 2 ml. of toluene, 1.04 g. (0.005 mole) of finely powdered Ig was added at 0°. Ig remained undissolved in part. The mixture was then stored in a refrigerator. After a month, ether was added to the sticky contents, when 0.2 g. of Ig was recovered unchanged. Evaporation of the solvent gave a yellow polymer-like residue from which 0.3 g. (20%) of IIg″, melting at 108–109° with brown coloration, was extracted with ether.

At 35°. To a solution of 1.07 g. (0.010 mole) of *p*-toluidine in 1 ml. of toluene, 2.08 g. (0.010 mole) of Ig was added at 35°. Ig gradually dissolved. After the mixture had stood at 35° for 4 days, the contents were recrystallized from alcohol. III″, 0.3 g. (17%) melting at 193° was obtained as flakes, and then from the filtrate, about 0.2 g. (6%) of IIg″, melting at 108° with brown coloration, was obtained.

An example of the reaction of ethyleneurethane with amine in dioxane at 55°. Reaction of O-p-nitrophenyl-N,N-ethyleneurethane (Ig) *with p-phenetidine.* A 1.04-g. sample (0.005 mole) of Ig and 0.69 g. (0.005 mole) of *p*-phenetidine in 10 ml. of dioxane were allowed to stand at 55° for 48 hr. Fine flakes, melting at 210° (III′), were filtered, and the filtrate was concentrated under reduced pressure. An additional crop of III′ was filtered and the filtrate was again concentrated to dryness. The residue was a polymer-like substance from which pure compound was not obtained by extraction with ether. The yield of III′ was 440 mg. (43%).

An example of conversion of a type II *compound to a type* III *in refluxing pyridine. O-p-Chlorophenyl-N-(β-p-phenetidinoethyl)-urethane* (IIh′). A 100-mg. sample of IIh′ was refluxed in 1 ml. of pyridine for 1 hr. After the pyridine was removed by distillation under reduced pressure, the residue was recrystallized from alcohol. A 20-mg. sample (32%) of III′, melting at 210°, was obtained first. From the filtrate, 50 mg. (50%) of IIh′ was recovered.

Conversion of IIh′ *in p-phenetidine.* A 100-mg. sample of IIh′ was allowed to stand in *p*-phenetidine, at 35° for 3 days, at 55° for 2 days, and at 65° for a day. In all cases, IIh′ was recovered unchanged. But at 70°, after a day, a small quantity of III′ was obtained with 70 mg. of IIh′.

A 340-mg. sample of IIh′ was allowed to stand in *p*-phenetidine at 75° for 24 hr. By addition of ether and alcohol, 160 mg. (76%) of III′, melting at 210°, was obtained. Attempts to recover IIh′ were unsuccessful.

Acknowledgment. The authors wish to express their thanks to Prof. Kunio Kozima for his advice in interpreting the results of infrared absorption spectra.

TOKYO, JAPAN

(19) S. Akiya, *J. Pharm. Soc. Japan*, **57**, 967 (1937).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION, PITTSBURGH PLATE GLASS COMPANY]

Reaction of Acrylamide and Pyridinium Chloride

ROSTYSLAW DOWBENKO

Received January 5, 1960

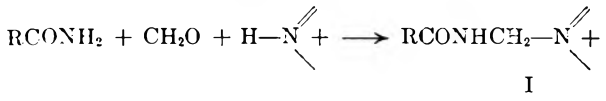
Acrylamide and pyridinium chloride react to give *N*-(2-carbamylethyl)pyridinium chloride, II, whose structure was proved by hydrogenation of it to the piperidinium analog which was synthesized independently. The reaction was extended to several other heterocyclic base salts and α,β-unsaturated amides.

Some time ago it was disclosed in a patent[1] that aliphatic amides, formaldehyde (or *N*-hydroxymethylamides) and salts of the tertiary heterocyclic bases react to form *N*-amidomethylinium salts (I). More recently, Weaver and coworkers[2] investigated this reaction in more detail

(1) A. W. Baldwin and E. E. Walker, U. S. Patent 2,146,392 (February 7, 1939).

(2) J. W. Weaver, H. A. Schuyten, J. G. Frick, Jr., and J. D. Reid, *J. Org. Chem.*, 16, 1111 (1951).

and, for stearamidomethylpyridinium chloride, demonstrated several of its transformations. In

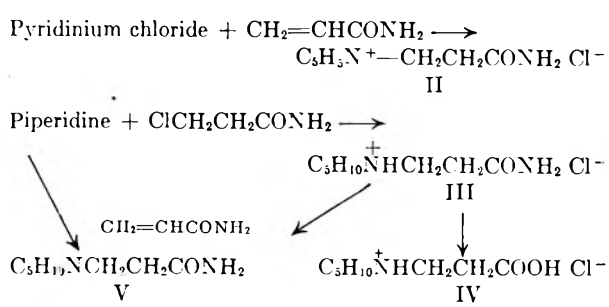


I

particular they studied reactions leading to *N*-alkoxymethylstearamides. In connection with other work done in these laboratories it was of interest to extend this reaction to acrylamide and other unsaturated amides in order to obtain compounds analogous to I. The reaction with acrylamide, however, took a different course and its examination forms the subject of this report.

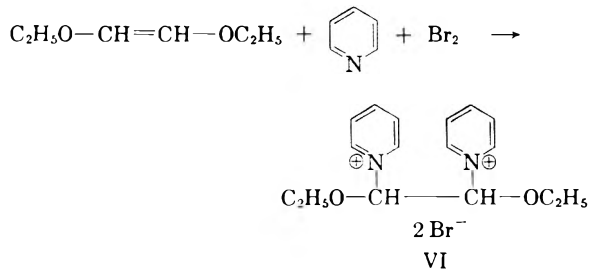
When an equimolar mixture of acrylamide, trioxane, and pyridinium chloride was heated at 65° in pyridine solution, there was obtained a solid, m.p. 197°, which was unreactive toward methanol under Weaver's conditions[2] and could be recovered from the reaction mixture. Similarly, when alcohols were substituted for pyridine as solvent, or when formaldehyde was replaced by acetaldehyde, butyraldehyde, or benzaldehyde, still the same compound was obtained. In contrast, from the reaction of *N*-(hydroxymethyl)acrylamide and pyridinium chloride under conditions[2] known to give compound I, only the starting materials were recovered. Finally, omission of the aldehyde from the reaction still gave the same compound above. These results clearly indicated that aldehydes did not participate in the reaction of acrylamide and that, therefore, *N*-acrylamidomethylpyridinium chloride was not formed, but instead an adduct of acrylamide and pyridinium chloride was obtained. This was confirmed by analysis which revealed an empirical formula $C_8H_{11}ClN_2O$ and showed no unsaturation. The latter finding was supported also by the fact that the compound was unreactive toward cyclopentadiene and did not polymerize on heating in the presence of ammonium persulfate in aqueous or methanolic solution. This information, along with the fact that the compound was salt-like (soluble in water and methanol, insoluble in ether, acetone, and hydrocarbons), led to assignment of the structure *N*-(2-carbamylethyl)pyridinium chloride (II).

Structure II was proved unequivocally by catalytic hydrogenation to a crystalline piperidinium compound (III), identical with that obtained directly from 3-chloropropionamide and piperidine.



Moreover, III could be transformed into the same free base (V) that was obtained by the addition of piperidine to acrylamide. Hydrolysis of III with hydrochloric acid yielded IV.

Addition of salts of heterocyclic bases to α,β-unsaturated carbonyl compounds has been reported on several occasions. Thus Barnett *et al.*[3] described addition of pyridine salts to benzoquinone, and Goerdeler[4] described addition of pyridine to maleic and acrylic acids from which the pyridinium betaines were obtained. The reaction of β-benzoylacrylic acid with pyridine[5] apparently is also of the same type and may be considered in effect a reaction of a pyridine salt.[6] Similarly, addition of pyridine to unsaturated compounds in the presence of halogens is also known and may be exemplified by the reaction of pyridine and 1,2-diethoxyethylene in the presence of bromine[7] in which compound VI is



VI

obtained. A recent example of interest is that reported by Heininger,[8] who found that cyanoethylation of pyrrolidinium chloride with acrylonitrile gives *N*-(2-cyanoethyl)pyrrolidinium chloride. The present case, however, apparently constitutes the first example of addition of pyridinium chloride to α,β-unsaturated amides.

In order to test the generality of this unusually facile addition of pyridinium chloride to acrylamide, several other compounds were used in the conditions under which the former gave the adduct II. The results are summarized in Table I and are

(3) E. de B. Barnett, J. W. Cook, and W. C. Peck, *J. Chem. Soc.*, **125**, 1035 (1924).

(4) J. Goerdeler, *Methoden d. org. Chemie* (*Houben-Weyl*), E. Müller, ed., Georg Thieme Verlag, Stuttgart, 1958, Vol. XI/2, p. 612. For similar reactions *cf.* also O. Lutz, *Ber.*, **43**, 2636 (1910); O. Lutz, *J. Russ. Phys. Chem. Soc.*, **47**, 1549 (1915); P. Pfeiffer and A. Langenberg, *Ber.*, **43**, 2926 (1910); P. Pfeiffer, *Ber.*, **47**, 1580 (1914); O. Lutz, R. Klein, and A. Jirgenson, *Ann.*, **505**, 307 (1933); O. Lutz and A. Krauklis, *Ber.*, **69**, 419 (1936); G. LaParola, *Gazz. Chim. Ital.*, **67**, 645 (1937); F. Bergmann, *J. Am. Chem. Soc.*, **60**, 2811 (1938); Y. Ogata, K. Tsunemitsu, and R. Oda, *Bull. Inst. Phys. Chem. Research* (Tokyo) Chem. Ed., **23**, 281 (1944); R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952); C. D. Hurd and S. Hayao, *J. Am. Chem. Soc.*, **77**, 117 (1955).

(5) J. Bougault and P. Chabrier, *Compt. rend.*, **237**, 1420 (1953).

(6) *Cf.* also N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956) for a more recent discussion of this work.

(7) H. Baganz, *Chem. Ber.*, **87**, 1373 (1954); *cf.* also ref. 3.

(8) S. A. Heininger, *J. Org. Chem.*, **22**, 704 (1957).

TABLE I

REACTION OF α,β-UNSATURATED AMIDES WITH HETEROCYCLIC SALTS[a]

Base	Amide	% Yield of Product[b]	M.P., °	Formula	Calcd. C	Calcd. H	Calcd. Cl	Calcd. N	Found C	Found H	Found Cl	Found N
Pyridine	Acrylamide	93	195–197	$C_8H_{11}ClN_2O$	51.48	5.94	19.00	15.01	51.69	5.77	18.81	14.78
									51.73	5.90	18.86	14.88
2-Methylpyridine	Acrylamide	93	171.5–172.5	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.68	6.45	17.59	14.16
									53.77	6.69	17.61	14.12
2,6-Dimethylpyridine[c]	Acrylamide	—										
Quinoline	Acrylamide	82	199–200	$C_{12}H_{13}ClN_2O$	60.80	5.54	14.98	11.84	60.24	5.62	14.92	11.59
									60.04	5.83	14.61	11.70
Isoquinoline	Acrylamide	85	210.5–212	$C_{12}H_{11}ClN_2O$	60.80	5.54	14.98	11.84	61.17	5.47	15.07	11.59
									61.06	5.54	15.19	11.73
Phenanthridine	Acrylamide	84	234	$C_{16}H_{14}ClN_2O$	67.01	5.27	12.37	9.77	67.20	5.45	12.41	9.60
									67.09	5.36	12.38	9.58
Pyridine	Methacrylamide	38	205	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.21	6.59	17.49	13.77
									53.33	6.57	17.46	13.91
Pyridine	Crotonamide	51	183–184	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.03	6.57	17.46	13.91
									53.08	6.63	17.58	14.13

[a] According to the general procedure (Experimental). [b] Before recrystallization from a mixture of methanol and acetone. [c] 2,6-Dimethylpyridinium chloride was recovered unchanged.

for the most part self-explanatory. It should be noted, however, that 2,6-dimethylpyridinium chloride was unreactive, and methacrylamide and crotonamide gave lower yields of the products. Although nonreaction of the former compound is probably due to steric hindrance in the 2,6-dimethylpyridinium ion, the lower yields from the latter are probably a real reflection of decreased reactivity of these compounds, although no attempts to obtain the best yields were made. Therefore, the facile addition of salts of heteroaromatic amines to α,β-unsaturated amides is quite general.

Several things may be said relating to the mechanism of this reaction, although no efforts were made to examine it in great detail. Two main paths appear to exist by which the reaction may proceed. The first (1) requires addition of hydrogen

$$\text{pyridinium chloride} \xrightarrow{CH_2=CHCONH_2} ClCH_2CH_2CONH_2 \xrightarrow[\text{Pyridine}]{} \text{II} \quad (1)$$

chloride to acrylamide and subsequent alkylation of pyridine with the resulting 3-chloropropionamide. That the chloroamide is not an intermediate in the reaction, however, was demonstrated when 3-chloropropionamide and pyridine under the conditions of acrylamide reaction gave a very low yield of II.[9] An alternative mode of reaction is that represented by (2).[10] As required by this scheme, the reaction appears to be acid-catalyzed, and if this were valid the mechanism (2) is to be preferred. A still more attractive mechanism is the concerted one (3) involving the formation of a quasi six-membered ring.

$$\text{pyridinium chloride} \xrightarrow{CH_2=CHCONH_2} \text{Pyridine} + {}^{+}CH_2{-}CH{=}\underset{\displaystyle OH}{\underset{|}{C}}{-}NH_2 + Cl^- \longrightarrow$$

$$Cl^- + C_5H_5\overset{+}{N}CH_2CH{=}C(OH)NH_2 \rightleftharpoons \text{II} \quad (2)$$

EXPERIMENTAL[11]

Reaction of acrylamide and pyridinium chloride in the presence of trioxane. A solution of 71 g. (1.0 mole) of acrylamide, 116 g. (1.0 mole) of pyridinium chloride, 30 g. (1.0

(9) *Cf.* F. N. Hayes, H. K. Suzuki, and D. E. Peterson, *J. Am. Chem. Soc.*, **72**, 4524 (1950), for the failure to obtain *N*-(2-bromocyclohexyl)pyridinium bromide from 1,2-dibromocyclohexane on one hand, and its facile formation from cyclohexene, bromine, and pyridine on the other.

(10) For a similar formulation of the *cis-trans* interconversion of α,β-unsaturated ketones, *cf.* P. L. Southwick and R. J. Shozda, *J. Am. Chem. Soc.*, **81**, 8298 (1959).

(11) All melting points are uncorrected. Analyses by Dr. H. W. Galbraith, Knoxville, Tennessee.

mole) of trioxane, and 1 g. of hydroquinone in 500 ml. of methanol was refluxed for 3 hr. and then was allowed to stand at room temperature overnight. On concentration of the reaction mixture, dilution with acetone, and filtration there was obtained 175 g. (93%) of a hygroscopic white powder, m.p. 181–186°. Several recrystallizations from a mixture of methanol and acetone gave an analytical sample of II, m.p. 195–197°, as large needles grown in spheres.

Anal. Calcd. for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; Cl, 19.00; N, 15.01. Found: C, 51.69, 51.73; H, 5.77, 5.90; Cl, 18.81, 18.86; N, 14.78, 14.88.

The compound was soluble in water and methanol, but insoluble in acetone, ether, ethyl acetate, and hydrocarbon solvents. It showed no unsaturation.

Substituting pyridine or butanol for methanol as solvent, or changing the aldehyde component to acetaldehyde, butyraldehyde, or benzaldehyde gave comparable yields of compound II. Omission of trioxane from the reaction mixture still gave compound II. None of II could be obtained from *N*-(hydroxymethyl)acrylamide and pyridinium chloride.

Compound II was recovered unchanged on heating with cyclopentadiene in methanol solution at 110° for 10 hr. Similarly, it was unchanged on refluxing its methanolic or aqueous solution 8 hr. in the presence of potassium persulfate.

A general procedure of reaction of heterocyclic amine hydrochlorides with α,β-unsaturated amides. To a solution of 0.20 mole of unsaturated amide and 0.20 mole of heterocyclic amine in 50 ml. of methanol is added with cooling a solution of 0.20 mole of dry hydrogen chloride in 50 ml. of methanol. The resulting solution is refluxed for 4 hr., filtered if necessary, and evaporated to about half of its original volume. It is then diluted with acetone and cooled. The product is isolated by filtration and purified by recrystallization from a mixture of methanol and acetone. Alternatively, the amine hydrochloride may be used instead of the free base and hydrochloric acid solution where more convenient.

Acrylamide and pyridinium chloride refluxing for 2 hr. gave about 85% of compound II. The yield was comparable when the reaction was run at room temperature for 1.5 hr.

Reaction of 3-chloropropionamide with pyridine. A solution of 15.8 g. (0.20 mole) of pyridine and 21.6 g. (0.20 mole) of 3-chloropropionamide[12] in 100 ml. of methanol was refluxed for 4 hr. and filtered. The filtrate was reduced in volume to 50 ml. and diluted with acetone. No crystallization occurred, but on standing at room temperature for over a week and further dilution with acetone the solution deposited 4.5 g. of a white solid, m.p. 185–188°, apparently compound II.

Reaction of acrylamide with pyridinium chloride with added acid and base. Three experiments were carried out using 0.20 mole of the two reactants in 50 ml. of methanol. The first was the control experiment. The second contained an additional 1 g. of pyridine and the third 5 ml. of concd. methanolic hydrogen chloride. All three runs were allowed to stand at room temperature for the same period of time; then they were diluted simultaneously with 20 ml. of acetone and allowed to stand in the cold for 1 hr. The quantities of the pyridinium compound II obtained were as follows (theoretical yield 37.4 g.): control, 6.2 g., m.p. 168–170°; pyridine added, 5.2 g., m.p. 168–171°; hydrogen chloride added, 9.1 g., m.p. 164–168°.

Hydrogenation of N-(2-carbamylethyl)pyridinium chloride (II). A solution of 19.9 g. (0.107 mole) of II in 200 ml. of methanol and 1.0 g. of 5% palladium on charcoal was shaken with hydrogen at an initial pressure of about 50 p.s.i. until 0.11 mole was absorbed. The catalyst was filtered off and the solvent removed almost completely. Addition of acetone caused separation of 18.5 g. of a cream-colored solid, m.p. 155–165°. Recrystallization from a mixture of methanol and acetone raised the m.p. to 172–175°, but further purification through recrystallization caused yellowing and decomposition.

When a solution of 18.5 g. (0.10 mole) of II in 200 ml. of methanol was shaken with 0.5 g. of platinum oxide until the pressure was constant, it absorbed in 1 hr. 105% of the theoretical 0.30 mole of hydrogen to give 17.0 g. (88.5%) of the piperidinium compound III. Several recrystallizations from a mixture of methanol and acetone gave the analytical sample, m.p. 196–197°.

Anal. Calcd. for $C_8H_{17}ClN_2O$: C, 49.86; H, 8.89; Cl, 18.40; N, 14.54. Found: C, 49.75; H, 9.14; Cl, 18.42; N, 14.60.

Hydrolysis of N-(2-carbamylethyl)piperidinium chloride (III). A mixture of 10.0 g. (0.052 mole) of III and 50 ml. of concd. hydrochloric acid was refluxed for 6 hr. Hydrochloric acid was removed by evaporating *in vacuo*, adding water and repeating the process several times. The residue was dissolved in a minimum amount of hot water, filtered, and allowed to crystallize. Filtration and recrystallization of the solid from aqueous acetone gave 7.0 g. (70%) of white shiny platelets of the acid IV, m.p. 210–212°. The analytical sample, prepared by several recrystallizations from the same solvent melted at 212–213°.

Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; Cl, 18.31; N, 7.23. Found: C, 50.03, 49.84; H, 8.40, 8.36; Cl, 17.05, 17.26; N, 7.04, 6.88.

Preparation of N-(2-carbamylethyl)piperidinium chloride (III). A solution of 17.0 g. (0.20 mole) of piperidine and 21.6 g. (0.20 mole) of 3-chloropropionamide[7] in 100 ml. of methanol was refluxed for 4 hr., then filtered hot and evaporated to one-half of its original volume. Acetone was added and the mixture was allowed to crystallize. Filtration gave 30.5 g. (79%) of a nearly white solid, m.p. 193–196°. The analytical sample was prepared by several recrystallizations from a mixture of methanol and acetone, m.p. 197–198°. Its melting point was not depressed by admixture of the sample prepared by the hydrogenation of *N*-(2-carbamylethyl)pyridinium chloride. Infrared spectra of the two compounds were indistinguishable.

Anal. Calcd. for $C_8H_{17}ClN_2O$: C, 49.86; H, 8.89; Cl, 18.40; N, 14.54. Found: C, 50.32, 50.35; H, 8.85, 8.87; Cl, 18.34, 18.37; N, 14.85, 14.65.

Reaction of N-(2-carbamylethyl)piperidinium chloride with potassium carbonate. A solution of 9.35 g. (0.0485 mole) of the piperidinium compound III and 6.9 g. (0.05 mole) of potassium carbonate in a mixture of 200 ml. of methanol and 30 ml. of water was allowed to stand overnight. The solvent was evaporated *in vacuo* and the residue was dried by azeotropic distillation with benzene. It was then dissolved in ethyl acetate, filtered from inorganic salts, and evaporated to obtain a straw-colored oil which crystallized on standing. Recrystallization from a mixture of ether and hexane gave 6.5 g. (86%) of nearly white, highly hygroscopic plates, m.p. 63–68°, dissolving in water to give a strongly alkaline solution. Several recrystallizations from the same solvent gave an analytical sample, m.p. 80–81°.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.89, 61.61; H, 10.15, 9.99; N, 17.63, 17.60.

Preparation of 3-N-piperidylpropionamide (V). A solution of 14.2 g. (0.20 mole) of acrylamide in 50 ml. of 1,2-dimethoxyethane was added dropwise to a stirred solution of 17.0 g. (0.20 mole) of piperidine in 50 ml. of the same solvent. After stirring at room temperature for 3 hr. the solution was refluxed for the same period of time. Evaporation of the solvent *in vacuo* gave a straw-colored solid which was recrystallized from a mixture of ether and hexane to give 22.0 g. (70.5%) of a nearly white hygroscopic solid, m.p. 77–78°. The analytical sample was prepared by several recrystallizations from ether containing a small amount of methanol and hexane, m.p. 80–81°. Its melting point was undepressed on admixture of the sample prepared by treat-

(12) H. Henecka and P. Kurtz in *Methoden d. org. Chemie (Houben-Weyl)*, E. Müller, ed., Georg Thieme Verlag, Stuttgart, 1952, Vol. VIII, p. 663.

ment of III with potassium carbonate and the infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.51, 61.34; H, 10.00, 10.19; N, 17.62, 17.59.

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SPRINGDALE, PA.

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

The Synthesis of Some Derivatives of Methioprim and Related Pyrimidines[1,2]

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Methioprim (2-methylthio-4-amino-5-hydroxymethylpyrimidine) was used for the preparation of several 2-substituted 4-amino-5-hydroxymethylpyrimidines. The conversions were conveniently accomplished by oxidation of the acetate of methioprim to 2-methanesulfonyl-4-amino-5-acetoxymethylpyrimidine which was subsequently treated with ammonia or amines to give the 2-substituted pyrimidines. The preparation of several esters and amides of methioprim and several sulfones of related pyrimidines are also described.

Interest in 2-methyl-4-amino-5-hydroxymethylpyrimidine (toxopyrimidine), 5-hydroxymethylcytosine, and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I, methioprim)[2] has led to the synthesis of analogs of these substances in several laboratories. Emphasis has been centered on 2-substituted-4-amino-5-hydroxymethylpyrimidines, some of which have been used as intermediates in the synthesis of thiamin analogs. Usually these 5-hydroxymethylpyrimidines are prepared by reduction of the corresponding 5-carbethoxypyrimidines with lithium aluminum hydride[2,6] although other routes have been useful. For example, 5-hydroxymethyluracil and related compounds have been prepared by the addition of formaldehyde to the pyrimidones.[7]

The discovery by Guthrie[8] of the unusual antimetabolite activity of I has led to a search for related, more potent compounds for experimental cancer chemotherapy. 2-Trifluoromethyl-, 2-methylthio-4-arylamino-5-carbethoxy-, and 2-methylthio-4-arylamino-5-hydroxymethylpyrimidines have been prepared.[6c,9a,b,c]

The present report deals mainly with the synthesis of derivatives from I. The availability of this compound[10] has made it an attractive intermediate for the synthesis of other 2-substituted-4-amino-5-hydroxymethylpyrimidines. The presence of the 5-hydroxymethyl group in the starting material avoids its repeated formation. In addition, the presence of the 2-methylthio group suggested facile substitution at this position. Sprague and Johnson[11] have shown that the oxidation of 2-alkylthiopyrimidines to 2-alkanesulfonylpyrimidines followed by amination or hydrolysis is a convenient route to 2-aminopyrimidines, 2-alkoxypyrimidines, and 2-pyrimidones. Chlorine water was used as the oxidizing agent. This method is often effective in cases where direct substitution of amino for alkylthio is difficult. However, failures have been noted.[12]

We were unable to substitute amino- or alkylamino- for methylthio- in I. Furthermore, it was not possible to isolate 2-methanesulfonyl-4-amino-5-hydroxymethylpyrimidine (V) from a reaction mixture of I and chlorine water. When the hydroxyl group was protected by acetylation (II), the sulfone (III) could be prepared by oxidation with chlorine. This sulfone was readily converted to V, 2,4-

(1) Supported in part by a Grant, CY-2857, from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) For leading references see T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1958).

(3) In part from the dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Buffalo.

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(6) (a) A. Dornow and G. Petsch, *Ann.*, **588**, 45 (1954). C. S. Miller, *J. Am. Chem. Soc.*, **77**, 752 (1955). (b) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956). (c) J. A. Barone, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, **24**, 198 (1959).

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(9) (a) J. F. Holland, R. Guthrie, F. Sheehe, and H. Tieckelmann, *Cancer Research*, **18**, 776 (1958). (b) J. F. Holland, R. Guthrie, H. Tieckelmann, and R. Cuddihy, *Cancer Research Suppl.*, **18**, 335 (1958). (c) E. Peters, J. F. Holland, B. Bryant, H. J. Minnemeyer, C. Hohenstein, and H. Tieckelmann, *Cancer Research* **19**, 729 (1959).

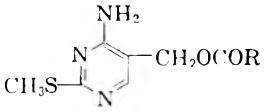
(10) We thank Dr. Stanton Harris, Merck, Sharp & Dohme, Inc. for a generous sample of methioprim.

(11) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 2252 (1935); **58**, 423 (1936) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

(12) K. J. M. Andrews, N. Anand, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 2490 (1949).

TABLE I

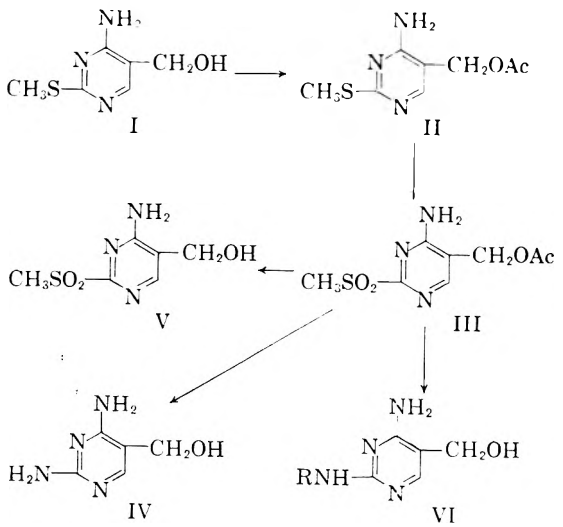
ESTERS OF METHIOPRIM



R	Yield, %	M.P.	Formula	Analyses	
				Calc., %	Found, %
CH_3 (II)[a]	94	137–138	$C_9H_{11}N_3O_2S$	C 45.0	44.8
				H 5.2	5.1
C_2H_5	64	159–161	$C_{10}H_{13}N_3O_2S$	C 47.6	48.1
				H 5.8	6.0
				S 14.1	13.7
$(CH_2)_2CH_3$	47	110–111	$C_{11}H_{15}N_3O_2S$	S 13.3	13.5
$(CH_2)_2COOH$[b]	47	184–187	$C_{11}H_{13}N_3O_4S$	C 44.3	44.2
				H 4.8	4.8
				S 11.8	11.3
C_6H_5[c]	84	186–187	$C_{13}H_{13}N_3O_2S$	N 15.3	15.0

[a] 50 ml. of ethyl acetate used, recrystallized from carbon tetrachloride. [b] 0.7 g. of succinic anhydride in 25 ml. ethyl acetate added to I in ethyl acetate, recrystallized once from dioxane and once from ethyl alcohol. [c] 13.5 g. of benzoic anhydride and 2 g. of methioprim in 100 ml. of ethyl acetate used. After evaporation of solvent the residue was extracted with 10% hydrochloric acid. The extract was treated with sodium hydroxide to precipitate product, which was recrystallized from methanol.

diamino-5-hydroxymethylpyrimidine (IV), and 2-substituted aminopyrimidines (VI).



The properties of IV were different from those previously reported. Huber[13] has recorded a melting point of 265° with decomposition and a picrate which decomposed at 244–246°. Our compound (IV) melted at 231–234° with decomposition and formed a picrate which decomposed at 243–244°. A discussion of the structure of these substances appears in the succeeding paper.[14]

Peters, *et al.*,[9c] have prepared some 2-methylthio-4-arylamino-5-carbethoxypyrimidines and have found that members of this series inhibit the growth of mouse tumors. The conversion of two of these pyrimidines to 2-methanesulfonyl- and 2-aminopyrimidines has been accomplished. In general, pyrimidines with electron-attracting groups on the 5- position were converted to sulfones in good yields.

In addition to the acetate, other esters of I have been prepared. A rapid disappearance of I in serum and a poor recovery in urine has been noted.[15] Experiments with rat liver homogenates showed that, in this system, I is oxidized to the corresponding 5-formylpyrimidine and 5-pyrimidinecarboxylic acid.[16] These observations and the inactivity of I in clinical trials[15] has suggested that esters, which are less susceptible to oxidation, might be better candidates. The hydrochloride of II was prepared from I and acetyl chloride using the method of Bretschneider.[17] The amides of esters of I were relatively difficult to prepare requiring an excess of the anhydride and long reflux.

EXPERIMENTAL[18,19]

Esters of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I). Three ml. of the anhydride was added to a solution of 1.0 g. of I in 100 ml. of ethyl acetate. After refluxing for 2 hr., the solvent was removed under reduced pressure. The esters were recrystallized from toluene after decolorizing with Norit. Yields given in Table I are for recrystallized materials.

2-Methylthio-4-amino-5-acetoxymethylpyrimidine hydrochloride. This compound was prepared from I by the method developed for esters of aminoalcohols by Bretschneider[17] in 69% yield. It was recrystallized from methanol-ethyl acetate, m.p. 155–159°.

(13) W. Huber, *J. Am. Chem. Soc.*, **65**, 2222 (1943).

(14) H. Tieckelmann, R. Guthrie, and J. G. Nairn, *J. Org. Chem.* **25**, 1257 (1960).

(15) J. F. Holland and R. Guthrie. Unpublished results.

(16) I. J. Slotnick, A. W. Spears, and H. Tieckelmann, *Proc. Soc. Exptl. Biol. Med.* **102**, 239 (1959).

(17) H. Bretschneider, *Monatsh.*, **76**, 368 (1947); H. Bretschneider, K. Biemann, W. Koller, and W. Sachsenmaier, *Monatsh.*, **81**, 31 (1950).

(18) Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected.

(19) Analyses by Geller Microanalytical Laboratories, Bardonia, N. Y.

Anal. Calcd. for $C_8H_{12}N_3O_2SCl$: C, 38.5; H, 4.8; S, 12.8. Found: C, 38.1; H, 5.0; S, 13.0.

When dissolved in water and treated with 10% ammonium hydroxide the free amino ester was formed, m.p. 134–137°. A mixed melting point with 2-methylthio-4-amino-5-acetoxymethylpyrimidine (II) prepared from I and acetic anhydride gave no depression.

2-Methylthio-4-acetamido-5-acetoxymethylpyrimidine. Acetic anhydride (150 ml.) was added to 5.0 g. of I dissolved in 500 ml. of ethyl acetate. After reflux for 15 hr. the solvent was removed under reduced pressure. The dry solid was recrystallized from carbon tetrachloride to give 4.3 g. (58%), m.p. 135–138°. The analytical sample, m.p. 141–142°, was obtained by crystallizing from carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{13}N_3SO_3$: C, 47.0; H, 5.1; S, 12.6. Found: C, 47.4; H, 5.0; S, 12.3.

2-Methylthio-4-propionamido-5-propionoxymethylpyrimidine. Eight ml. of propionic anhydride was added to a solution of 1.7 g. of I dissolved in 50 ml. of ethyl acetate. After reflux for 15 hr. the solvent was removed under reduced pressure. The residue was mixed with methanol and after removal of the methanol, the residue was crystallized from ethyl alcohol and water to give 1.85 g. (65%). The analytical sample, m.p. 93–94°, was recrystallized again from alcohol-water.

Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: N, 14.8. Found: N, 14.9.

2-Methylthio-4-n-butyramido-5-n-butyroxymethylpyrimidine. Butyric anhydride (20 ml.) was refluxed with 1.7 g. of I and 40 ml. of ethyl acetate for 22 hr. The solvent and some excess anhydride were removed under reduced pressure. Alcohol was added to the oil and removed under reduced pressure. This procedure was repeated twice with benzene. On standing, the oil solidified. After washing thoroughly with 3% hydrochloric acid, the residue was crystallized from ethyl alcohol–water to give 0.95 g. (30%) of a white solid, m.p. 76–86°. The analytical sample, m.p. 88–89°, was recrystallized from ligroin–ether.

Anal. Calcd. for $C_{14}H_{21}N_3O_3S$: N, 13.5. Found: N, 13.3.

2-Methanesulfonyl-4-amino-5-acetoxymethylpyrimidine. (III). Five g. of II was dissolved in 300 ml. of 1% hydrochloric acid. The solution was cooled to 1–2° and chlorine passed in rapidly for 10 min. Seven g. of sodium bisulfite was added with stirring and the temperature maintained below 5°. After stirring for an additional 5 min. the white precipitate was filtered, washed thoroughly with ice cold water, and immediately dried at room temperature under vacuum. The dried solid was recrystallized from dry isopropyl alcohol to give 3.1 g. (53%) of III, m.p. 153–154°. The analytical sample, m.p. 154–155°, was recrystallized from dry isopropyl alcohol.

Anal. Calcd. for $C_8H_{11}N_3O_4S$: C, 39.2; H, 4.9; S, 13.1. Found: C, 39.4; H, 5.1; S, 12.6.

Chlorination of 5.0 g. of II in 300 ml. of 5% hydrochloric acid for 17 min. at 3° gave a yellow precipitate, which was washed with water and a little 10% sodium bisulfite solution. The precipitate changed to a gum which crystallized on standing in water. It was crystallized from water and gave a compound which melted at 217–220° in 15% yield. The analysis corresponded to 4-amino-5-acetoxymethyl-5-chloro-5,6-dihydro-6-hydroxypyrimidine-2(1H)-one.

Anal. Calcd. for $C_7H_{10}N_3O_4Cl$: C, 35.7; H, 4.3; Cl, 15.1. Found: C, 35.6; H, 3.8; Cl, 14.7.

Chlorination of 1 g. of II in 60 ml. of 5% hydrochloric acid cooled to below 5° for 75 min. 0.95 g. of a compound, m.p. 191–192°, crystallized from water, which corresponded to a 4-amino-2,5-dichloro-5,6-dihydro-6-hydroxy-5-hydroxymethylpyrimidine.

Anal. Calcd. for $C_5H_7N_3O_2Cl_2$: C, 28.3; H, 3.3; Cl, 33.5. Found: C, 28.3; H, 2.8; Cl, 33.9.

2-Methanesulfonyl-4-amino-5-hydroxymethylpyrimidine (V). Nine-tenths g. of III was dissolved in 18 ml. of warm methanol. After the addition of 9 ml. of concd. ammonium hydroxide, the solution was allowed to stand at room temperature for 2 hr. and then cooled overnight at 0–5°. The solvent was removed at reduced pressure and the residue recrystallized from isopropyl alcohol and methanol to give 0.48 g., m.p. 157–159° (64%) of V. The analytical sample from isopropyl alcohol and methanol melted at 172–173°.

Anal. Calcd. for $C_6H_9N_3O_3S$: C, 35.5; H, 4.5. Found: C, 35.9; H, 4.5.

2,4-Diamino-5-hydroxymethylpyrimidine (IV). Five g. of III was dissolved in 75 ml. of methanol and saturated with ammonia at 0° in a Carius tube. After heating to 110–115° for 9 hr. the mixture was cooled to 0° and filtered to give 1.5 g. (53%), m.p. 218–223° of VI. The analytical sample, m.p. 231–234°, was recrystallized from methanol.

Anal. Calcd. for $C_6H_8N_4O$: C, 42.9; H, 5.8; N, 40.0. Found: C, 43.1; H, 5.9; N, 39.8.

2-Methylamino-4-amino-5-hydroxymethylpyrimidine. Methylamine was absorbed in 30 ml. of absolute methanol containing 2 g. of III in a Carius tube until the total volume was 50 ml. After heating for 12 hr. at 110–115°, the solvent was removed thoroughly under reduced pressure. Acetone was added to the resulting oil and the mixture cooled to 0–5°. A solid formed which was dissolved in 4 ml. of 5% sodium hydroxide and extracted four times with 10-ml. portions of acetone. The product, after removal of the acetone, weighed 0.89 g. (71%), m.p. 135–137°. The analytical sample was recrystallized from isopropyl alcohol and melted at 142–144°.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.7; H, 6.5; N, 36.3. Found: C, 47.0; H, 6.5; N, 36.1.

2-Ethylamino-4-amino-5-hydroxymethylpyrimidine. This compound was prepared by the same method used for the methyl homolog. Acetone treatment was omitted. Ether was used as the extraction solvent. The crude product, after removal of the ether, and after crystallization took place, was washed with ethyl acetate and recrystallized from chloroform. One g. of III gave 0.22 g. (32%) of 4-amino-2-ethylamino-5-hydroxymethylpyrimidine, m.p. 133–136°.

Anal. Calcd. for $C_7H_{12}N_4O$: N, 33.3. Found: N, 33.2.

2-n-Propylamino-4-amino-5-hydroxymethylpyrimidine. One g. of III in 13 ml. of methanol and 13 ml. of *n*-propylamine was heated at 115–120° for 19 hr. After removing the solvent under reduced pressure the oil was dissolved in 4 ml. of 5% sodium hydroxide. Ether was used as the extraction solvent. After dissolving in ethyl acetate the pyrimidine was precipitated with ligroin, 0.4 g. (54%). The analytical sample, m.p. 114–117°, was crystallized from benzene.

Anal. Calcd. for $C_8H_{14}N_4O$: N, 30.8. Found: N, 30.6.

2-Methylthio-4-amino-5-carboxamidopyrimidine. Ten g. of 4-amino-2-methylthio-5-cyanopyrimidine[20] was added to a boiling solution of 1 l. of 0.1*N* sodium hydroxide. After refluxing 15 min., the mixture was cooled rapidly and cooled overnight in the refrigerator. The amide was filtered and washed with cold water to give 8.9 g. (80%), m.p. 280–281°. Recrystallized from methanol, the analytical sample melted at 280–281°.

Anal. Calcd. for $C_6H_8N_4OS$: C, 39.1; H, 4.4; S, 17.4. Found: C, 39.4; H, 4.3; S, 17.1.

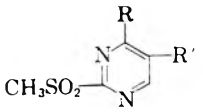
2-Methanesulfonylpyrimidines. 2-Methylthio-4-amino-5-cyanopyrimidine,[20] 2-methylthio-4-amino-5-pyrimidinecarboxamide, 2-methylthio-4-*o*-chloranilino-5-carbethoxypyrimidine,[9c] 2-methylthio-4-*o*-bromoanilino-5-carbethoxypyrimidine,[9c] and 2-methylthio-4-chloro-5-carbethoxypyrimidine[9c] were converted to the corresponding 2-methanesulfonylpyrimidines (Table II). The 2-methylthiopyrimidine (0.5 g.) was dissolved or suspended in 60 ml. of 1% hydrochloric acid and cooled to 0–5°. Chlorine was passed in rapidly for 5–10 min. After treatment with sodium bisulfite the precipitated sulfone was filtered while cold, washed with cold water, and dried thoroughly under vacuum. The sulfone was crystallized from isopropyl alcohol.

2-Amino-4-o-chloroanilino-5-carbethoxypyrimidine. 2-Meth-

(20) Steve G. Cottis, M. A. thesis, University of Buffalo, 1959.

TABLE II

2-METHANESULFONYLPYRIMIDINE



R	R′	Yield, %	M.P.	Molecular Formula	Analyses	
					Calcd.	Found
NH_2	CN	67[a]	211–214	$C_6H_6N_4O_2S$	N 28.3	28.6
NH_2	$CONH_2$	29[b,c]	216–218	$C_6H_8N_4O_3S$	N 25.9	25.4
o-NHC_6H_4Cl	—CO_2Et	87	180–181	$C_{14}H_{14}N_3O_4SCl$	N 11.8	11.6
o-NHC_6H_4Br	—CO_2Et	92	172–174	$C_{14}H_{14}N_3O_4SBr$	N 10.5	11.0
Cl	—CO_2Et	94[b]	129–130	$C_8H_9N_2O_4SCl$	N 10.6	10.1

[a] Oxidation solvent was 60 ml. of 5% hydrochloric acid for 0.5 g. of the pyrimidine. Recrystallization solvent was ethyl acetate. [b] Oxidation solvent was 30 ml. of 1% hydrochloric acid. [c] Recrystallization solvent was 95% ethyl alcohol.

ylsulfonyl-4-*o*-chloroanilino-5-carbethoxypyrimidine (0.5 g.) was heated in 15 ml. of absolute methanol. Ammonia was passed in for 10 min. while the mixture was still warm. After standing at room temperature for 12 hr the mixture was allowed to cool to 0–5° for 12 hr. and filtered to give 0.3 g. (73%), m.p. 209–213°. The analytical sample, m.p. 215–216°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Cl$: C, 53.3; H, 4.5; N, 19.1. Found: C, 53.5; H, 4.6; N, 19.1.

2-Amino-4-o-bromoanilino-5-carbethoxypyrimidine. This compound was prepared by the method used for the 4-*o*-chloroanilino- analog. The yield was 0.3 g. (71%), m.p. 204–211° of 2-amino-4-*o*-bromoanilino-5-carbethoxypyrimidine from 0.5 g. of sulfone. The analytical sample, m.p. 213–214°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Br$: N, 16.6. Found: N, 16.8.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM HOFFMANN-LA ROCHE, INC.]

Pyridindene Derivatives. IV. Alkylated Pyridindenes

JOHN T. PLATI AND WILHELM WENNER

Received December 14, 1959

The reaction of crotonophenone and methylamine yielded a condensation product which on treatment with alkali gave 1,2,6-trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III). Dehydration followed by partial reduction gave 1,2,3-trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI). The reaction of methylmagnesium iodide with 1-methyl-3-benzoyl-4-phenyl-4-hydroxypiperidine (VIII) yielded a diol (IX) which on dehydration gave 2,9-dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XI).

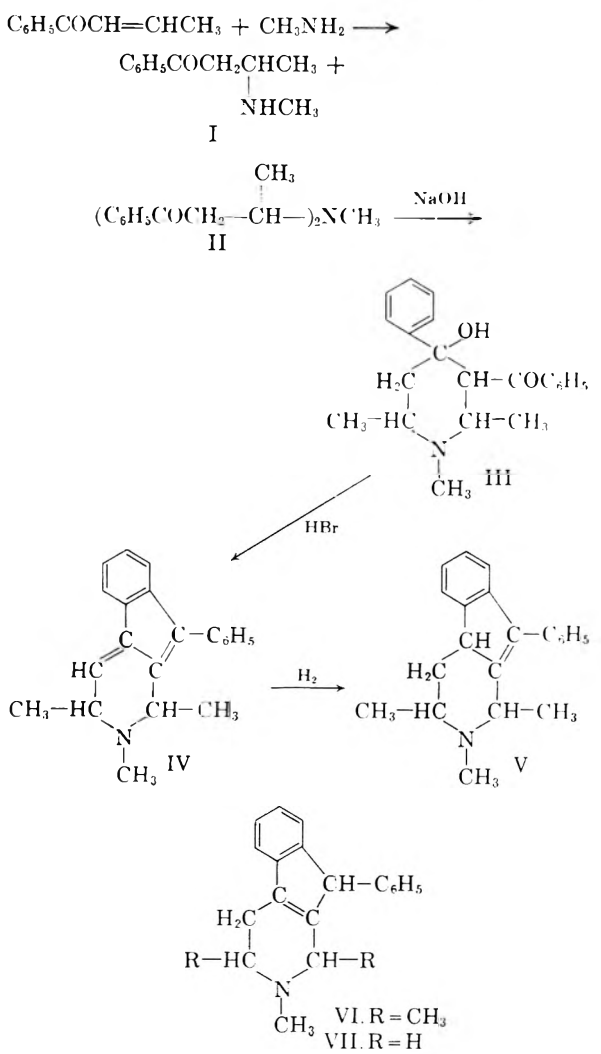
This paper deals with an extension of our earlier work on pyridindene derivatives. Our first concern was the introduction of alkyl groups into the hetero ring in order to ascertain the antihistamine properties of the resulting compound. A type of Mannich reaction between acetophenone, methylamine, and acetaldehyde was briefly considered for the preparation of the starting material, but this scheme was discarded in favor of the reaction between crotonophenone and methylamine.

When the reaction was allowed to proceed for a relatively short period of time, it was possible to isolate the product (I) formed by the addition of one mole of methylamine to one mole of crotonophenone. The bis product (II) may also have been formed, but efforts at isolation were not pursued vigorously, since our primary concern was to obtain the piperidine derivative (III). It was reasoned after our earlier work[1] that this compound could be obtained not only by ring closure of the bis product (II) but also by disproportionation of the mono-addition product (I). The mother liquor from (I) should contain both products, with the bis product predominating after a prolonged reaction time. Accordingly, treatment with alkali should yield the piperidine (III), and actually this expectation was realized. By refluxing with hydrobromic acid, the piperidine (III) underwent dehydration and ring closure to give the pyridindene (IV). On hydrogenation, a mixture of (V) and (VI) was apparently obtained. The (VI) base was obtained by purification through the thiocyanate salt, followed by prolonged treatment with alkali. It is noteworthy that the ultraviolet spectrum (Curve 1) of the VI base is almost identical with that of VII.[2] The treatment with alkali was

(1) J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).

(2) J. T. Plati and W. Wenner, *J. Org. Chem.*, **20**, 1413 (1955).

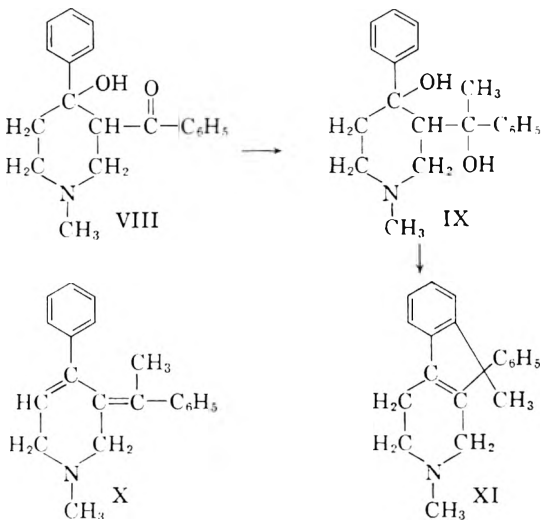
intended to cause isomerization of V into VI just as in the previously described parent series.



The second part of our investigation was aimed at the preparation of a pyridindene molecule containing an alkyl group as well as a phenyl group in the 9-position, as in formula XI. The type of isomerization, represented by a shift of the ethylenic linkage from its position in V to its position in VI, has been shown to be readily reversible, and, in fact, in the case of VII mere salt formation was sufficient to cause a shift in either direction.[2] Maximum antihistamine activity is associated with the double bond in the hetero ring. The shifting of the double bond to the 9- position results in a considerable reduction of antihistamine activity. In XI we have a compound of particular interest, because shifting of the ethylenic linkage to the 9-position is blocked. In addition, the spectrum of such a compound should confirm our earlier assignments of structure.

To obtain the compound XI, the piperidinol (VIII) was utilized as a starting material. Reaction with methylmagnesium iodide gave the diol (IX). Dehydration with the loss of two molecules of water was effected by treatment with hydrobromic acid. Two formulas, (X) and (XI), were considered for the structure of the dehydration product. Its ultraviolet absorption spectrum (Curve 2) strongly resembles that of the pyridindene VI (Curve 1). In any event, the spectrum of the conjugated diene (X) would be expected to be completely different. Accordingly, structure XI was assigned to the dehydration product.

In our earlier work (2), it was shown that deviations from the structure of the parent compound (VII) led to compounds with lower antihistamine activity. In the case of compounds VI and XI, a significant antihistamine activity was found. This finding is quite compatible with the structures assigned.



EXPERIMENTAL[3]

β-Methylaminobutyrophenone hydrochloride (I). To a solution of 6.8 g. of methylamine hydrochloride in 200 cc. of methanol, 6.0 g. of powdered sodium methylate was added with stirring. On addition of 29.2 g. of crotonophenone,[4] the temperature rose to 35°. The mixture was stirred for about 4 hr., 15 cc. of concd. hydrochloric acid was added, and the insoluble material removed by filtration. The solvent was removed by distillation *in vacuo*, and the residue was crystallized from 80 cc. of ethyl acetate. In this manner 10.2 g. of β-methylaminobutyrophenone hydrochloride, m.p. 152–154°, was obtained. Further purification can be effected by crystallization from ethanol.

Anal. Calcd. for $C_{11}H_{15}NO.HCl$: Cl, 16.6. Found: Cl, 16.6.

1,2,6-Trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III). To a solution of 89.8 g. of methylamine hydrochloride in 2640 cc. of methanol, 79.2 g. of powdered sodium methylate was added with stirring. During 20 min., 383 g. of crotonophenone (3) was added, during which the temperature rose to 36°. After stirring for 3 hr., the mixture was allowed to stand for 13 days and then acidified with 198 cc. of concd.

(3) All melting points are uncorrected.

(4) R. C. Fuson, R. E. Christ, and G. M. Whitman, *J. Am. Chem. Soc.*, **58**, 2450 (1936).

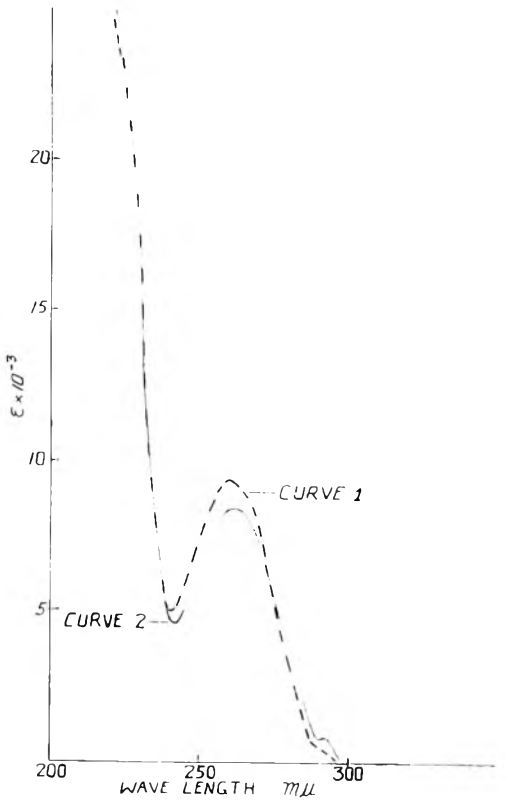


Fig. 1. Ultraviolet absorption spectra in 0.1*N* hydrochloric acid:
Curve 1. 1,2,3-Trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI)
Curve 2. Hydrobromide of 2,9-dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XI)

hydrochloric acid. The mixture was filtered, the filtrate was distilled to dryness under reduced pressure, and the residue was digested with 660 cc. of boiling ethyl acetate. The insoluble material was removed by filtration from the hot solvent, and the filtrate allowed to stand in the refrigerator for 2 days. On filtration, 75 g. of a crude crystalline mixture was obtained, which probably consisted of a mixture of the hydrochlorides of β-methylaminobutyrophenone (I), and of the bis product (II). The ethyl acetate was removed *in vacuo*, and the residue was stirred with a solution of 80 g. of sodium hydroxide and 1.2 l. of water. On standing overnight, the oil gradually hardened. After crystallization from a solvent, b.p. 86–100°, consisting essentially of *n*-heptane, 133 g. of 1,2,6-trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III), m.p. 103–105°, was obtained.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79. Found: C, 78.35; H, 7.86.

Hydrobromide. The hydrobromide was obtained by dissolving the base in ether and passing in hydrogen bromide. After crystallization from ethanol, it melted at 186–187°.

Anal. Calcd. for $C_{21}H_{25}NO_2$.HBr: C, 62.37; H, 6.48. Found: C, 62.58; H, 6.48.

1,2,3-Trimethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide (IV). A mixture of 13 g. of the hydroxy ketone (III) and 50 cc. of 48% hydrobromic acid was refluxed for 6 hr. and 40 min. and then poured into 200 cc. of water, where it was allowed to stand for 2 days. The supernatant liquor was removed by decantation, and the insoluble matter was digested with 100 cc. of ethyl acetate. After crystallization from 50 cc. of ethanol, 4.2 g. of the hydrobromide, m.p. 198–201°, was obtained.

Anal. Calcd. for $C_{21}H_{21}N$.HBr: C, 68.48; H, 6.02. Found: C, 68.19; H, 6.19.

Mixture of 1,2,3-trimethyl-9-phenyl-2,3,4,4A-tetrahydro and 1,2,3-trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrobromides. A mixture of 7.4 g. of the dihydropyridindene hydrobromide (IV), 20 cc. of Raney nickel catalyst, and 160 cc. of ethanol was hydrogenated at room temperature during 3.25 hr. at an initial gauge pressure of 52 lbs. until hydrogen uptake was extremely slow. The catalyst was filtered, the solvent removed *in vacuo*, and the residue crystallized from 15 cc. of acetone. In this manner, 4.6 g. of the tetrahydro compound, m.p. 226–232°, was obtained. Further crystallization from ethanol gave crystals melting at 230–235°.

Anal. Calcd. for $C_{21}H_{23}N$.HBr: C, 68.10; H, 6.53. Found: C, 68.35; H, 6.58.

The ultraviolet spectral curve of the compound was practically parallel to that of the base (VI) but displaced by about 2 mμ towards the higher wave lengths. We have concluded that the hydrobromide is composed preponderantly of the VI species.

1,2,3-Trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI). A mixture of 28 g. of the dihydropyridindene hydrobromide (IV), 25 cc. of Raney nickel catalyst, and 150 cc. of ethanol was hydrogenated at room temperature during a period of 2.5 hr. at an initial gauge pressure of 49 lb. Approximately the theoretical amount of hydrogen was absorbed. The catalyst was filtered, the solvent was removed *in vacuo*, and the residue was dissolved in 200 cc. of warm water. The base was liberated by the addition of 63 cc. of 10% sodium hydroxide, extracted with 200 cc. of ether, washed with water, and dried over sodium sulfate. The ether solution was divided into two portions. One of these portions was extracted with a mixture of 200 cc. of water and 43 cc. of 0.87*N* hydrochloric acid. Addition of 13 g. of potassium thiocyanate in 20 cc. of water to the acid solution gave 9.9 g. of a crude thiocyanate salt. A sample of this salt after crystallization from 50% ethanol melted at 186–189°.

A hot solution of 7.9 g. of the crude thiocyanate in 50 cc. ethanol was cooled, treated with 50 cc. of 6% sodium hydroxide, and allowed to stand with occasional scratching for about 3 days. An oil was first obtained, but on standing it eventually solidified. After washing with 50% ethanol and drying, the substance weighed 5.7 g. and melted at 100–102°. After crystallization from dilute alcohol, it melted at 101–103°.

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01. Found: C, 87.13; H, 7.98.

α-Methyl-α-(1-methyl-4-hydroxy-4-phenyl-3-piperidyl)-benzyl alcohol (IX). To a solution of methyl magnesium iodide prepared from 129 g. of methyl iodide and 22.1 g. of magnesium in 500 cc. of dry ether, was added with stirring during 30 min. 128 g. of 1-methyl-3-benzoyl-4-phenyl-4-hydroxy-piperidine (VIII) (1). When the spontaneous refluxing had ceased within a short time after the addition, the mixture was warmed to reflux during about 3 hr., allowed to stand overnight, and then introduced into 1 kg. of cracked ice. The mixture was neutralized with a solution of 25 cc. of concd. sulfuric acid in 100 cc. of water and filtered. The insoluble matter was digested with 1200 cc. of hot acetone and filtered. On cooling, 16.0 g. of the diol, m.p. 194–197°, was obtained. An additional 3.7 g. was obtained from the other fractions. Further crystallization from acetone gave the pure diol, m.p. 197–198°.

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.05; neut. equiv. 311. Found: C, 77.22; H, 7.88; neut. equiv. 313 (with perchloric acid).

2,9-Dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrobromide (XI). A mixture of 10.4 g. of the diol (IX) and 40 cc. of 48% hydrobromic acid was refluxed in an oil bath at 137–140° during 1 hr. and 16 min., and cooled. On addition of 80 cc. of water, a gum was obtained which gradually

solidified on standing overnight. The solid was filtered and crystallized from 15 cc. of ethanol to give 7.73 g. of the pyridindene (XI), m.p. 245–248°. After recrystallization, it melted at 246–248 .

Anal. Calcd. for $C_{29}H_{22}NBr$: C, 67.41; H, 6.22. Found: C, 67.15; H, 6.29.

Acknowledgment. We are indebted to Dr. Al Steyermark for the microanalyses, to Mr. A. Motchane for the ultraviolet spectra, and to Mr. Pat Bevilacqua for technical assistance.

NUTLEY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

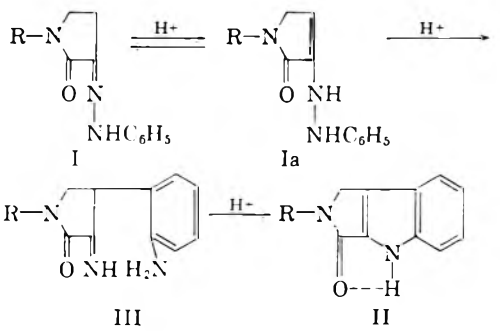
Synthesis of Compounds in the Pyrrolo[3,4-b]indole Series[1]

PHILIP L. SOUTHWICK AND RICHARD J. OWELLEN[2]

Received December 29, 1959

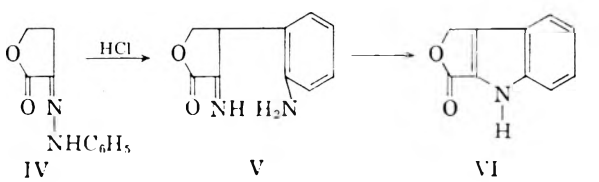
The previously unknown pyrrolo[3,4-b]indole ring system is represented in a series of compounds which were produced when the Fischer indole synthesis was conducted with phenylhydrazones of 1-substituted 2,3-dioxopyrrolidines (I). Seven 2-substituted 1,4-dihydropyrrolo[3,4-b]indol-3(2H)ones (II) have been prepared in this manner; the 2-substituents were *n*-propyl, *n*-butyl, cyclohexyl, phenyl, β-phenylethyl, β-phenylisopropyl, and homoveratryl. The three compounds containing the cyclohexyl, β-phenylethyl, and β-phenylisopropyl groups have been reduced with lithium aluminum hydride and converted into corresponding 2-substituted 1,2,3,4-tetrahydropyrrolo[3,4-b]indoles (VII).

Apparently no compounds containing the relatively simple fused-ring heterocyclic system of pyrrolo[3,4-b]indole have been described in the literature. The report of the preparation of two such compounds by Heller and Wunderlich[3] has been shown by Taylor and Kalenda[4] to be in error. The fact that other compounds containing the indole nucleus have been known to display a variety of interesting types of physiolcgical activity provided the incentive for an attempt to prepare compounds of this class. It seemed possible that the ring system could be created by conducting the



Fischer indole synthesis using phenylhydrazones of 2,3-dioxopyrrolidines (I), a number of which had been prepared in this laboratory.[5]

The result of subjecting the phenylhydrazones I to the conditions of the Fischer indole synthesis was, however, considered subject to uncertainty because of reports in the literature regarding the course of acid-catalyzed reactions of certain similar compounds. Meyer and Vaughan[6] had shown that the phenylhydrazone of 1,5-diphenyl-2,3-dioxopyrrolidine rearranges to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxanilide when treated with hydrochloric acid, and this type of behavior might have proved general for phenylhydrazones of 2,3-dioxopyrrolidines. On the other hand, the work of Plieninger[7] with the phenylhydrazone of α-keto-γ-butyrolactone (IV) suggested that another interesting departure from the normal course of the Fischer indole synthesis might well be encountered. Compound IV, when treated with hydrogen chloride in acetic acid at 90°,



had yielded the hydrochloride of α-imino-β-*o*-aminophenyl-γ-butyrolactone (V). Compound V required treatment with a boiling mixture of concentrated hydrochloric and glacial acetic acids to undergo cyclization to the indole derivative VI. Whether the failure of compound V to undergo rapid spontaneous ring-closure to VI is the result of a steric or an electronic effect, the close resemblance

(1) Supported principally by a research grant (RG-4371) from the National Institutes of Health, U. S. Public Health Service.

(2) National Science Foundation Cooperative Predoctoral Fellow, 1959–1960.

(3) G. Heller and P. Wunderlich, *Ber.*, **47**, 1617 (1914).

(4) E. C. Taylor, Jr., and N. W. Kalenda, *J. Org. Chem.* **18**, 1755 (1953).

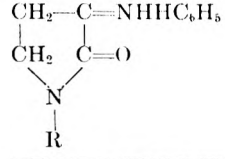
(5) (a) P. L. Southwick, E. F. Previc, Joseph Casanova, Jr., and E. Herbert Carlson, *J. Org. Chem.* **21**, 1087 (1956); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.* **75**, 3413 (1953); (c) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949). The concern expressed in ref. 5a over the possibility that the phenylhydrazine derivatives of the 2,3-dioxopyrrolidines might not represent the expected phenylhydrazone structure (or the related enhydrazine tautomeric form Ia) was evidently unwarranted. *Cf.* discussion by Meyer and Vaughan, ref. 6.

(6) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.* **22**, 1565 (1957).

(7)(a) H. Plieninger, *Ber.* **83**, 273 (1950); (b) H. Plieninger and I. Nógrádi, *Ber.*, **88**, 1965 (1955).

TABLE I

1-SUBSTITUTED 2,3-DIOXOPYRROLIDINE PHENYLHYDRAZONES,



R	M.P., °	Yield,[b] %	Starting Material,[b] g.	Hydrolysis Mixture Volume,[b] ml.	Hydrolysis Mixture HCl concn., %	Heating Period, min.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found[c]
n-C_3H_7—	205–207	9(A)	15(A)	600	10	90	67.50	67.18	7.41	7.29	18.17	19.70 17.54
n-C_4H_9—	193–194[a]	56(B)	20(B)	400	20	60						
cyclo-C_6H_{11}—	213–214[a]	47(A) 63(B)	30(A) 30(B)	170	37	50						
C_6H_5—	218–219	19(A)	10(A)	500	10	240	72.40	72.42	5.70	5.39	15.84	14.78
$C_6H_5CH_2CH_2$—	213–214[a]	60(A) 37(B)	50(A) 50(B)	1000	20	60						
$C_6H_5CH_2CH(CH_3)$—	178–179	50(A) 42(B)	15(A) 25(B)	240(A)[d] 400(B)[e]	25	90	74.24	74.56	6.89	6.94	13.67	14.17 13.30
3,4-$(CH_3O)_2C_6H_3(CH_2)_2$—	206–207	48(A) 38(B)	20(A) 15(B)	500	20	60	67.97	68.48	6.56	6.42	11.89	11.6

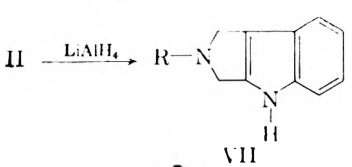
[a] Characterization of these compounds is described in ref. 5a. [b] The letters in parentheses following the figures in these columns indicate the procedure (A or B) for which the value is given. [c] Nitrogen analyses on these phenylhydrazones have been erratic, but no explanation of the difficulty is apparent. [d] Ethanol (15 ml.) was added to increase the solubility of the starting material. [e] Ethanol (25 ml.) was added.

in structure of V to the expected intermediate III in the conversion of I to II suggested that III might also prove stable. Such a result could have complicated the synthesis of the pyrrolo[3,4-b]indole derivatives II but would have been of interest as another of the rare instances in which an intermediate could be isolated in the Fischer indole synthesis.

The phenylhydrazones of seven 1-substituted 2,3-dioxopyrrolidines (I) (see Table I) have been prepared and subjected to treatment in acetic acid solution with dry hydrogen chloride (Plieninger's procedure for preparing Compound V) or with concentrated aqueous hydrochloric acid at the boiling point. Under either set of conditions a rapid reaction occurred. It was apparent from the composition of the products obtained in this way that they were not simply rearrangement products, either of the type III or of the type encountered by Meyer and Vaughan; the elimination of one nitrogen (as ammonium chloride) from the molecule indicated that the reaction which had occurred was the Fischer indole synthesis. The yields of 2-substituted 1,4-dihydropyrrolo[3,4-b]indol-3(2H)ones (II) produced (see Table II) were good enough (59–86%) to make the reaction of preparative value. It was not possible to isolate an intermediate of the type III; cyclization occurred even at 30° in glacial acetic acid containing hydrogen chloride. Data concerning the preparation and characterization of the seven compounds of type II which were prepared are given in Table II.

The assignment of structure II to these products was supported not only by their composition and method of preparation, but also by their properties. All were stable, high-melting compounds of insufficient basicity to yield salts with aqueous acids. The infrared spectra of the compounds (measured in Nujol mulls) showed broad N–H bands at the relatively long wave length of 3.19 μ (overlapping, on the long wave-length side, the aromatic C–H bands), and the band for the lactam carbonyl was displaced to 6.01–6.03 μ from its position at 5.86 μ in the parent 2,3-dioxopyrrolidines. Conjugation with a carbon to carbon double bond has probably shifted the carbonyl band, and it seems reasonable to assume that the positions of both carbonyl and N–H absorptions may have been influenced by the opportunity for intramolecular hydrogen bonding as pictured in formula II.

To obtain compounds in the series with basic properties and some likelihood of showing physiological activity, reduction of the lactam carbonyl of the compounds II with lithium aluminum hydride was undertaken. Attempts to bring about the reduction according to the usual procedures were unsuccessful. In order to secure higher reaction temperatures a procedure was adopted in which the reaction mixtures were prepared in the usual way with ether as the solvent, then were diluted with dry toluene and distilled until the ether was removed and the reflux temperature had reached 110°. Under these conditions reduction was accomplished during a heating period of 1 to 3.5 hours. The yields of 2-substituted 1,2,3,4-tetrahydropyrrolo[3,4-b]indoles (VII), however, were only fair (47–52%). The data relating to the preparation and characterization of the compounds VII are given in Table III. When treated with aqueous hydrochloric acid, these substances formed sparingly soluble hydrochlorides and were characterized in this form. The free bases darkened when exposed to the air. The hydrochlorides appeared to be quite stable but were not easily freed of colored impurities developed during manipulation of the compounds in the basic form. Susceptibility to air oxidation has been observed in other compounds in which the carbon atoms of the 2- and 3-positions of the indole nucleus are incorporated into a fused ring which is not aromatic.[8]



VII

The assigned structure (VII) for these compounds is supported by ultraviolet spectroscopic data. The spectrum of the member of the group in which R is β-phenylethyl was measured in 95% ethanol. (The compound was dissolved as the hydrochloride and the free base was liberated with sodium hydroxide.) Comparison with a similarly determined spectrum of 1,2,3,4-tetrahydrocarbazole revealed a striking similarity. Structure VII showed maxima at 225 mμ (ϵ 38,100) and 277 mμ (ϵ 7500) with an inflection at *ca.* 289 mμ (ϵ 5750). The minimum was at 245 mμ (ϵ 2450). Tetrahydrocarbazole showed maxima at 228 mμ (ϵ 33,400) and 283 mμ (ϵ 7100) with a marked inflection almost amounting to another maximum at 291 mμ (ϵ 6100). There was a minimum at 250 mμ (ϵ 2000).

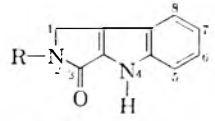
The infrared spectrum in chloroform of the same new compound (VII. R = β-phenylethyl) in the hydrochloride form showed no carbonyl band, and an N–H band (sharp) was observed at 2.87 μ, as was expected for an indole N–H. (The N–H band for 1,2,3,4-tetrahydrocarbazole was found at 2.89 μ in chloroform.) There should be no reason to doubt that the desired compounds of the structure VII have been obtained.

The 2,3-dioxopyrrolidines from which the phenylhydrazones (I) were obtained were themselves prepared by the acid hydrolysis of 4-carbethoxy-2,3-dioxopyrrolidines.[5] In most cases the 2,3-dioxo-

(8) See (a) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2188, 2196 (1951); (b) B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.* **73**, 2641 (1951); (c) R. B. Carlin and M. S. Moores, *J. Am. Chem. Soc.*, **81**, 1259 (1959). References to earlier literature on autoxidation of indoles are cited in these papers.

TABLE II

2-SUBSTITUTED 1,4-DIHYDROPYRROLO[3,4-b]INDOL-3(2H)ONES

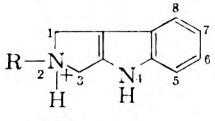


R	M.P., °	Yield,[a] %	Reaction Mixture: Starting Material,[a] g.	Reaction Mixture: Volume[a] of HCl soln., ml.	Reaction Mixture: Volume[a] of HOAc, ml.	Heating[a] Period, min.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen Calcd.	Nitrogen Found
n-C_3H_7—	207–208	68(B)	0.8(B)	—	8(B)	5(B)	72.87	72.44	6.59	6.19	—	
n-C_4H_9—	216–218	76(A)	12(A)	15(A)	50(A)	20(A)	73.65	73.59	7.06	6.94	12.27	12.18
cyclo-C_6H_{11}—	251–253	59(A)	20(A)	70(A)	100(A)	10(A)	75.56	75.73	7.31	7.24	11.02	10.9
C_6H_5	303–305	71(A)	1.5(A)	7(A)	20(A)	15(A)	77.40	77.80	4.87	4.68	11.28	11.25
$C_6H_5CH_2CH_2$—	253–254	85(A)	20(A)	50(A)	200(A)	30(A)	78.23	77.77	5.84	5.79	10.14	10.22
		69(B)	20(B)	—	200(B)	15(B)		78.05		5.83		
$C_6H_5CH_2CH(CH_3)$—	159–160[b]	80(A)	8(A)	15(A)	50(A)	15(A)	78.59	78.21	6.25	6.23	9.65	9.95
3,4-$(CH_3O)_2C_6H_3(CH_2)_2$—	216–217	68(B)	17(B)	—	300(B)	15(B)	71.41	71.46	5.99	6.08	8.33	8.24

[a] The letters in parentheses following the figures in these columns indicate the procedure (A or B) for which the value is given. [b] Recrystallized from a 1:1 isopropyl alcohol-acetone mixture. $[\alpha]_D = +168°$ (c 1.5, acetone).

TABLE III

HYDROCHLORIDES OF 2-SUBSTITUTED 1,2,3,4-TETRAHYDROPYRROLO[3,4-b]INDOLES,



Cl⁻

R	M.P.,[a]	Yield, %	Starting Material, g.	Weight of $LiAlH_4$, g.	Heating Period, hr.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
cyclo-C_6H_{11}—	206–207[b]	50	15	13.5	3.5	69.42	68.90	7.65	7.49	10.12	10.0
$C_6H_5CH_2CH_2$—	207–208	52	18	21	2.5	72.35	72.19	6.41	6.39	9.38	9.28
$C_6H_5CH_2CH(CH_3)$—	219–220[c]	47	7	7	1	72.94	72.44	6.77	6.59	8.96	8.82

[a] These compounds melted with decomposition. [b] A picrate, m.p. 175–177° dec. was obtained by treating the hydrochloride with picric acid in ethanol. *Anal.* Calcd. for $C_{22}H_{23}N_5O_7$: C, 56.28, H, 4.94. Found: C, 56.53, H, 4.89. [c] $[\alpha]_D$ +88.2° (c 0.4, 95% ethanol).

pyrrolidines were isolated in the crude form but were not purified prior to conversion to the phenylhydrazones. In other cases it was desirable to prepare the phenylhydrazone in the hydrolysis mixture without isolating the 2,3-dioxopyrrolidine at all. This could be done by reducing the acidity of the solutions to *p*H 4–5 by addition of sodium acetate, then adding the requisite amount of phenylhydrazine. Both procedures are described in the Experimental. Also described are two new 1-substituted 4-carbethoxy-2,3-dioxopyrrolidines which were prepared during the present investigation. One, in which the 1-substituent was β-(3,4-dimethoxyphenyl)ethyl, was obtained from homoveratrylamine. The second, in which the 1-substituent was β-phenylisopropyl, was an optically active compound obtained from *d*-β-phenylisopropylamine, and led to a series of optically active products.

Three of the compounds (II. R = β-phenylethyl and III. R = phenylethyl or cyclohexyl) have been tested in the screening program of the Cancer Chemotherapy National Service Center, but did not show significant antitumor activity. Other tests of possible physiological activity are in progress.

EXPERIMENTAL[9]

1-Substituted 2,3-dioxopyrrolidine phenylhydrazones (I). *Procedure A.* 1-Substituted 4-carbethoxy-2,3-dioxopyrrolidines were hydrolyzed and decarboxylated by treating the compounds with refluxing hydrochloric acid solutions.[5] The quantities of materials used and other details of the individual experiments are recorded in Table I. The crude 2,3-dioxopyrrolidines were taken up in chloroform by three extractions of the hydrolysis mixtures. The chloroform solutions were dried over magnesium sulfate, filtered, and evaporated under reduced pressure on a steam cone. The resulting residues were dissolved in 95% ethanol (5 ml. per g. of 2,3-dioxopyrrolidine) and a few drops of glacial acetic acid were added, followed by the calculated amount of phenylhydrazine (calculated on the basis of the amount of 4-carbethoxy-2,3-dioxopyrrolidine hydrolyzed). The mixtures were heated to boiling on a steam bath, then allowed to cool. After further cooling in an ice bath, the crystalline products were removed by filtration and recrystallized from 95% ethanol. Yields in Table I are for recrystallized products.

Procedure B. In procedure B the 1-substituted 4-carbethoxy-2,3-dioxopyrrolidines were hydrolyzed and decarboxylated as in procedure A. At the end of the reflux period the aqueous acid solution was cooled and filtered. Sodium acetate was then added until the *p*H of the solution became 4 to 5. The calculated amount of phenylhydrazine for the quantity of 4-carbethoxy-2,3-dioxopyrrolidine hydrolyzed was then added while the mixture was vigorously stirred. Separation of the phenylhydrazone usually began at once and appeared to be complete after a few minutes. The product was collected by filtration and recrystallized from 95% ethanol. The amounts of materials used and other details of individual experiments are recorded in Table I.

2-Substituted 1,4-dihydropyrrolo[3,4-b]indol-3(2H)ones (II). *Procedure A.* The 1-substituted 2,3-dioxopyrrolidine phenylhydrazones (I) were treated with refluxing mixtures of concd. hydrochloric acid and glacial acetic acid. Heating was continued until the phenylhydrazones dissolved and for approximately 10 min. thereafter. (The total reaction times ranged from 15 to 30 min.) Several of the products separated as crystalline precipitates when the reaction mixtures were cooled, and were then collected by filtration. In other cases the cooled reaction mixture was diluted with an equal volume of water and cooled in an ice bath to induce separation of the product. The compounds were purified by crystallization from 95% ethanol. Details of individual experiments are recorded in Table II.

Procedure B. The 1-substituted 2,3-dioxopyrrolidine phenylhydrazones (I) were suspended in glacial acetic acid which was kept at the boiling point under a reflux condenser. A slow stream of dry hydrogen chloride was passed into the mixture while refluxing was continued and the phenylhydrazones dissolved. After a reflux period of 5 to 15 min. the solution was cooled and filtered, either directly or after dilution with water, to collect the products, which were then recrystallized from 95% ethanol. Details of these experiments are also included in Table II.

2-Substituted 1,2,3,4-tetrahydropyrrolo[3,4-b]indole hydrochlorides (VII). The 1,4-dihydropyrrolo[3,4-b]indol-3(2H)-ones (II) were added in solid form in small portions to vigorously stirred solutions or suspensions of excess lithium aluminum hydride in ether (7 to 21 g. of lithium aluminum hydride in 100 ml. of dry ether). After about 10 min. of stirring, 300 ml. of dry toluene was added. The ether was then removed from the reaction mixture by distillation through a short packed column. After the temperature of the distilling vapors reached 110°, the distilling column was replaced by a reflux condenser, and heating and stirring under reflux were continued for an additional period of time to complete the reduction.

The mixture was cooled and the excess lithium aluminum hydride was destroyed by cautious addition of water while the mixture was kept in an ice bath. The cold mixture was then acidified by addition of a considerable excess of 20% hydrochloric acid while ice bath cooling was maintained. Stirring was continued for an additional 30 min. to dissolve all of the inorganic reaction products. The hydrochlorides of the tetrahydropyrrolo[3,4-b]indoles (VII), which were not soluble in either the aqueous or the organic phase of the mixtures, were then collected by filtration of the mixtures through a pad of glass wool. The products were purified by crystallization from 95% ethanol. (Yields quoted are for products obtained after one recrystallization.) The characterization of individual compounds and details of their preparation are given in Table III.

1-Homoveratryl-4-carbethoxy-2,3-dioxopyrrolidine. The previously recommended one-step procedure[5a] for similar compounds was modified by using excess sodium ethoxide and slightly simplifying the method of isolating the product. A solution of 78 g. (0.42 mole) of homoveratrylamine and 42 g. (0.42 mole) of ethyl acrylate in 200 ml. of absolute ethanol was allowed to stand overnight. Ethyl oxalate (61.3 g.; 0.42 mole) was added and the mixture was stirred while a solution of sodium ethoxide prepared from 15 g. (0.695 g.-atom) of sodium and 250 ml. of absolute ethanol was added slowly. The mixture was heated under reflux and stirred for 2 hr., then cooled in an ice bath. Water (100 ml.) was added and the mixture was acidified to a *p*H of less than 2 by careful addition of 20% aqueous hydrochloric acid while cooling and stirring were continued. The crude product which precipitated was removed by filtration and dried. The yield was 123 g. (88%) of a light-tan product melting at 127–128°. Recrystallization from 95% ethanol did not change the melting point.

(9) Melting points are uncorrected. Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Microanalytical Laboratories, Bardonia, N. Y. Infrared spectra were determined with a Perkin-Elmer model 21 spectrophotometer, ultraviolet spectra with a Cary recording spectrophotometer.

Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.53; H, 6.17; N, 4.23.

d-1-(β-Phenylisopropyl)-4-carbethoxy-2,3-dioxopyrrolidine. The compound was prepared by the one-step procedure previously described.[5a] From 78 g. (0.58 mole) of *d*-β-phenylisopropylamine, 90 g. (59% yield) of the 4-carbethoxy-2,3-dioxopyrrolidine was obtained. After recrystallization from an ethanol-water mixture white needles were obtained, m.p. 115–116°, $[\alpha]_D = +75.48°$ (c 4.0, 95% ethanol).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.55; H, 6.81.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY LEHIGH UNIVERSITY]

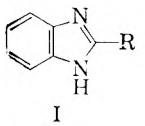
Study of the Synthesis and Chemistry of the 5,6-Dihydroimidazo[ij]quinoline Series[1]

ALFRED RICHARDSON, JR.,[2] AND E. D. AMSTUTZ

Received September 23, 1959

A series of 2-substituted 5,6-dihydroimidazo[ij]quinolines has been synthesized by the condensation of 8-amino-1,2,3,4-tetrahydroquinoline with carboxylic acids or their derivatives. These condensations may lead directly to the final product or to amides which may be subsequently cyclized. In general, the amino-amides are obtained and isolated in the case of substituted or unsubstituted aromatic acid chlorides. Attempts to form 2-substituted imidazo[ij]quinolines from 8-amino-1,2-dihydroquinoline led only to 8-amidoquinolines. Certain pyridoquinoxalines were synthesized from 8-amino-1,2,3,4-tetrahydroquinoline and benzoin-type compounds. The spectra of the dihydroimidazo[ij]quinolines are similar to those of the benzimidazoles.

In view of the fairly wide range of physiological activities shown by benzimidazole (I.R = H) and its derivatives, it was of interest to prepare a series of derivatives of the related 5,6-dihydroimidazo-[ij]quinolines (II). This paper describes the synthetic methods employed in the preparation of a variety of new members of this virtually unexplored group.



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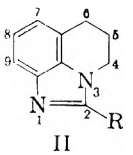

II

The first synthesis of a 5,6-dihydroimidazo-[ij]quinoline was realized by Kunckell,[3] who condensed 8-amino-6-bromo-1,2,3,4-tetrahydroquinoline with acetic acid. The product he obtained was 8-bromo-2-methyl-5,6-dihydroimidazo[ij]quinoline. Other earlier workers[4–12] synthesized compounds in this series where the 2-substituent was an alkyl group sometimes containing hydroxyl groups or aromatic residues. The diamine usually was 8-amino-1,2,3,4-tetrahydroquinoline, although at times, an 8-amino-1,2,3,4-tetrahydroquinoline was employed which contained substituents on the aromatic ring.[6–9] In most cases, the appropriate diamine was heated with the corresponding acid in the absence of solvent,[4–9] although a few members of the series were synthesized by condensing an 8-amino-1,2,3,4-tetrahydroquinoline with aliphatic aldehydes and ketones.[10–12]

Although simple amidines are readily hydrolysed in aqueous acid,[13] the dihydroimidazoquinolines, which are essentially cyclic amidines, are stable in a refluxing 4*N* hydrochloric acid medium and many can be prepared by its use. This inertness toward acid hydrolysis is apparently due to a resonance stabilization of the benzimidazole system.

Tables I and II list the dihydroimidazo[ij]-quinolines and benzimidazoles synthesized during this research, while the condensation procedures are discussed in detail in the paragraphs which follow.

Condensations with carboxylic acids.[16] The methods used in condensing 8-amino-1,2,3,4-tetrahydroquinoline with carboxylic acids were either to reflux in 4*N* hydrochloric acid or to heat the reactants without a solvent. Other methods which were attempted without success were heating in

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(6) R. C. Elderfield and G. L. Kreuger, *J. Org. Chem.*, **17**, 358 (1952).

(7) R. C. Elderfield, F. J. Kreysa, J. H. Dunn, and D. D. Humphreys, *J. Am. Chem. Soc.*, **70**, 40 (1948).

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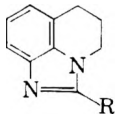
TABLE I. 2-SUBSTITUTED 5,6-DIHYDROIMIDAZO[ij]QUINOLINES

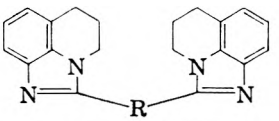


No.	R	Method[a]	Yield, %	M.P.°		Analyses, C	H	N	Picrate, M.P.°
III	H—	B; 14 hr.	50	58–60[b]	Known				225
IV	CH_3—	B; 24 hr.	35	128[c]					
		B[l]; 4 hr.	35	119					
		C; 3 hr.	17	128	Known				237–238
V	$HOCH_2$	A; 24 hr.	74	185[d]	Known				216
VI	$HSCH_2$	A; 24 hr.	39	160–161	Calcd.:[j]	64.71	5.88	13.73	215–216
					Found:	65.20	5.51	13.63	dec.
VII	$HSCH_2CH_2$—	A; 24 hr.	63	oil	Calcd.:[u]	48.30	3.84	15.66	190
					Found:	48.40	4.14	15.35	
VIII[e]	$HOCH_2CH_2CH$—$_2$	A[m]; 24 hr.	85	128–130	Calcd.:	72.22	7.41	12.96	157
					Found:	72.30	7.20	12.90	
IX	$CH_3CO_2CH_2CH_2CH_2$—	E; 17 hr.	56	47–49	Calcd.:	69.74	7.04	10.84	144–145
					Found:	69.85	7.12	10.84	
X[f]	Cyclohexyl-	D[n]; 6.5 hr.	67	93–95	Calcd.:	74.38	8.59	10.84	183–184
					Found:	74.80	8.50	10.97	
XI	HO—[g]	C[o]; 1 hr.	75	213–214	Calcd.:	68.94	5.80	16.07	None
					Found:	68.65	6.02	15.73	
XII	HS—[g]	B[p]; 24 hr.	32	214.5–215.5	Calcd.[k]:	63.14	5.31	14.72	None
					Found:	63.25	5.40	14.68	
XIII	Cl—	F	60	75–76	Calcd.:	62.32	4.72	14.53	175 dec.
					Found:	62.60	4.55	14.50	
XIV	C_6H_5—	D[q]; 12 hr.	Quant.	80–82	Calcd.:	82.05	5.98	11.97	196–197
		D[r]; 1–2 hr.	43	80–82	Found:	81.90	6.02	12.07	
XV	3,4,5-Trimethoxyphenyl	C; 24 hr.	62	181–182	Calcd.:	70.37	6.17	8.64	208–210
		D[q]; 2 hr.	Quant.	179–180	Found:	70.50	6.22	8.70	
XVI	4-Nitrophenyl-	D[q]; 2 hr.	35	179–180	Calcd.:	68.82	4.66	15.05	214–215
		D[s]; 5 hr.	43	176–179	Found:	68.70	4.52	15.35	
XVII[h]	β-Naphthyl-	C; 18 hr.	51	206–207	Calcd.:	84.51	5.63	9.86	221–222
					Found:	84.30	5.88	10.00	
XVIII[i]	γ-Pyridyl-	A; 24 hr.	14	142.5	Calcd.:	76.60	5.53	17.90	183–185
		C; 24 hr.	62	142.5	Found:	76.38	5.76	17.70	
XIX	p-$H_2NC_6H_4SCH_2$—	A; 69 hr.	53	92–94	Calcd.:	69.10	5.82	14.21	169
					Found:	69.40	5.80	14.30	
XX	β-Indolyl-CH_2—	A; 69 hr.	10.3	232–233	Calcd.:	79.40	5.98	14.61	211–213
					Found:	79.15	6.01	14.23	
XXI[t]	CH_3O—	G; 5.5 hr.	Quant.	oil	Calcd.[u]:	48.91	3.64	16.79	154–155
					Found:	48.90	3.67	16.45	

[a] Method A: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid were refluxed in 4*N* hydrochloric acid. Neutralization with dilute ammonium hydroxide afforded the product which was recrystallized from aqueous alcohol. Method B: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid were refluxed or heated over a free flame until effervescence ceased. The product was extracted with alcohol and recrystallized from aqueous alcohol. Method C: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid chloride were refluxed in benzene-pyridine. The solvent was evaporated, the residue slurried with ammonium hydroxide, and the product recrystallized from aqueous alcohol. Method D: The amide intermediate was cyclodehydrated by heating with an appropriate reagent as listed elsewhere in the table. Evaporation of the solvent followed by neutralization of the residue with dilute ammonium hydroxide gave the product which was recrystallized from aqueous alcohol. Method E: A solution of the carbinol in acetyl chloride was allowed to stand at room temperature. The solution was poured onto ice, neutralized with dilute ammonium hydroxide, and the product extracted with ether. Method F: The hydroxy compound (XI) was refluxed in phosphorus oxychloride for 1.5 hours. The solution was poured onto ice and neutralized with dilute ammonium hydroxide. The product was recrystallized from aqueous alcohol. Method G: The chloro compound was refluxed with a 9*M* excess of sodium methoxide in methanol. The solution was cooled, filtered and evaporated. The residue was extracted with ether and the product obtained by evaporating the dried ethereal solution. [b] Hazlewood, *et al.*[4] erroneously reported a melting point of 148°. [c] Hazlewood, *et al.*[4] reported a melting point of 128°. [d] Hazlewood, *et al.*[4] reported a melting point of 183°. [e] Hydrochloride, m.p. 255°. [f] Melting point and analyses are for the monohydrate. [g] Although the product is shown here in the imidol form, the authors believe an equilibrium exists and that the amide or urea form predominates. Refer to section on the discussion of the spectra. [h] Hydrochloride, m.p. 250° dec. [i] Hydrochloride, m.p. 256–258°. [j] Sulfur analysis: Calcd.: 15.69. Found: 15.18. [k] Sulfur analysis: Calcd.: 16.88. Found: 16.65. [l] Acetic anhydride was employed. [m] The reactant was γ-butyrolactone. [n] The amide was cyclized using a 9 mole excess of phosphorus pentoxide and 19 mole excess of phosphorus oxychloride in refluxing xylene. [o] The 8-amino-1,2,3,4-tetrahydroquinoline was dissolved in glacial acetic acid, treated with an equivalent quantity of phosgene in chlorobenzene, and refluxed. [p] The 8-amino-1,2,3,4-tetrahydroquinoline was treated with an equivalent of carbon disulfide in ethanol, refluxed until the evolution of hydrogen sulfide ceased, and cooled, whereupon the products separated. [q] The amide was cyclized *via* a 9-mole excess of phosphorus pentoxide in refluxing benzene. [r] The amide was cyclized in refluxing phosphorus oxychloride. [s] The amide was cyclized by employing a 9-mole excess of phosphorus pentachloride in phosphorus oxychloride under reflux. [t] Hydrochloride, m.p. 212–214°. [u] Analysed as the monopicrate.

TABLE II

A. 2,2′-Bis(5,6-Dihydroimidazo[ij]quinolines)



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XXII	No. Bridge[f]	H;[h] 16 hr.	very low	261–262	Calcd.:	76.40	5.79	17.81	210
		B;[h] 0.5 hr.	11	259–260	Found:	76.90	5.56	17.60	
XXIII	—CH_2—	B;[i] 0.5 hr.	11	262–263	Calcd.:	77.74	6.23	16.03	245–246
					Found:	77.40	6.22	15.80	
XXIV	—CH_2CH_2—	A; 48 hr.	24	256–258	Calcd.:	77.16	6.48	16.36	dwmb 350
		A; 65 hr.	73	255–256	Found:	77.40	6.60	16.35	
XXV	—$CH_2CH_2CH_2$—	A; 48 hr.	32	198[c]	Calcd.:	70.37	7.21	14.27	268 dec.
		A; 65 hr.	61	198[c]	Found:	70.60	7.38	14.08	
XXVI	—$CH_2CH_2CH_2CH_2$—	B; 0.5 hr.	5.4	217–218	Calcd.:	77.79	7.10	15.11	dwmb 300
		A; 48 hr.	70	215	Found:	77.50	7.29	15.00	
XXVII	—CH=CH—[d]	A; 48 hr.	11	318–320[c]	Calcd.:	70.19	6.43	14.88	dwmb 360
					Found:	70.55	6.56	14.74	
XXVIII	—CH_2OCH_2—	A; 5 days	61	171–172	Calcd.:	73.72	6.19	15.62	254 dec.
					Found:	73.80	6.30	15.60	
XXIX[g]	—CH_2SCH_2—	A; 48 hr.	47	190–193[e]	Calcd.:	67.31	6.17	14.27	247 dec.
		A; 113 hr.	26	194[e]	Found:	67.75	6.30	14.28	
XXX	—$CH_2CH_2SCH_2CH_2$—	I.	65	139.5–140.0	Calcd.:	71.58	6.53	13.91	228 dec.
					Found:	71.20	6.65	13.48	
XXXI	—CH_2—CH(OH)—	A; 72 hr.	14	225.0–225.5[e]	Calcd.:	70.17	6.43	14.88	dwmb 360
					Found:	70.80	6.43	14.28	
XXXII	$HOCH_2$—	A; 24 hr.	1.5	280–283[j]	Known				252–253 dec.
XXXIII	$HSCH_2$—	A; 13.5 hr.	36	164–166[k]	Calcd.:	58.49	4.93	17.05	192–194
					Found:	58.40	4.97	16.85	
XXXIV	$HOCH_2CH_2CH_2$—	A;[l]	8.6	165–166	Calcd.:	68.16	6.87	15.90	None
					Found:	68.20	7.01	15.83	

[a] Methods A–F are listed in footnote *a* of Table I. The benzimidazoles were prepared from *o*-phenylenediamine instead of 8-amino-1,2,3,4-tetrahydroquinoline. Method H: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the corresponding amide were refluxed in ethylene glycol. The solution was cooled, diluted with water, and the product recrystallized from methanol. Method I: The β-mercaptoethyl compound VII was placed under vacuum at room temperature until effervescence ceased. The residue was recrystallized from ethanol-water. [b] The notation "dwmb" indicates, "darkens without melting below." [c] As a dihydrate. [d] Product assumed to be the *trans* isomer. [e] As a monohydrate. [f] Product is 2,2′-bis(5,6-dihydroimidazo[ij]quinoline). Starting material was ammonium oxalate hydrate. [g] Sulfur analysis: Calcd.: 8.18, found, 7.91. [h] Ammonium oxalate employed instead of oxamide or oxalic acid. [i] Malonamide employed instead of malonic acid. [j] Bistozycki and Przeworski[14] reported a melting point of 171–172°, however ultraviolet confirmed the benzimidazole structure. [k] Hughes and Lions[15] reported a melting point of 158°. [l] The diamine was condensed with γ-butyrolactone.

4*N* hydrochloric acid in a sealed tube at 165° and heating in polyphosphoric acid.

The most successful method by far was refluxing with 4*N* hydrochloric acid, which is a modification of the Phillips[17] benzimidazole synthesis. A disadvantage of this method for dihydroimidazoquinoline formation is that while it is generally applicable to the synthesis of aliphatic substituted compounds, it is usually unsuccessful in the synthesis of aromatic-, heterocyclic-, or unsaturated aliphatic-substituted products. In this connection, it is interesting to note that thiophenoxyacetic acid, *p*-aminobenzoic acid, and *N*-phenylglycine yielded no product, but *p*-aminothiophenoxyacetic acid and indole-3-acetic acid (vinylog of *N*-phenylglycine) each formed the desired product (XIX and XX, respectively).

Decarboxylation of the acid played an important hindering role in some condensations. Thus, picolinic, nicotinic, isonicotinic, and β-(2-pyridyl)acrylic acids were observed to decarboxylate as evidenced by a strong pyridine-like odor during the work-up. In addition, benzylamine was isolated when a condensation of α-aminophenylacetic acid with 8-amino-1,2,3,4-tetrahydroquinoline was attempted. In contrast to the lack of reactivity of glycine, both glycollic acid and thioglycollic acid con-

(14) A. Bistozycki and G. Przeworski, *Ber.*, **45**, 3483 (1912).

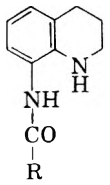
(15) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 209 (1938); *Chem. Abstr.* **32**, 5830 (1948).

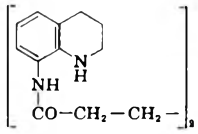
(16) Those acids which yielded no product in all attempted condensations with 8-amino-1,2,3,4-tetrahydroquinoline are: acrylic, aspartic, chloroacetic, cyclohexanecarboxylic, diethylacetic, fumaric, glutamic, glycine, isobutyric, levulinic, maleic, malonic, oxalic, trimethylacetic, *p*-aminobenzoic, benzoic, α-naphthoic, *p*-nitrobenzoic, terephthalic, 3,4,5-trimethoxybenzoic, imidazole-2-carboxylic, nicotinic, picolinic, thiophene-2-carboxylic, α-aminophenylacetic, cinnamic, dibenzylacetic, α-naphthylacetic, *N*-phenylglycine, β-(2-pyridyl)acrylic, thiophenoxyacetic.

(17) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

TABLE III

8-*N*-ACYLAMINO-1,2,3,4-TETRAHYDROQUINOLINES



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XXXV	CH_3—	A	16	116.5–117.5	Calcd.:	69.45	7.41	14.72	233–234[b]
					Found:	69.65	7.21	14.65	
XXXVI		A	11	235 dec.	Calcd.:	71.05	7.44	13.75	
		A[f]	29	235 dec.	Found:	70.70	7.47	13.10	
XXXVII	Cyclohexyl-	B	80	184–186	Calcd.:	74.42	8.53	10.85	183–184
		A	49	191.0–191.5	Found:	74.70	8.79	11.25	
XXXVIII[c]	$C_6H_5CH_2$—	A	17	171–172	Calcd.:	76.69	6.77	10.53	152–153
					Found:	76.55	6.99	10.21	dec.
XXXIX[c]	C_6H_5—	B	59	186–187	Calcd.:	76.19	6.35	11.11	not formed
XL[d]	3,4,5-Trimethoxyphenyl-	A	35	182–183	Found:	76.35	6.41	11.18	
		B	37	223–225	Calcd.:	66.67	6.43	8.19	not formed
					Found:	66.45	6.33	8.08	
XLI[e]	4-Nitrophenyl-	A	90	210–212	Calcd.:	64.65	5.05	14.14	170–172
		B[g]	20	191–194	Found:	64.55	4.98	14.10	

[a] Method A: The 8-amino-1,2,3,4-tetrahydroquinoline was treated with an equivalent of the acid chloride in benzene at room temperature. The mixture was allowed to stand overnight and was then filtered. The solid was slurried with dilute ammonium hydroxide and recrystallized from methanol or methanol-water. Method B: a modification of Method A. A small amount of pyridine was added to the mixture. [b] Formed the picrate of 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV). [c] *N*-Nitroso derivative, m.p. 145–150°. [d] *N*-Nitroso derivative, m.p. 160°. [e] *N*-Nitroso derivative, m.p. 165–170°. [f] The mixture was refluxed for 5 hr. [g] The mixture was refluxed overnight.

densed readily with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid to yield the corresponding 2-hydroxymethyl- (V), and 2-mercaptomethyl-5,6-dihydroimidazo[ij]quinoline (VI). The next higher homolog of the latter compound, 2-(β-mercaptoethyl)-5,6-dihydroimidazo[ij]quinoline (VII) was synthesized in an analogous manner from β-mercaptopropionic acid. This product was an oil, the only liquid product observed during the course of this work. Upon continued standing or with heating under vacuum, the β-mercaptoethyl compound yielded a solid in addition to hydrogen sulfide. This solid was β,β′-bis-2-(5,6-dihydroimidazo[ij]quinolyl)ethyl sulfide (XXX) which may have formed by an addition of a second molecule of VII to 2-vinyl-5,6-dihydroimidazo[ij]quinoline, which should be the initial product.

A convenient synthesis of 2-mercapto-5,6-dihydroimidazo[ij]quinoline (XII) involved the condensation of 8-amino-1,2,3,4-tetrahydroquinoline with carbon disulfide in refluxing ethanol.

Another interesting condensation, which led to 2-(γ-hydroxypropyl)-5,6-dihydroimidazo[ij]quinoline (VIII), involved the condensation of γ-butyrolactone with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid. That this reaction first involved a hydrolysis of the lactone to γ-hydroxybutyric acid was shown by the inability of γ-butyrolactone to condense with 8-amino-1,2,3,4-tetrahydroquinoline hydrochloride when the reactants were heated without a solvent.

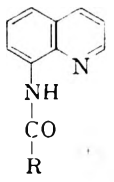
Dibasic acids such as succinic, glutaric, and adipic acids condensed readily forming the expected bisdihydroimidazo[ij]quinolines when refluxed with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid. The series was further extended by the condensations of diglycollic and thiodiglycollic acids to form the corresponding bismethyl ether (XXVIII) and bismethyl sulfide (XXIX). Malic acid condensed with 8-amino-1,2,3,4-tetrahydroquinoline in refluxing 4*N* hydrochloric acid to yield two products. One of them was the expected α-hydroxy-2,2′-ethylenebis- (XXXI), and the other was 2,2′-vinylenebis(5,6-dihydroimidazo-[ij]quinoline) (XXVII). The fact that maleic and fumaric acids did not yield any condensed products indicates that the unsaturated compound (XXVII) was formed from the carbinol (XXXI) by the elimination of water. Thiomalic acid formed only XXVII.

Condensations with acid chlorides. Tables III and IV list the 8-*N*-acylaminotetrohydroquinolines and 8-*N*-acylaminoquinolines synthesized during the course of this work and are found below.

Acid chlorides were successfully condensed with 8-amino-1,2,3,4-tetrahydroquinolines in many cases

TABLE IV

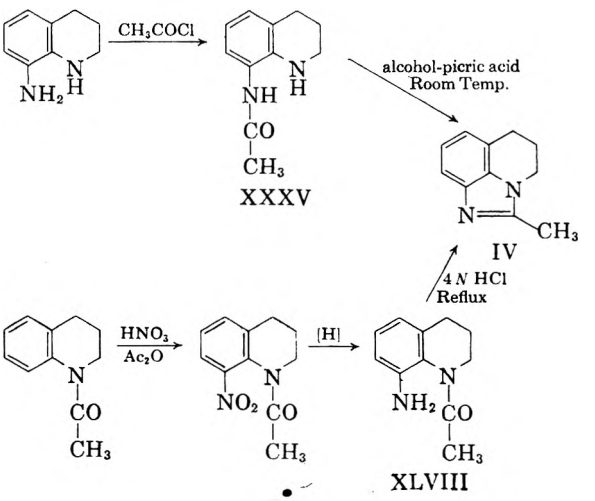
8-N-ACYLAMINOQUINOLINES



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XLII	H—	C	Quant.	152–154	Calcd.:	69.77	4.65	16.27	140
					Found:	69.90	4.96	16.78	
XLIII	CH_3—	A	85	100–101[d]	Calcd.:	70.94	5.42	15.05	196–197
					Found:	71.05	5.43	14.80	
XLIV	C_6H_5—	A	49	91–92[c]	Calcd.:	77.42	4.84	11.29	189–190
					Found:	77.40	5.15	11.28	
XLV	3,4,5-Trimethoxyphenyl-	A	18	134	Calcd.:	67.46	5.33	8.28	195–198
		B[e]	62	132–133	Found:	67.30	5.28	8.27	
XLVI	4-Nitrophenyl-	A	93	182–183[b]	Calcd.:	65.53	3.75	14.33	155–156
					Found:	65.65	3.64	14.38	

[a] See footnote *a* in Table III for Methods A and B. Method C: A solution of 8-amidoquinoline in 85% formic acid was refluxed overnight. The solution was cooled and made alkaline with dilute ammonium hydroxide. The solid was recrystallized from methanol-water. [b] Gorvin[19] reported a melting point of 188°. [c] Hall[20] claimed to have synthesized this compound but reported no physical properties. [d] Ochiai *et al.*[21] reported a melting point of 102–103°. [e] The mixture was refluxed for 3 hr.

and were especially useful in the synthesis of aromatic- and heterocyclic-substituted dihydroimidazo[ij]quinolines which could not be attained *via* the corresponding carboxylic acid.[18] In refluxing benzene or benzene-pyridine, the desired product was sometimes attained directly (IV, XV, and XVII), while at room temperature the amide intermediate was isolated exclusively. That the acyl group was located on the primary nitrogen of 8-amino-1,2,3,4-tetrahydroquinolines was shown by the fact that the amides readily formed a solid *N*-nitroso derivative with nitrous acid. In addition, 8-benzamidotetrahydroquinoline (XXXIX) formed a precipitate with benzenesulfonyl chloride in an alkaline medium and another with nickel chloride–carbon disulfide reagent, both reactions being indicative of a free secondary amino function. It was further found that 8-benzamido-1-benzoyltetrahydroquinoline (XLVII) did not react with nitrous acid, thus ruling out the possibility of *N*-nitrosation of an amide function. Conclusive proof of the reactive nitrogen in 8-amino-1,2,3,4-tetrahydroquinoline was attained by the synthesis of both of the isomeric, monoacetylated 8-amino-1,2,3,4-tetrahydroquinoline derivatives (XXXV and XLVIII). One isomer (XXXV) was synthesized by treating a benzene solution of 8-amino-1,2,3,4-tetrahydroquinoline with acetyl chloride in a procedure identical with that employed in the synthesis of some of the 8-amidotetrahydroquinolines described above. The product was a solid with an analysis corresponding to a monoamide of 8-amino-1,2,3,4-tetrahydroquinoline. It could not be diazotized, but formed an alkali insoluble solid with benzenesulfonyl chloride. An absorption spectrum (λ-max, log ε: 251, 3.91; 306, 3.52 mμ) was typical of an 8-acylaminotetrahydroquinoline. In alcoholic picric acid solution, it formed the picrate of 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV), which indicates the ease of cyclization of the amide which has been assigned structure XXXV. The other isomer, 8-amino-1-acetyltetrahydroquinoline (XLVIII) was synthesized by reduction of 8-nitro-1-acetyltetrahydroquinoline either catalytically or with iron and acetic acid. It (XLVIII) was an oil which had the correct analysis for a monoamide of 8-amino-1,2,3,4-tetrahydroquinoline and could be diazotized and coupled with β-naphthol.



(18) Where the desired product could be obtained through the acid as well as *via* the acid chloride, it was observed (Table I) that generally, the acid chloride led to a better yield of the dihydroimidazo[ij]quinoline.

(19) J. H. Gorvin, *J. Chem. Soc.*, 61 (1946).

(20) D. M. Hall, *J. Chem. Soc.*, 1603 (1948).

(21) E. Ochiai, J. Haginiwa, and K. Komatsu, *J. Pharm. Soc., Japan*, 70, 372 (1950), *Chem. Abstr.*; 45, 2476a (1951).

Treatment with refluxing 4*N* hydrochloric acid for two hours caused cyclization to 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV). An absorption spectrum (λmax, log ε: 257, 4.11; 282.7, 3.74 mμ) was different from that of XXXV, and the amide did not cyclize in alcoholic picric acid solution, but formed a picrate of the desired product as indicated by the analysis. These results leave no doubt that the reactive nitrogen in 8-amino-1,2,3,4-tetrahydroquinoline, is the primary nitrogen.

Occasionally it was necessary to treat an amide separately with a cyclizing agent to form the desired dihydroimidazoquinoline. Thus, 8-(4′-nitrobenzamido)tetrahydroquinoline (XLI) could be cyclized to 8-(4′-nitrophenyl)-5,6-dihydroimidazo[ij]quinoline (XVI) by phosphorus pentoxide in refluxing benzene, or better, by phosphorus oxychloride. This amide could not be ring-closed by heating under vacuum above its melting point or by employing polyphosphoric acid at 80°. In the only attempt at cyclization of 3′,4′,5′-trimethoxybenzamidotetrahydroquinoline (XL), a nearly quantitative yield of product (XV) was obtained by the use of phosphorus pentoxide in refluxing benzene. A nearly quantitative yield of the desired ring-closed product (XIV) was also obtained when 8-benzamidotetrahydroquinoline (XXXIX) was treated under the same conditions. The latter could also be cyclized in refluxing phosphorus oxychloride to give a 43% yield of the product, although no cyclized product was obtained when this amide was heated under vacuum above its melting point. The most difficult amide to cyclize was 8-cyclohexylcarboxamidotetrahydroquinoline (XXXVII). This compound failed to lose the elements of water when heated above its melting point under vacuum, when treated with polyphosphoric acid at 80°, when refluxed with phosphorus pentoxide in benzene, or when refluxed with phosphorus pentachloride in phosphorus oxychloride. It did ring-close (X), however, when refluxed with phosphorus pentoxide and phosphorus oxychloride in xylene.

A most interesting application of these methods was the use of phosgene. When 8-amino-1,2,3,4-tetrahydroquinoline was heated with phosgene in an acetic acid-chlorobenzene solution, a 75% yield of 2-hydroxy-5,6-dihydroimidazo[ij]quinoline resulted (XI). Like the 2-mercapto compound (XII) the product appeared to exist mainly as the keto form since the absorption spectrum (Figure V) resembled that of 8-amino-1,2,3,4-tetrahydroquinoline which is essentially an *N*-substituted phenyleneurea. By refluxing the 2-hydroxy compound (XI) in phosphorus oxychloride for one to two hours, the corresponding 2-chloro-5,6-dihydroimidazo[ij]quinoline (XIII) was formed in 60% yield. In addition, 2-methoxy-5,6-dihydroimidazo[ij]quinoline (XXI) formed quantitatively when the chloro compound (XIII) was treated with sodium methoxide.

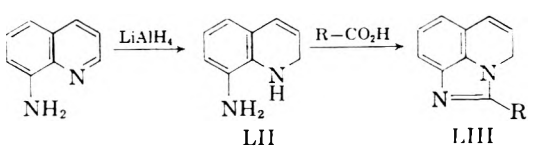
The use of dibasic acid chlorides was generally unsuccessful, although in two cases, a characterizable product was isolated. Adipyl chloride formed *N*,*N*′-bis[8′-(1′,2′,3′,4′-tetrahydroquinolyl)]adipamide (XXXVI) at room temperature and at reflux temperature in benzene. As the corresponding tetramethylenebisdihydroimidazoquinoline (XXVI) formed readily with adipic acid in 4*N* hydrochloric acid, no attempt was made to ring-close this amide. Oxalyl chloride produced only a pyridoquinoxaline (XLIX) with 8-amino-1,2,3,4-tetrahydroquinoline.

Other dibasic acid chlorides were not successfully condensed with 8-amino-1,2,3,4-tetrahydroquinoline; thus, terephthalyl chloride formed an intractable product, while reactions with fumaryl, maleyl, chloroacetyl, diethylcarbamyl, and β-diethylaminopropionyl chlorides all led to tars.

Condensations with amides. The use of amides proved fruitful in the synthesis of 2,2′-bis(5,6-dihydroimidazo[ij]quinoline) (XXII) and 2,2′-methylenebis(5,6-dihydroimidazo[ij]quinoline) (XXIII) where other methods failed. Because oxamide is probably the immediate precursor to the former product, ammonium oxalate was employed with success in ethylene glycol or in the absence of solvent, as it decomposes to oxamide above 150°. The products were best synthesized by heating the required reactant with an equivalent quantity of 8-amino-1,2,3,4-tetrahydroquinoline in the absence of solvent. Under these conditions, both ammonium oxalate and malonamide formed the desired products (XXII and XXIII respectively). When ethylene glycol was employed as a high boiling solvent, ammonium oxalate formed the desired product (XXII) in a very low yield while malonamide formed a small amount of a high-melting, unidentified product. Benzamide did not condense in ethylene glycol or in the absence of solvent.

Condensations with benzoins. Hazlewood[4] found that benzoin condensed with 8-amino-1,2,3,4-tetrahydroquinoline to form the disubstituted pyridoquinoxaline (L) and we were likewise successful with anisoin in obtaining LI. Pyridoin, however, did not give any recognizable product and decomposition was obvious.

Imidazo[ij]quinolines. A route to this series which appeared probable is as follows:

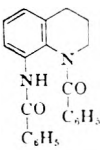
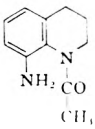
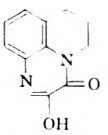
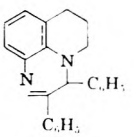
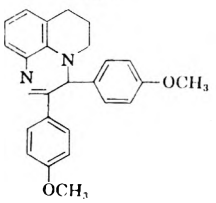


LII LIII

The required intermediate, 8-amino-1,2-dihydroquinoline (LII), is not a known compound, and attempts were made to synthesize it *via* a lithium aluminum hydride reduction of 8-aminoquinoline. A green-yellow oil formed whose elemental analysis was close to that calculated for the desired product. The compound formed a picrate which

TABLE V

MISCELLANEOUS COMPOUNDS

No.	Structure	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XLVII[a,d]		84	155–157	Calcd.:	77.52	5.62	7.86	Not formed
				Found:	78.05	5.71	7.92	
XLVIII		77	oil	Calcd.[c]:	48.68	4.10	16.71	205
				Found:	48.60	4.00	16.60	
XLIX[a,e]		low	258–260	Calcd.:	65.35	4.95	13.86	Not formed
				Found:	65.45	5.26	13.67	
L		28	148.0–148.5[b]					150–151 dec.
LI[f]		30	148–149	Calcd.:	78.10	6.30	7.28	166
				Found:	78.20	6.40	7.12	

[a] Refer to method B and footnote *g* of Table III for experimental details. [b] Hazlewood, *et al.*[4] reported a melting point of 146°. [c] Analyzed as the monopicrate, $C_{17}H_{17}N_5O_8$. [d] Two moles of benzoyl chloride were employed per mole of 8-amino-1,2,3,4-tetrahydroquinoline. [e] Oxalyl chloride was condensed with 8-amino-1,2,3,4-tetrahydroquinoline. [f] The method of Hazlewood, *et al.*[4] was employed. The appropriate benzoin was heated with 8-amino-1,2,3,4-tetrahydroquinoline over a free flame until effervescence ceased. The product was extracted with ethanol and recrystallized from ethanol or ethanol-water.

TABLE VI

ABSORPTION MAXIMA OF 2-SUBSTITUTED 5,6-DIHYDROIMIDAZO[ij]QUINOLINES

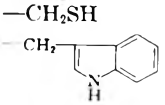
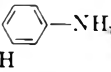
—R	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε
—H	—	—	257	3.78	274	3.65	283.1	3.59
—CH_3	—	—	255.2	3.73	273.6	3.63	282.4	3.62
—CH_2OH	—	—	259	3.83	276	3.77	285	3.63
—CH_2SH	—	—	—	—	—	—	282	4.14
	225	4.37	258	4.06	274.6	4.10	283.5	4.08
—CH_2—S—  —NH_2	—	—	265	4.21	—	—	—	—
—CH_2CH_2SH	222.2	4.06	256.7	3.86	275	3.77	284	3.72
—$CH_2CH_2CH_2OH$	—	—	256	3.85	274	3.79	282.8	3.77
—$CH_2CH_2CH_2OCOCH_3$	—	—	256	3.86	274	3.79	283	3.73
Cyclohexyl	—	—	256.5	3.69	274.5	3.64	283.2	3.67
—OH	225–234	3.82	—	—	—	—	284	3.76
—OCH_3	—	—	242.5	3.72	275	3.58	282	3.63
—SH	225	4.27	247.6	4.26	—	—	304.8	4.47
—Cl	—	—	256.0	3.88	275.0	3.82	283.5	3.78
C_6H_5	—	—	240	4.19	—	—	290	4.22
p-NO_2—C_6H_4—	—	—	240–248	4.10	—	—	337.5	4.20
3,4,5-Trimethoxyphenyl	222–225	4.55	252.5	4.07	—	—	298	4.35
β-Naphthyl	—	—	243	4.69	280	435	308	4.36
4-Pyridyl	—	—	250.7	3.95	—	—	306	4.21

TABLE VII

ABSORPTION MAXIMA OF 2,2′-BIS(5,6-DIHYDROIMIDAZO[ij]QUINOLINE) COMPOUNDS

No G— Present	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε
—CH₂—	—	—	240.8	4.39	264	4.22	327.5	4.41	368	3.13	387	3.45	409	3.63	435	3.53
—CH₂CH₂—	—	—	258	4.14	276	4.11	284.8	4.09	360	3.12	—	—	—	—	—	—
—(CH₂)₃—	221	4.34	258	4.16	275.3	4.13	284	4.09	—	—	—	—	—	—	—	—
—(CH₂)₄—	—	—	256.5	4.18	274.9	4.14	283.5	4.09	—	—	—	—	—	—	—	—
—CH₂OCH₂—	—	—	256.6	4.13	275	4.07	284	4.04	—	—	—	—	—	—	—	—
—CH₂SCH₂—	222	4.33	261.3	4.18	274	4.15	—	—	—	—	—	—	—	—	—	—
—CH₂—CH(OH)—	222	4.37	265	4.14	280	4.17	—	—	—	—	—	—	—	—	—	—
—CH₂CH₂SCH₂CH₂—	—	—	259	4.18	276	4.17	284	4.09	—	—	—	—	—	—	—	—
—CH=CH—	221	4.38	258.5	4.17	275.5	4.15	284.4	4.10	—	—	—	—	—	—	—	—
	—	—	251	4.08	—	—	285	3.56	360	4.40	277	4.42	396	4.34	—	—

reverted to the picrate of 8-aminoquinoline upon recrystallization. When refluxed with formic or acetic acid, the corresponding 8-aminoquinolines resulted (XLII and XLIII respectively). No 2-substituted imidazo[ij]quinolines (LIII) were isolated nor were any of the corresponding 5,6-dihydro derivatives (II) found; the latter would most certainly have formed were there any 8-amino-1,2,3,4-tetrahydroquinolines present.

The spectra of the 5,6-dihydroimidazo[ij]quinolines. The compounds in this series exhibited spectra which were characteristic of the benzimidazoles and could often be identified through their spectra. Tables VI and VII list the absorption maxima of the compounds described in this paper. Fig. 1 illustrates the similarity of the spectrum of 5,6-dihydroimidazo[ij]quinoline (III) to that of benzimidazole, while the other figures indicate the effect of the 2-substituent upon the spectrum of the parent compound (III).

The difference in the spectra of the parent compound (III) and the 2-alkyl substituted compounds was negligible. Alkyl groups with substituents further removed from the heterocyclic system than

Fig. 1. Absorption maxima of 5,6-dihydroimidazo[ij]-quinoline as compared with benzimidazole

Fig. 2. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

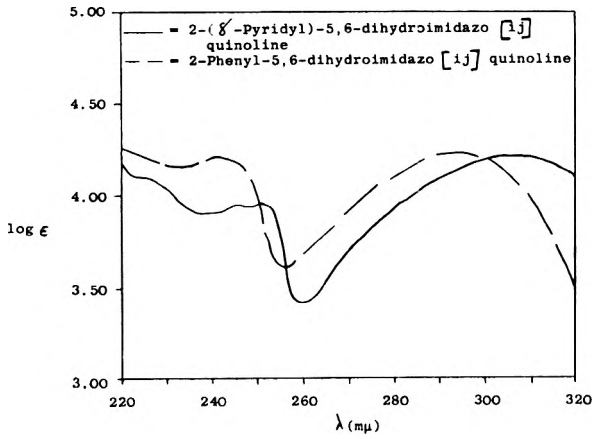


Fig. 3. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

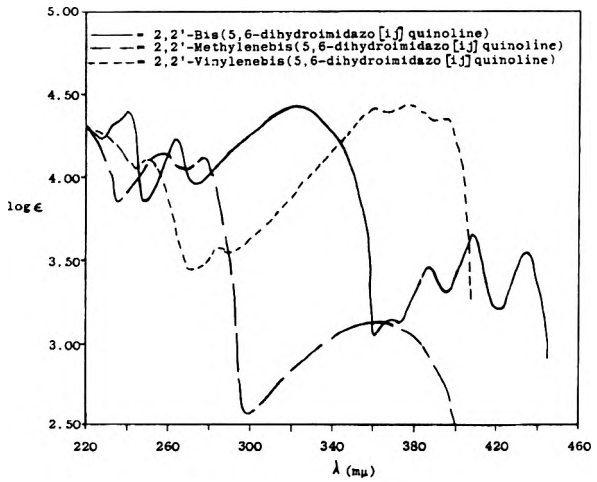


Fig. 4. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

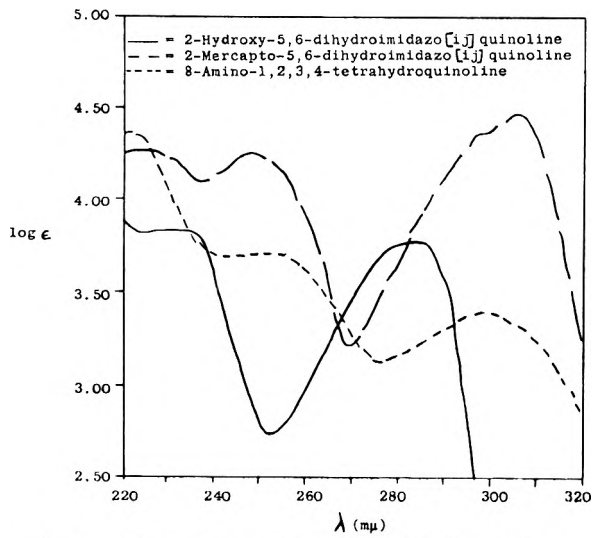
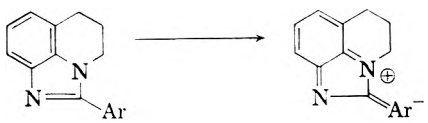
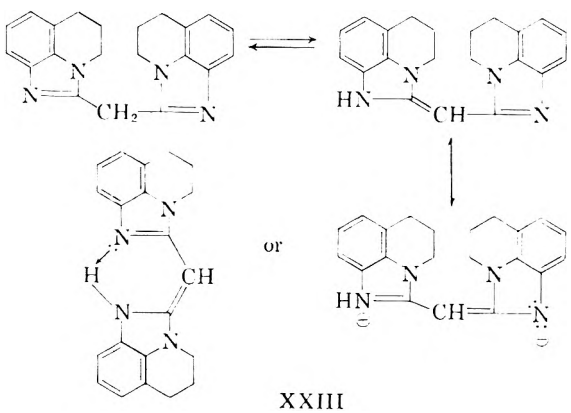


Fig. 5. Absorption maxima of substituted quinolines

one methylene group likewise had a negligible effect upon the resultant spectrum. A definite effect was noted, however, where α-substituted alkyl groups were present in the 2-position of the dihydroimidazo[ij]quinoline nucleus. In certain cases [2-hydroxymethyl- (V), 2-mercaptomethyl- (VI), 2-(3′-indolylmethyl)- (XX) and 2-(*p*-aminothiophenoxymethyl - 5,6 - dihydroimidazo[ij]quinoline (XIX)], the effect may have been merely inductive as the fine structure disappeared and a broad maximum resulted, while in others, the effect appeared to be mesomeric in nature. The latter appeared to be important in the case of the 2-aromatic or 2-heterocyclic substituted compounds as well as in the case of certain bisdihydroimidazo-[ij]quinolines capable of conjugation through the bridge (XXII, XXIII, and XXVII). Furthermore, as the aromatic or heterocyclic substituent was increasingly capable of accepting a negative charge, the long wave length maximum shifted bathochromically. One of the major contributors to the excited state may therefore be:



A unique compound is 2,2′-methylenebis(5,6-dihydroimidazo[ij]quinoline) (XXIII). Although this molecule exhibited a typical spectrum in the ultraviolet, it also absorbed in the visible (Figure IV). For this to occur, a conjugation of the heterocyclic groups through the methylene group is necessary. Such a conjugation may be brought about by an initial tautomerism of a methylene hydrogen; furthermore, the charged species which appears to be responsible for the long wave length absorption may be stabilized by a cyclization which would result in the formation of hydrogen bonded six-membered ring. The resulting system is distinctly reminiscent of the pyrromethenes.



XXIII

A comparison of the spectra of the 2-hydroxy- (XI) and 2-mercapto- (XII) compounds with those of 2-methoxy-5,6-dihydroimidazo[ij]quinoline (XXI) and 8-amino-1,2,3,4-tetrahydroquinoline revealed that these substances exist primarily in the corresponding keto forms.

Pharmacological results. To date, eight of the substituted dihydroimidazo[ij]quinolines (VI, VII, VIII, XV, XVII, XVIII, XXIV, XXVI) have

been screened for pharmacological activity. One of those examined, 2-mercaptomethyl-5,6-dihydroimidazo[ij]quinoline (VI) was active toward dextran edema; however, the remaining seven compounds displayed no pharmacological activity.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Commercial intermediates were used without further purification. Yields correspond to the amount of pure product obtained.

Starting materials. The 8-aminoquinoline (m.p. 63–64°) was produced by an iron and acetic acid reduction of the 8-nitro compound[22] or in 67% yield from oxine[23] employing a reaction ratio of 1:2:10 of oxine, ammonium sulfite, and ammonia. When the amount of sodium in the sodium-alcohol reduction of 8-aminoquinoline[4] was increased to 14–15 g.-atoms per mole of 8-aminoquinoline, the yield rose to 84% of pure 8-amino-1,2,3,4-tetrahydroquinoline, b.p. 145° at 2 mm. Isonicotinyl chloride was obtained from the acid with thionyl chloride in 88% yield, b.p. 95–96° at 25 mm, by an adaptation of Koo's method.[24]

Directions for the methods used in the preparation of the dihydroimidazo[ij]quinolines and related compounds are to be found as footnotes to the appropriate table.

8-Nitro-1-acetyl-1,2,3,4-tetrahydroquinoline. A solution of 1-acetyltetrahydroquinoline (6.7 g. 0.0382 mole) in 10 ml. of acetic anhydride was cooled and treated cautiously with a solution of 3.6 g. (0.04 mole) of 70% nitric acid in 10 ml. of acetic anhydride. After 0.5 hr. in an ice bath, the red mixture was allowed to stand at room temperature overnight (12 hr.). The solution was poured onto ice. The oil which separated was extracted with ether and the ethereal solution was washed with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent yielded 7.3 g. (89%) of the product as a red oil, which, on acid hydrolysis afforded the known 8-nitro-1,2,3,4-tetrahydroquinoline, m.p.: 82–84° (lit.,[25] m.p. 82–83°).

8-Amino-1,2-dihydroquinoline (LII). A slurry of 6.5 g. (0.174 mole) of lithium aluminum hydride in 150 ml. of absolute diethyl ether was heated to boiling with stirring. To the slurry was added 5.0 g. (0.0347 mole) of 8-aminoquinoline (Eastman) dissolved in 50 ml. of absolute diethyl ether. The mixture was refluxed for 24 hr. during which time the initially blood-red slurry became lighter and a yellow solid remained. The slurry was cooled to 0° and water was added cautiously with stirring under a nitrogen atmosphere until hydrolysis was complete. The mixture was filtered, the filtrate dried over magnesium sulfate, and the solvent evaporated and the residue distilled. The green-yellow oil boiled at 157–160° (6 mm.).

Anal. Calcd. for: $C_9H_{10}N_2$: C, 73.94; H, 6.91; N, 19.17. Found: C, 73.10; H, 6.71; N, 18.50–18.63.

A picrate formed as golden-brown needles which melted at 204–205° and showed no depression in melting point when admixed with authentic 8-aminoquinoline picrate. In another experiment, an orange picrate formed which melted at 192–194° and showed a depression of 20° when admixed with 8-aminoquinoline picrate. When the orange picrate was recrystallized from 95% ethanol, however, golden-brown needles resulted which melted at 200–201° and proved to be 8-aminoquinoline picrate by a mixture melting point.

Condensation of certain acids with 8-amino-1,2-dihydroquinoline. A. Formic acid. A solution of 1.1 g. (0.0075 mole) of 8-amino-1,2-dihydroquinoline in 25 ml. of 85% formic acid was refluxed overnight (13–17 hr.). The orange solution was cooled and made alkaline with dilute ammonium hydroxide, whereupon a silvery solid separated which was filtered, washed with water, and recrystallized from methanol to yield colorless needles which melted at 148.0–148.5°. A mixture melting point with authentic 8-formamidoquinoline (XLII) showed no depression, and an analysis and ultraviolet spectrum confirmed the 8-formamidoquinoline structure.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.77; H, 4.65; N, 16.27. Found: C, 69.90; H, 4.96; N, 16.78.

B. Acetic acid. Reaction with acetic acid afforded only 8-acetamidotetrahydroquinoline, m.p. 100–101° (lit.,[21] m.p. 102–103°).

Acknowledgment. The authors wish to express their thanks to Dr. C. H. Tilford, Dr. G. L. Krueger, and the Wm. S. Merrell Company for their interest, advice, and financial assistance during the course of this work. Thanks are due also to Dr. V. B. Fish of Lehigh University who performed the analyses.

BETHLEHEM, PA.

(22) R. P. Dikshoorn, *Rec. Trav. Chim.*, **48**, 147 (1929).

(23) N. W. Woroshtzow and J. M. Kogan, *Ber.*, **65**, 142 (1932).

(24) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

(25) R. Stoermer, *Ber.*, **31**, 2523 (1898).

[CONTRIBUTION FROM THE DIVISION OF SCIENCES, LOUISIANA STATE UNIVERSITY IN NEW ORLEANS]

Preparation of 5,6-Dihydro-1,3-thiazines and 2-Thiazolines from Mercaptoalcohols and Nitriles[1]

ALBERT I. MEYERS

Received January 18, 1960

Treatment of certain mercaptoalcohols with nitriles in cold concentrated sulfuric acid results in a one-step nuclear synthesis of dihydro-1,3-thiazines and 2-thiazolines. This ring closure has been found to be applicable to a wide variety of nitriles.

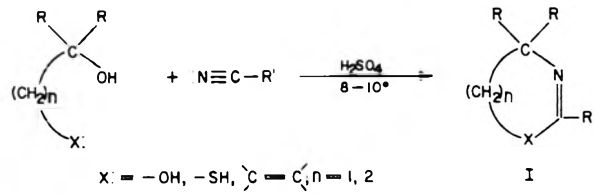
Earlier methods of synthesis of dihydro-1,3-thiazines and 2-thiazolines have been extensively reviewed by Elderfield[2] and Kuhn and Drawert[3]

(1) Presented before the 15th Annual Southwest Regional meeting of the American Chemical Society, Baton Rouge, La., December 3–5, 1959.

(2) R. C. Elderfield and E. E. Harris, *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, 1957, p. 604.

(3) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).

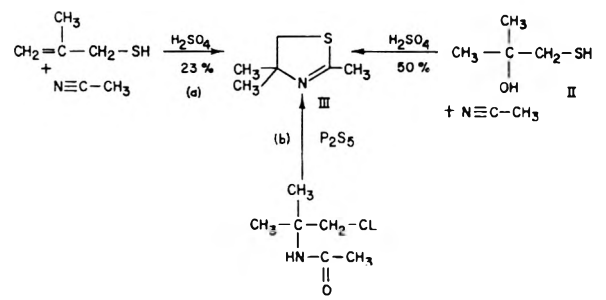
respectively. More recently there have appeared several reports on new methods of obtaining these heterocyclics from the treatment of diacylated aminoalcohols with phosphorus pentasulfide[4] and the reaction of nitriles with methallyl mercaptan in sulfuric acid.[5] The latter method is part of a new



X = −OH, −SH, >C=C<; n = 1, 2 I

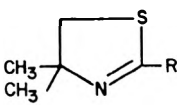
and general synthetic route to *N*-heterocycles of the type, I. Heterocyclic bases which have been prepared by this method and reported to date include 5,6-dihydro-1,3-oxazines,[6] 1-pyrrolines, 5,6-dihydropyridines, and 2-thiazolines.[5] This type of ring closure is presently considered as an extension of the Ritter *N*-alkylamide[7] synthesis which is brought about by the sulfuric acid-catalyzed reaction of nitriles and tertiary alcohols or olefins.

2-Thiazolines. Addition of 2-methyl-2-hydroxypropanethiol (II) to a cold solution of acetonitrile in concentrated sulfuric acid leads to the formation of 2,4,4-trimethyl-2-thiazoline (III) in about 50% yield. Comparison of the physical properties of this product with that prepared from (a) methallyl mercaptan and acetonitrile and (b) *N*-(2-chloro-*tert*-butyl)acetamide and phosphorus pentasulfide[8] revealed the product to be the same *via* all three routes.



The use of the mercaptoalcohol, rather than the unsaturated mercaptan, in the preparation of the 2-thiazolines possesses two distinct advantages. First, the yield of the 2-thiazoline was considerably higher (Table I) when the mercaptoalcohol was employed. This is attributed to the fact that the alcohol does not polymerize as readily as the methallyl mercaptan in concentrated sulfuric acid. This contrast in behavior has been previously observed[5] in the preparation of other *N*-heterocycles by this method. The second advantage in using the mercaptoalcohol lies in the fact that only an equimolar ratio of nitrile to mercaptoalcohol is required whereas a twofold excess of the methallyl mercaptan was necessary to yield the 2-thiazoline in approximately half the amount. The excess methallyl mercaptan was originally employed in an attempt to overcome the extensive polymerization that it had undergone in the acid medium.

TABLE I

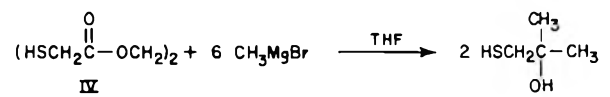


2-SUBSTITUTED 4,4-DIMETHYL-2-THIAZOLINES

Nitrile	R	% Yield of 2-Thiazoline from: Methallyl Mercaptan[a]	% Yield of 2-Thiazoline from: 2-Methyl-2-hydroxypropanethiol
Acetonitrile	Methyl	23	50
Acrylonitrile	Vinyl	22	47
Benzonitrile	Phenyl	24	51
p-Aminobenzonitrile	*p*-Aminophenyl	....	55

[a] See ref. 5.

The mercaptoalcohol, previously unreported, was prepared in 40% yield by the action of glycol dimercaptoacetate (IV) with methylmagnesium bromide in tetrahydrofuran. This reaction proceeded poorly in diethyl ether, due to the insolubility of the magnesium salt of the mercaptoester.



5,6-Dihydro-1,3-thiazines. When 3-methyl-3-hydroxy-*n*-butanethiol was added to a previously cooled solution of a nitrile in concentrated sulfuric acid, there was obtained a 2-substituted-4,4-dimethyl-5,6-dihydro-1,3-thiazine (VI) in 41–53% yield. A considerable quantity of polymeric material accompanied the formation of the product. Eight 5,6-dihydro-1,3-thiazines were prepared in this manner and their physical constants appear in Table II. This dihydro-1,3-thiazine synthesis further illustrates the scope of this nuclear nitrogen heterocyclic synthesis from nitriles. The formation of the thiazine ring is currently considered to occur in a manner completely analogous to the 2-thiazoline synthesis. As previously pointed out,[5] the primary adduct, V, which is similar to that which forms in Ritter *N*-alkylamide synthesis, is capable of ring closure if an electron-rich group is suitably situated elsewhere in the molecule.

(4) V. G. Bach and M. Zahn, *J. Prakt. Chem.*, **8**, 68 (1959).

(5) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

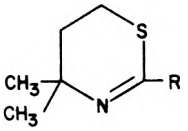
(6) E. J. Tillmans and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

(7) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045, 4048 (1948).

(8) S. H. Babock and R. Adams, *J. Am. Chem. Soc.*, **59**, 2260 (1937).

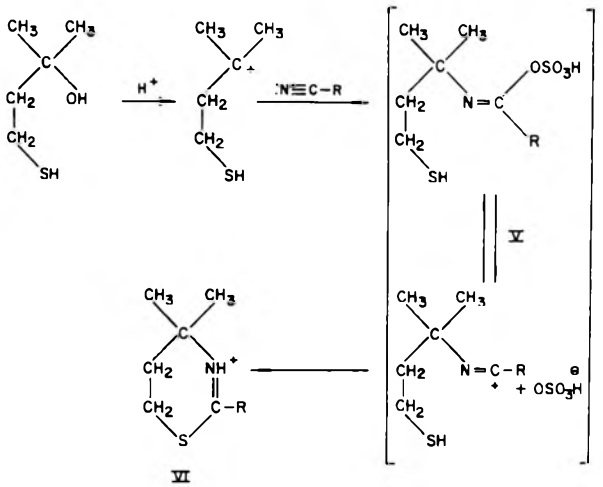
TABLE II

2-SUBSTITUTED 4,4-DIMETHYL-5,6-DIHYDRO-1,3-THIAZINES



No.	R	B.P.°, mm.	n_D^{30}	Yield, %	Formula	C Calcd.	C Found	H Calcd.	H Found	Picrate[a] M.P.,°
1	H	63–64/11	1.5109	42	$C_6H_{11}NS$	55.81	55.91	8.54	8.48	198–201
2	CH_3	53–54/1.5	1.5051	41	$C_7H_{13}NS$	58.71	58.39	9.01	8.93	176–177
3	C_2H_5	62–63/1.3	1.4943	46	$C_8H_{15}NS$	61.14	61.07	9.55	9.42	145–146
4	CH_2=CH	60–62/1.3	1.5273	51	$C_8H_{13}NS$	61.93	62.01	8.38	8.29	144–146
5	C_6H_5	119–121/1.3	1.5810	48	$C_{12}H_{15}NS$	70.22	70.31	7.33	7.30	141–142
6	p-$CH_3C_6H_4$	136–137/1.3	1.5750	50	$C_{13}H_{17}NS$	71.23	71.03	7.76	7.66	173–174
7	o-$CH_3C_6H_4$	130–131/1.5	1.5656	45	$C_{13}H_{17}NS$	71.24	70.89	7.70	7.44	166–167
8	p-$NH_2C_6H_4$	95–96[b]	...	53	$C_{12}H_{16}N_2S$	65.46	65.46	7.27	7.19	133–134

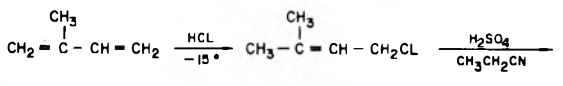
[a] Recrystallized from ethanol. [b] Melting point, recrystallized twice from 50% aqueous ethanol.

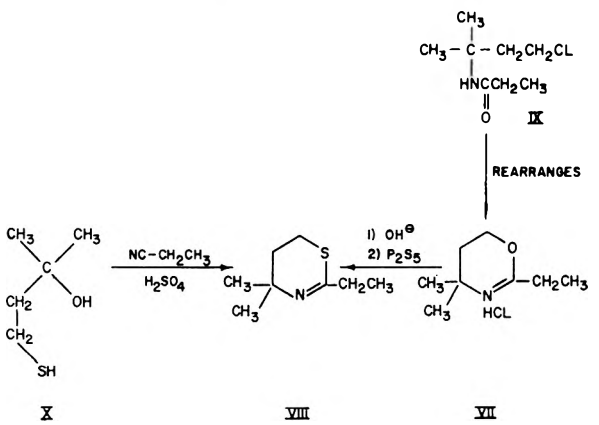


Thus far, the hydroxyl, thiol, and alkene groups have served as nucleophilic centers which have participated in ring closure with the *nitrilium* ion (R—N=C—R). The question of the existence of the *nitrilium* species in this reaction is still at hand. The possibility also exists that the ring closure may occur by the nucleophilic attack of the thiol group on the *nitrilium* sulfate (R—N=C(OSO_3H)R) with subsequent displacement of the bisulfate ion. These possibilities are currently under consideration and an attempt to establish the mechanism of this step in the ring closure is in progress. One fact that lends support to the over-all proposed mechanism of this reaction is that on the basis of the dihydro-1,3-oxazine synthesis,[6] all the subsequent heterocyclic systems prepared by this method were predicted before actually being performed.

The structure of the 5,6-dihydro-1,3-thiazines were proven by an alternative method of synthesis. By heating 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (VII) with phosphorus pentasulfide for two hours at 150°, 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (VIII) was obtained. The oxazine was prepared by treating 4-chloro-2-methyl-2-butene[9] with propionitrile according to the method of Ritter and Lusskin.[10] The oxazine, rather than the expected *N*-(3-chloro-1-methyl-butyl-2) propionamide (IX) was isolated directly.[11]

These workers found that in some cases the *N*-(chloroalkyl)amides rearranged directly without treatment with base. Comparison of the physical properties of the thiazine prepared from propionitrile and the mercaptoalcohol with those of the thiazine prepared directly[12] from the oxazine showed both products to be identical.





The infrared spectra of the 2-alkyl-5,6-dihydro-1,3-thiazines revealed a strong band in the 6.11–6.15μ region which is attributed to the cyclic unconjugated C=N link on the basis of a previous

(9) (a) W. J. Jones and H. W. T. Chorley, *J. Chem. Soc.*, 1946, 832; (b) A. J. Ultee, *Rec. trav. chim.*, **68**, 125 (1949).

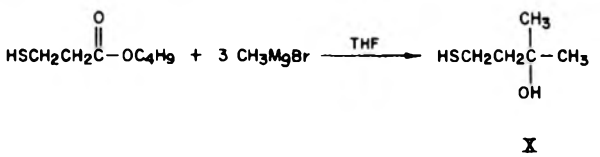
(10) J. J. Ritter and R. M. Lusskin, *J. Am. Chem. Soc.*, **72**, 5577 (1950).

(11) See footnote in reference 5.

(12) S. Gabriel and T. Posner, *Ber.*, **27**, 3519 (1894).

investigation.[13] The spectra of the 2-aryl derivatives and the 2-vinyl derivatives showed strong bands in 6.20–6.30μ region. A comparison of the C=N absorption of these dihydro-1,3-thiazines with the C=N absorption of dihydro-1,3-oxazines will be reported in a subsequent communication.

The synthesis of 3-hydroxy-3-methyl-*n*-butanethiol (X) in 63% yield was accomplished by treating *n*-butyl 3-mercaptopropionate with an excess of methylmagnesium bromide in tetrahydrofuran. As mentioned earlier, the use of tetrahydrofuran was necessary due to the insolubility of the magnesium salt of the mercaptoester in diethyl ether.



X

EXPERIMENTAL[14,15]

Glycol dimercaptoacetate (b.p. 129–130° at 5 mm., n_D^{25} = 1.5150) and *β-mercaptopropionic acid* (m.p. 18–19°) were kindly supplied by Evans Chemetics, New York City, N. Y.

2-Hydroxy-2-methylpropanethiol (II). Into a suspension of 91.0 g. (3.72 g.-atoms) of magnesium in 600 ml. of freshly distilled tetrahydrofuran[16] was passed *via* a sulfuric acid drying trap, sufficient methyl bromide to react completely with all the magnesium. The methyl bromide was introduced just above the surface of the suspension at a rate which produced a mild reflux. The completion of the methylmagnesium bromide took approximately 9 hr. Sixty-five grams (0.31 mole) of glycol dimercaptoacetate in 100 ml. of tetrahydrofuran was added to the refluxing Grignard solution in a dropwise manner and soon thereafter the external heating was discontinued due to the exothermic reaction which followed. The addition of the ester took 3.5 hr. and when addition was complete, the mixture was refluxed for an additional 3 hr., after which the condenser on the reaction flask was replaced by a simple distilling head and the solvent removed at reduced pressure. The dark slurry residue was then treated with 1.5 l. of saturated ammonium chloride solution and allowed to stand overnight at room temperature. The resulting two-layer system was separated into an organic and an aqueous phase. The latter was extracted several times with ether and the organic phase and the ethereal extracts were combined and dried over magnesium sulfate. Distillation of the residue, after the ether had been removed at atmospheric pressure, yielded 26.3 g. (40%) of a colorless liquid, b.p. 61–63° (15 mm.), n_D^{20} = 1.4710.

Anal. Calcd. for $C_4H_{10}OS$: C, 45.28; H, 9.43; S, 30.19. Found: C, 45.14; H, 9.36; S, 29.98.

2-(p-Aminophenyl)-4,4-dimethyl-2-thiazoline. This procedure can be considered as typical of all the 2-thiazolines prepared by this method. The physical constants of the other 2-thiazolines were reported in a previous paper.[5]

To a solution of 3.5 g. (0.03 mole) of *p*-aminobenzonitrile in 25 ml. of concd. sulfuric acid, previously cooled to 3°, was added with stirring 2.1 g. (0.02 mole) of 2-hydroxy-2-methylpropanethiol over a period of 30 min. The reaction mixture, which was golden yellow, was stirred at 3–5° for an additional hour after which it was poured on 300 g. of chipped ice. The cold aqueous acid solution was then extracted with chloroform until the chloroform layer was colorless. After passing the aqueous solution through filter paper (fluted) to remove the excess chloroform, it was carefully neutralized with 30% sodium hydroxide. The heterocyclic base appeared as a crude brown solid which was collected in a Buchner funnel and then washed several times with hot water to remove any unchanged nitrile. Recrystallization from aqueous ethanol yielded 2.3 g. (55%) of a very light yellow crystalline material, m.p. 162–164°. The picrate derivative melted at 91–93°.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.07; H, 6.79; N, 13.59. Found: C, 63.88; H, 6.90; N, 13.41.

Structure proof of 2-thiazolines. The sequence of reactions which led to the confirmation of the structure of the 2-thiazolines has already been described in a previous publication.[5]

n-Butyl 3-mercaptopropionate. β-Mercaptopropionic acid (102 g., 0.96 mole), *n*-butyl alcohol (216 g., 3.0 moles), 400 ml. of benzene, and 3 ml. of concd. sulfuric acid were heated in a flask equipped with a motor stirrer and an azeotrope trap. After 8 hr., 25.5 ml. of water had been removed and the resulting solution was washed with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and again with 100 ml. of water. After drying over magnesium sulfate, the benzene and excess butanol were removed initially at atmospheric pressure and finally at reduced pressure. The residue was distilled *in vacuo* through a 12-inch glass-helices packed column and 146 g. (93.5%) of a colorless oil was obtained; b.p. 102.5–103.0° (11 mm.), n_D^{25} = 1.4539.

Anal. Calcd. for $C_7H_{14}O_2S$: C, 51.85; H, 8.64. Found: C, 52.10; H, 8.56.

3-Hydroxy-3-methyl-n-butanethiol (X). This compound was prepared utilizing the same procedure as described for 2-hydroxy-2-methylpropanethiol. Upon distillation, this reaction yielded 62.5 g. (63%) of a colorless oil, b.p. 52.0–53.5° (1.5 mm.), n_D^{20} = 1.4750.

Anal. Calcd. for $C_5H_{12}OS$: C, 50.00; H, 10.00; S, 26.66. Found: C, 49.94; H, 9.93; S, 26.33.

2-Substituted 4,4-dimethyl-5,6-dihydro-1,3-thiazines. A general procedure is described for the preparation of the dihydro-1,3-thiazines and the physical constants for these compounds are listed in Table II.

To a cold solution of 0.025 mole of nitrile in 25 ml. of concd. sulfuric acid, was added dropwise, with efficient stirring, 0.020 mole of 3-hydroxy-3-methyl-*n*-butanethiol. The temperature of the reaction during the addition was kept below 10° by means of external cooling. The addition of the mercaptan derivative usually required 20–30 min., after which stirring continued at 0–5° for an hour. The resulting pale yellow solution was then poured on 300–400 g. of chipped ice and set aside for several hours in a refrigerator. The aqueous acid solution was then freed of the always present gummy polymers by extraction with chloroform. The excess chloroform remaining in the aqueous layer was removed by filtration through fluted filter paper. Subsequent cautious neutralization of the acidic solution with 30% sodium hydroxide resulted in the appearance of the dihydro-1,3-thiazine. If the product was an oil, it was taken up in ether, dried over anhydrous potassium carbonate and distilled. If the product was a solid, it was collected in a Buchner funnel and then recrystallized from aqueous ethanol.

The picrate derivatives were formed by dissolving 0.2 g. of the heterocyclic base in ethanol and adding to it an equal volume of saturated ethanolic picric acid. The derivative usually formed immediately, otherwise heating the reactants to boiling and storage in a refrigerator overnight caused

(13) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959)

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

(15) Microanalyses were performed by Alfred Bernhardt, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany.

(16) The tetrahydrofuran (Matheson Coleman and Bell) was purified by allowing it to stand over sodium wire for 2 days and then, after filtering into a flask containing 100 g. of lithium aluminum hydride, distilled through a 24-inch column containing glass helices as packing material; b.p. 65.5–66.0°.

precipitation to occur. The picrates were recrystallized once from ethanol, dried in air, and the melting points determined.

Structure proof of the 5,6-dihydro-1,3-thiazines. (a) *4-Chloro-2-methyl-2-butene.* The method of Ultee[9b] was employed to prepare this compound; b.p. 50–52° (107 mm.); n_D^{30} = 1.4431 (reported[9b]: b.p. 51.5–52° (100 mm.) n_D^{20} = 1.4450).

(b) *2-Ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine* (VII). To a previously cooled solution of 2.75 g. (0.05 mole) of propionitrile in 20 ml. of coned. sulfuric acid was added slowly with efficient stirring 5.21 g. (0.05 mole) of 4-chloro-2-methyl-2-butene. The temperature of the mixture was kept below 10° during the addition. When the addition was completed, the deep yellow solution was allowed to warm up to room temperature and stirred for 3 hr. after which it was poured onto 200 g. of chipped ice. The aqueous solution was partially neutralized to *p*H 5.5 (Beckman Zeromatic *p*H meter) and no *N*-alkylamide (VIII) appeared. The solution was then further neutralized to *p*H 8.7 and extracted four times with 50-ml. portions of ether. After drying the ethereal extracts with anhydrous potassium carbonate overnight, the ether was removed on a steam bath and the residue distilled. There was obtained 4.23 g. (59%) of a colorless liquid possessing a strong ammoniacal odor; b.p. 52–53° (4 mm.); n_D^{30} = 1.4740.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.11; H, 10.62; N, 9.93. Found: C, 67.99; H, 10.55; N, 9.91.

(c) *2-Ethyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine* (VIII). An intimate mixture of 4.0 g. of 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (VI) and 10.0 g. of phosphorus pentasulfide was heated at 125° for 2 hr. in an oil bath (Hood!). When the very dark mixture cooled to room temperature, 50 ml. of 10% sodium hydroxide was added and the suspension agitated until no further odor of hydrogen sulfide could be detected. The oil, which had appeared at this point, was separated from the aqueous layer and after several ether extractions of the aqueous layer, the oil and the extracts were combined and dried over anhydrous potassium carbonate. Distillation of the residual oil, after removal of the ether, yielded 3.2 g. (71%) of a colorless compound whose physical properties were identical to those of compound 3 (Table II).

Acknowledgment. The author is grateful to the Frederick Gardner Cottrell Fund of the Research Corporation and to the National Institutes of Health, U. S. Public Health Service (DGMS-6248) for funds granted to support this study. Gratitude is also expressed to R. T. O'Connor of the Southern Regional Laboratory, United States Department of Agriculture, for providing infrared data.

NEW ORLEANS 22, LA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW MEXICO]

Synthesis of Diaryloxazoles[1-3]

DUANE L. ALDOUS, J. L. RIEBSOMER, AND RAYMOND N. CASTLE

Received December 30, 1959

Nine new oxazoles have been prepared and methods have been devised for introducing reactive side chains into 4,5-diphenyloxazole and 2,4-diphenyloxazole.

In recent years considerable interest has developed in oxazoles and oxazole quaternary salts. Hayes, *et al.*[4,5] synthesized a considerable number of 2,5-diaryloxazoles after it was discovered that 2-phenyl-5-(4-biphenylyl)oxazole was an effective scintillation solute. In 1956 Ott, Hayes, and Kerr[6] reported the synthesis of series of oxazole quaternary ammonium salts after it had been shown that certain compounds of this type possessed an extraordinary ability to lower the body temperature of animals.[7]

In this study several oxazoles and derivatives have been prepared in the hope that compounds with interesting physiological properties would be found.

The general approach to the synthesis of these oxazoles was suggested by the work of Davidson, Weiss, and Jelling[8] and by Dornow and Eichholz.[9] An aryl ketone (I) was converted to the α-bromoketone (II) which was allowed to react with the sodium salt of an acid to produce the ester (III). Ring closure to form the oxazole (IV) was then effected on the ester by refluxing with ammonium acetate in a solution of acetic acid.

In Table I is presented a series of esters of type III which were prepared by this method in which (I) was propiophenone. Table II lists a series of oxazoles (type IV) which were prepared from the

(1) This communication is based on work done under the auspices of the Los Alamos Scientific Laboratory and the Atomic Energy Commission.

(2) The authors are grateful to the Department of Chemistry, New Mexico Highlands University, Weiler and Strauss of Oxford, England, and to Dr. S. Yamada of the Tokyo Research Laboratory of Tanabe Seiyaku Co., Ltd., Tokyo, Japan, for carbon, hydrogen, and nitrogen analyses.

(3) Presented before the Division of Medicinal Chemistry of the American Chemical Society, April, 1960, Cleveland, Ohio.

(4) F. N. Hayes, L. C. King, and D. E. Peterson, *J. Am. Chem. Soc.*, **74**, 1106 (1952).

(5) F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Am. Chem. Soc.*, **77**, 1850 (1955).

(6) D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Am. Chem. Soc.*, **78**, 1941 (1956).

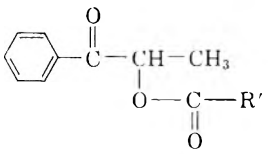
(7) C. C. Lushbaugh, F. N. Hayes, W. H. Langham, D. G. Scott, and P. C. Sanders, *J. Pharm. Exptl. Therap.*, **116**, 366 (1956).

(8) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).

(9) A. Dornow and H. Eichholz, *Ber.*, **86**, 384 (1953).

TABLE I

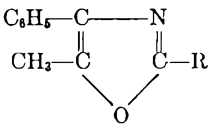
ESTERS OF α-HYDROXYPROPIOPHENONE



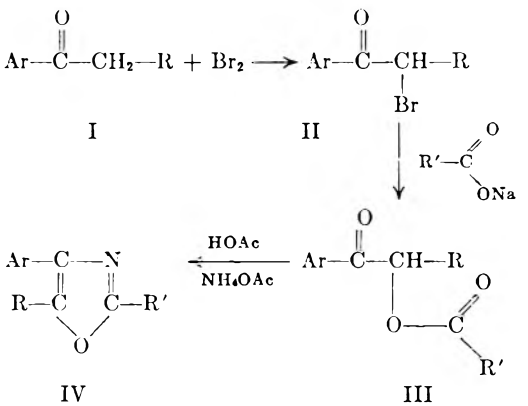
R′	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Phenyl	109–110	69	Ethyl acetate	$C_{16}H_{14}O_3$	76.20	75.70	5.60	5.67		
α-Naphthyl	104.5–105.5	83	Ethyl acetate	$C_{20}H_{16}O_3$	78.90	79.10	5.30	5.56		
β-Naphthyl	105–107	67	Ethyl acetate	$C_{20}H_{16}O_3$	78.94	79.29	5.30	5.44		
2-Quinolyl	121–122	55	Ethyl acetate	$C_{20}H_{15}NO_3$	74.74	74.80	4.95	5.04	4.62	4.95
6-Quinolyl	120–121	62	95% Ethanol	$C_{19}H_{15}NO_3$	74.70	74.30	4.95	5.09	4.62	4.53
4-Pyridyl	112–113	23	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.65	5.13	5.36	5.49	5.58
3-Pyridyl	84.5–85.5	trace	50% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.28	5.13	5.30	5.49	5.37
2-Pyridyl	93–94	39	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.39	5.13	5.33	5.49	5.75
2,6-Dipyridyl	187–189	5	Ethyl acetate	$C_{25}H_{21}NO_6$	69.60	69.70	4.91	4.90	3.25	3.24

TABLE II

OXAZOLES



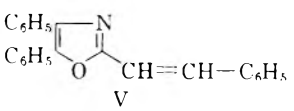
R	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
α-Naphthyl	77.5–78.5	53	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.46	5.30	5.54	4.91	5.23
β-Naphthyl	98.5–100	77	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.65	5.30	5.83	4.91	5.20
2-Quinolyl	163–163.5	18	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.58	4.93	5.09	9.79	10.33
6-Quinolyl	150–151	49	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.64	4.93	5.29	9.79	10.42



I II III IV

esters shown in Table I. It was not found possible to cyclize all the esters listed in Table I into oxazoles.

The position of the methyl group in 2-methyl-4,5-diphenyloxazole on a carbon atom between an electronegative oxygen and an electronegative nitrogen suggested that the hydrogen atoms on the methyl group might be relatively active and might, therefore, condense with aldehydes such as benzaldehyde to produce the corresponding styryloxazoles, *e.g.*, (V). The four styryloxazoles prepared are listed in Table III.



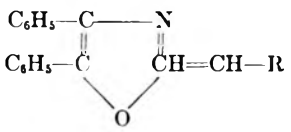
V

It does not appear that much effort has been made to introduce functional groups on carbon atoms 2, 4, or 5 in the oxazole ring system. The bromomethyl group was introduced in the 2-position of 4,5-diphenyloxazole by brominating 2-methyl-4,5-diphenyloxazole with *N*-bromosuccinimide. 4,5-Diphenyl-2-hydroxymethyloxazole was produced in good yield by hydrolysis of this 4,5-diphenyl-2-bromomethyloxazole in an aqueous alcohol solution of silver nitrate.

A method of introducing a carboxyl group in the 5-position of oxazoles has been discovered. For this purpose ethyl benzoylacetate was brominated, as in (I) following the general procedure. The bromo compound was converted to the ester, ethyl α-benzoyloxybenzoylacetate, which in turn was cyclized with ammonium acetate and acetic acid to ethyl 2,4-diphenylimidazole-5-carboxylate.[8] This imidazole was refluxed in aqueous potassium hydroxide solution and thus converted to 2,4-diphenyloxazole-5-carboxylic acid. To characterize

TABLE III

STYRYLOXAZOLES

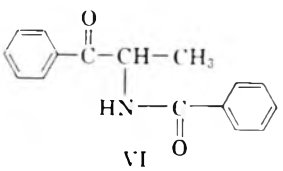


R	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Phenyl	119–119.5	29	95% Ethanol	$C_{23}H_{17}NO$[a]					4.33	4.16
p-Anisyl	269–271	Trace	95% Ethanol	$C_{24}H_{19}NO_2$	81.55	81.31	5.42	5.13		
o-Hydroxyphenyl	216–217	62	95% Ethanol	$C_{23}H_{17}NO_2$	81.37	81.49	5.05	5.44	4.13	3.95
3,4-Methylenedioxyphenyl	142.5–143	Trace	95% Ethanol	$C_{24}H_{17}NO_3$	78.43	77.93	4.67	4.84		

[a] See reference (9).

further this acid it was converted to its *N*,*N*-dimethylaminopropyl amide.

In three instances when ring closures of esters of type III were attempted, side products other than the expected oxazoles were formed. When 2-benzoyloxy-1-phenyl-1-propanone was refluxed with ammonium acetate in acetic acid, not only was the expected oxazole (m.p. 74–75°) produced in good yield but another solid (m.p. 108–109°) was formed whose properties seem to coincide with those expected of 2-benzoylamido-1-phenyl-1-propanone (VI). The structure of VI was established from the



VI

infrared spectra and from the preparation of a semicarbazone derivative. The amide I band at 2.9 μ the amide II band at 6.0 μ and the carbonyl band at 5.82 μ were observed.

Similar observations were made when the starting esters were 1 - phenyl - 2 - (6 - quinolinecarboxyloxy)-1-propanone and di-α-benzoylethyl pyridine-2,6-dicarboxylate.

EXPERIMENTAL[10]

The infrared absorption spectra were determined on a Perkin-Elmer Infracord in nujol mulls.

2-Bromo-1-phenyl-1-propanone. To 160.8 g. of propiophenone (1.2 moles) was added 150 ml. of anhydrous ether and the solution was stirred in an ice bath. To this cold solution was added 1.5 g. of anhydrous aluminum chloride. Over a 45-min. period, 192 g. (1.2 moles) of bromine was added. Additional ether (150 ml.) was added and the contents poured into water. The ether layer was washed with water until bromide ion was removed, the ether solution dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. There was obtained 228 g. (89%) of yellow oil boiling at 135–144° (19 mm.).

The esters in Table I were prepared by the model procedure illustrated below.

(10) All melting points are uncorrected.

2-Benzoyloxy-1-phenyl-1-propanone. Sodium benzoate, 14.4 g. (0.1 mole), 2-bromo-1-phenyl-1-propanone, 21 g. (0.1 mole), absolute ethanol, 125 ml., and 3 drops of concd. sulfuric acid were stirred and refluxed for 8 hr. The mixture was poured into 300 ml. of water with stirring and extracted with benzene. The benzene layer was washed with 200 ml. of 1% sodium hydroxide solution and twice with 200 ml. of water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. A white powder (14.9 g.) was obtained. A second crop amounted to 2.6 g. (69% yield). The product was recrystallized from ethyl acetate, m.p. 109–110°. Temnikova[11] reported 109°.

4,5-Diphenyl-2-methyloxazole. This compound was prepared according to the procedure of Davidson, Weiss, and Jelling.[8]

4,5-Diphenyl-2-styryloxazole. 4,5-Diphenyl-2-methyloxazole (4.7 g., 0.02 mole), benzaldehyde (15.7 g., 0.148 mole) and zinc chloride (1.4 g., 0.01 mole) were refluxed for 3 hr. under an atmosphere of nitrogen. The solution was cooled, benzene added and the mixture washed three times with water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. The unreacted benzaldehyde was removed by distillation (74° at 17.5 mm.). The unchanged oxazole was recovered by distillation (165–175° at 1 mm.). The residue in the distilling flask was dissolved in 95% ethanol and upon crystallization, 1.9 g. of a yellow-orange powder was obtained (29%). The product was recrystallized from 95% ethanol, m.p. 119–119.5° (previously reported 118.5°). This compound was previously prepared by direct cyclization by Dornow and Eichholz.[9]

Anal. Calcd. for $C_{23}H_{17}ON$: C, 85.43; H, 5.30; N, 4.33. Found: C, 86.05; H, 5.78; N, 4.16.

This general procedure was used for all the styryloxazoles shown in Table III.

2-Bromomethyl-4,5-diphenyloxazole. 4,5-Diphenyl-2-methyloxazole (11.8 g., 0.05 mole), *N*-bromosuccinimide (9 g., 0.05 mole), benzoyl peroxide, 2 g., and 40 ml. of dry carbon tetrachloride were refluxed for 6 hr. The mixture was cooled and the succinimide removed by filtration. The carbon tetrachloride was removed under reduced pressure leaving a viscous orange-red liquid, which was purified by distillation, b.p. 170° at 0.025 mm., micromelting point 104–106°.

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.16; H, 3.85. Found: C, 61.35; H, 4.13.

4,5-Diphenyl-2-hydroxymethyloxazole. 2-Bromomethyl-4,5-diphenyloxazole (15.7 g., 0.05 mole) was dissolved in 100 ml. of 95% ethanol. Silver nitrate, 10 g., was dissolved in 12 ml. of water and this solution was added to the swirled

(11) T. I. Temnikova and E. N. Kropacheva, *Doklady Acad. Nauk. S.S.S.R.*, **78**, 291 (1951). See *Chem. Abstr.*, **46**, 2010^{b} (1952).

alcoholic solution. The mixture was refluxed on a steam bath for 1 hr., the silver bromide filtered and the ethanol removed on the steam bath. The yellow oil which remained was dissolved in ether and washed several times with water to remove the silver ion. The ether layer was dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. It distilled at 151–156° at less than 0.1 mm. to yield a viscous yellow liquid.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.12; H, 5.53.

Ethyl α-bromobenzoylacetate. This was prepared in a manner similar to α-bromopropiophenone starting with ethyl benzoyl acetate. An 88% yield of a yellow oil boiling at 113–133° at 0.1 mm. was obtained.[12]

Ethyl-α-benzoyloxybenzoylacetate. This compound was prepared in a manner similar to 2-benzoyloxy-1-phenyl-1-propanone. The cream colored solid was recrystallized from 95% ethanol (75% yield), m.p. 61–62°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.24; H, 5.17. Found: C, 69.65; H, 5.45.

Ethyl 2,4-diphenylimidazole-5-carboxylate. This compound was prepared according to the procedure of Davison, Weiss, and Jelling.[8] A cream colored solid (24 g.) was obtained. It was recrystallized from 95% ethanol, m.p. 166–167.5°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.99; H, 5.52; N, 9.59. Found: C, 73.85; H, 5.67; N, 9.71.

2,4-Diphenyloxazole-5-carboxylic acid. Ethyl 2,4-diphenylimidazole-5-carboxylate (5.86 g., 0.02 mole), potassium hydroxide (1.6 g.), and 50 ml. of water were refluxed. The reflux condenser was equipped with a side arm for the removal of the condensate. The condensate was removed until a negative test was obtained for the presence of ethanol using ceric nitrate reagent. This required 1.75 hr. The solution was filtered and acidified with 5% hydrochloric acid. A white solid, 5.3 g., m.p. 222–223°, was obtained (quantitative).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.64; H, 4.41; N, 5.00.

N,N-Dimethylaminopropyl-2,4-diphenyloxazole-5-carboxamide. Potassium 2,4-diphenyloxazole-5-carboxylate (9.1 g., 0.03 mole) was passed through a 100 mesh sieve and dried overnight at 120°. This was added to 60 ml. of dry benzene in a three neck flask fitted with condenser, mercury seal stirrer, dropping funnel, and drying tube. Over a period of 20 min., a solution of 3.8 g. (0.03 mole) of oxalyl chloride in 15 ml. of dry benzene was added to the reaction mixture cooled in an ice bath. This cooled reaction mixture was stirred an additional 30 min., the ice bath removed, and the reaction mixture stirred an additional 3 hr. Dimethylaminopropylamine (3.2 g., 0.031 mole) was mixed with 15 ml. of dry benzene and added over a period of 20 min. The mixture was stirred for an additional 15 min., and then heated to boiling. The mixture was cooled and a 5% solution of hydrochloric acid was added. The dense yellow precipitate was filtered and the product dissolved in 5% hydrochloric acid solution. The acidic solution was filtered and upon neutralization with ammonium hydroxide, a white precipitate was obtained. The product was recrystallized from ethyl acetate whereupon long white needles separated, m.p. 161.5–163°.

Anal. Calcd. for $C_{21}H_{23}O_2N_3$: N, 12.02. Found: N, 11.65.

2,4-Diphenyl-5-methyloxazole. To 12.6 g. (0.05 mole) of 2-benzoyloxy-1-phenyl-1-propanone was added 19.3 g. (0.25 mole) of ammonium acetate in 50 ml. of glacial acetic acid. After the mixture had been refluxed for 1 hr., it was poured into ice and water and extracted with ether. The ether was washed with water and the ether layer dried over anhydrous magnesium sulfate. After filtration of the drying agent and evaporation of the ether the crude product was collected. Upon purification by repeated recrystallization from cyclohexane a buff-colored solid (m.p. 108–109.5°) separated. The 2,4-diphenyl-5-methyloxazole separated upon concentration of the mother liquors, m.p. 74–75°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.70; H, 5.57; N, 5.95. Found: C, 81.80; H, 5.54; N, 5.58.

The other oxazoles listed in Table II were prepared in a similar manner.

The product, m.p. 108–109.5°, described above as separating first during the purification proved to be 2-benzoylamido-1-phenyl-1-propanone.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.07; N, 5.82.

This compound was characterized by the infrared absorption spectra detailed in the discussion and by the preparation of a semicarbazone.

2-Benzoylamido-1-phenyl-1-propanone semicarbazone. The semicarbazone was prepared by the method of Shriner, Fuson, and Curtin,[13] m.p. 202–203°.

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.77; H, 5.58. Found: C, 65.22; H, 5.63.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the preparation of 5-methyl-4-phenyl-2-(6-quinolyl)oxazole. This compound was purified by crystallization from ethanol, m.p. 195–197°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.80; H, 5.70; N, 8.78.

This compound was characterized by the infrared spectra detailed in the discussion and by the preparation of a semicarbazone.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone semicarbazone. This derivative was prepared in the usual manner, m.p. 209–211°.

Anal. Calcd. for $C_{26}H_{19}N_5O_2$: C, 66.46; H, 5.30. Found: C, 66.72; H, 5.15.

N,N'-Bis(α-benzoylethyl)pyridine-2,6-dicarboxamide. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the attempted preparation of 2,6-bis[2-(5-methyl-4-phenyl)oxazolyl]pyridine, m.p. 211–213°.

Anal. Calcd. for $C_{25}H_{22}N_3O_4$: C, 69.90; H, 5.40; N, 9.78. Found: C, 70.36; H, 5.69; N, 9.86.

This compound was characterized by the infrared spectra detailed in the discussion.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Heterocyclic Spiranes. Oxazolidines from (1-Aminocyclohexyl)methanol

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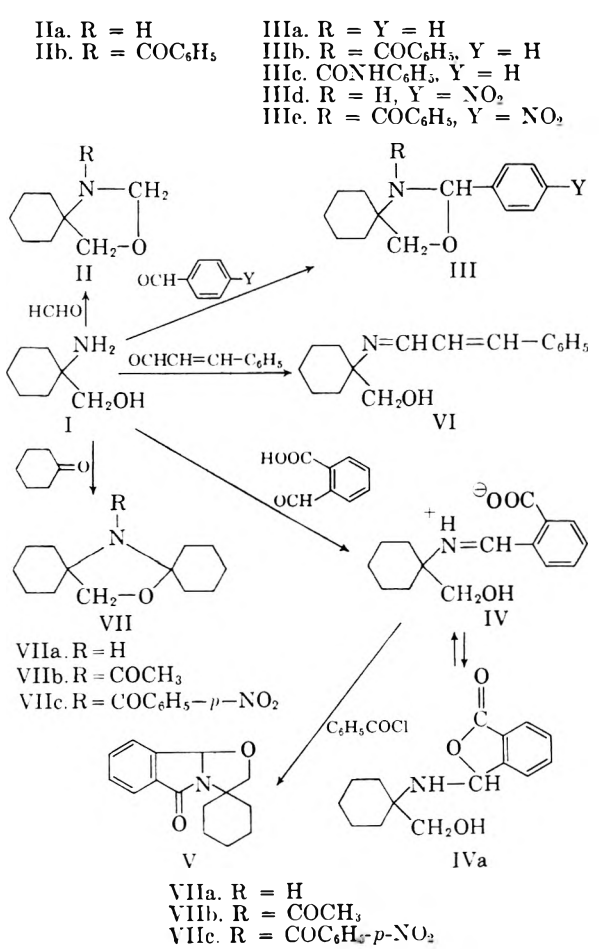
(1-Aminocyclohexyl)methanol (I) has been condensed with five aldehydes and a ketone, cyclohexanone. The reaction with ketones appears limited largely to cyclic ketones. Heterocyclic spiro oxazolidines or their derivatives were obtained from condensations with formaldehyde (II), benzaldehyde (IIa–IIc), *p*-nitrobenzaldehyde (IIId, IIIe), and cyclohexanone (VIIa–VIIc), dispiro oxazolidines being formed in the latter case. Structures were established by comparison of infrared and ultraviolet or molecular refraction data with appropriate analogs in the literature. Phthalaldehydic acid yielded an amino acid (tentatively formulated as IV, in the solid state), which isomerizes to a lactone (IVa) in chloroform solution. Dehydration of IV with benzoyl chloride yielded an interesting heterocyclic spiro oxazolidine lactam (V). Cinnamaldehyde yielded the Schiff base, (1-cinnamalaminocyclohexyl)methanol (VI). Several other new derivatives of (1-aminocyclohexyl)methanol are described.

The synthesis of a number of heterocyclic spiro oxazolidines by the condensation of cyclohexanone and ethanolamine derivatives has been described previously.[2] In all of these cases the preformed cyclic component is contributed by the cyclohexanone. There appear to be only two recorded cases, however, of the synthesis of spiro oxazolidines in which the preformed cyclic component is contributed by the aminoalcohol. In one case, 17α-aminomethyl-Δ^5-androstene-3β,17β-diol condensed with acetone to yield an anhydro product, which was assumed to have the spiro oxazolidine structure.[3] In the other case, (1-aminoethyl)cyclohexanol condensed with cyclohexanone to give an anhydro product, to which the dispiro oxazolidine structure, 7-oxa-14-aza-15-methyldispiro[5.1.5.2]pentadecane, was assigned on the basis of molecular refraction data.[2,4]

In the present work another and more readily available cyclic amino alcohol, (1-aminocyclohexyl)methanol (I)[5,6] has been utilized in the synthesis of four new heterocyclic spiro oxazolidines (IIa, IIIa, IIId, V) or their derivatives, from aldehydes, and a dispiro oxazolidine (VIIa) and its derivatives, from cyclohexanone. The corresponding reaction with cinnamaldehyde yielded a Schiff base condensation product, (1-cinnamalaminocyclohexyl)methanol (VI). In general, the method of azeotropic removal of water with benzene was employed.[7]

The oily formaldehyde product is assumed to have the spiro oxazolidine structure IIa by analogy with the product from formaldehyde and 3-amino-2-methyl-2-butanol, which has been shown by infrared and molecular refraction data to be in the oxazolidine form, with a slight amount of the Schiff base.[2,4] The benzoyl derivative is assigned the spiro oxazolidine structure IIb because its infrared spectrum contains only an amide-type carbonyl band and has no OH or NH stretching bands.



(1) Taken in part from the senior thesis of Roy A. Johnson, University of Minnesota, 1958–59, and from his work as a Research Corporation Research Assistant, summer 1959. We are indebted to the Research Corporation for a Frederick Gardner Cottrell grant which supported a part of this work.

(2) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).

(3) H. Heusser, P. T. Herzig, A. Fürst, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

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(7) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942).

The oily benzaldehyde product, as was the case with the 3-amino-2-methyl-2-butanol product,[2,4,8] appears to be a mixture of the two possible isomers. For the sake of brevity, only the oxazolidine structure IIIa has been shown in the reaction chart. The benzoyl derivative is assigned the spiro oxazolidine structure IIIb because its infrared spectrum contains only an amide-type carbonyl band and has no OH or NH stretching bands. The absence of any ultraviolet absorption maximum is also consistent with the benzamide-type structure IIIb and eliminates the possible presence of the strongly absorbing Schiff base, which would be present in the isomeric structure, (1-benzalaminocyclohexyl)-methyl benzoate. For example, 3-benzalamino-2-methyl-2-butanol has the typical Schiff base maximum at 245 mμ (log ε 4.01).[8] The phenylurea derivative is also assigned a spiro oxazolidine structure IIIc. While the position of the carbonyl band in the infrared spectrum does not permit a clear-cut distinction between the oxazolidine and Schiff base structures, the principal ultraviolet absorption maximum in ethanol at 239 mμ (log ε 4.31) is at too low a wave length for a Schiff base (245[8]–247[9] mμ) and too high a wave length for an *N*-phenylcarbamate ester, a system which would also be present in the phenyl isocyanate derivative of the Schiff base form. For example, isopropyl and *n*-hexyl *N*-phenylcarbamate have their principal absorption maximum at 235–236 mμ (log ε 4.23).[10] On the other hand, the ultraviolet absorption maximum of an analogous *N*-phenylurea, 1,1-diethyl-3-phenylurea, at 239–241 mμ (log ε 4.26),[10] is in good agreement with that of our derivative (IIIc).

Both the *p*-nitrobenzaldehyde product (IIId) and its benzoyl derivative (IIIe), have spiro oxazolidine structures, in contrast to the product from ethanolamine and *p*-nitrobenzaldehyde, which has been shown to be in the open, Schiff base form.[2,4] The infrared spectra of IIId and IIIe have no band in the C=N region, such as that present at 1654 cm.$^{-1}$ in 3-(4-nitrobenzalamino)-2-methyl-2-butanol,[4] thus excluding the Schiff base structure. The benzoyl derivative (IIIe) has only an amide-type carbonyl band, thus confirming the oxazolidine structure for it. Since compounds IIId and IIIe have very similar ultraviolet spectra, they must both be oxazolidines. Taken by themselves, the wave lengths of the ultraviolet absorption maxima, at 267 (log ε 4.04) in IIId and 265 mμ (3.96) in IIIe, allow no clear basis for distinction between the oxazolidine and Schiff base structures since *p*-nitrotoluene, a model compound for the oxazolidine structures, has a maximum at 273 mμ (3.98),[10] whereas the condensation product of *p*-nitroacetophenone and 3-amino-2-methyl-2-butanol, a model Schiff base for this system, has maxima at 275 (4.07) and 235 (3.52).[8]

In what is apparently the first example of the reaction of an amino alcohol with phthalaldehydic acid, (1-aminocyclohexyl)methanol gave an amino acid, obtained in dimorphic forms, m.p. 133–136° and 147–150°, having a neutralization equivalent corresponding to a 1:1 condensation product. The zwitterion form of the Schiff base structure (IV) is tentatively assigned to the crystalline amino acid because of its infrared spectrum in Nujol. The stronger band at 1634 cm.$^{-1}$ is tentatively assigned to the C=N structure and the band at 1560 cm.$^{-1}$ to the antisymmetrical stretching frequency of the carbonyl group of the ionized carboxyl group. In chloroform solution these two bands disappear and are replaced by a strong γ-lactone carbonyl band at 1754 cm.$^{-1}$, indicating that the amino acid has isomerized to the phthalide form (IVa). Phthalide itself has the carbonyl band at 1770 cm.$^{-1}$ in carbon tetrachloride solution.[11] The ultraviolet spectrum in ethanol solution is again suggestive of the phthalide (IVa) or oxazolidine form. The characteristic Schiff base maximum at about 245 mμ (possibly shifted to a higher wave length by conjugation with the *o*-carboxyl group) appears to be lacking. Instead, there are two maxima, the high intensity one at 237 (log ε 3.92), and the other at 294 mμ (3.15). These maxima are at higher wave lengths and intensities, but are similar in distance apart and in relative intensities to those of *o*-toluic acid at 228 (log ε 3.71) and 279 mμ (2.86),[12] or of phthalide at 227 (4.00), 273 (3.24), and 280 (3.22).[10]

The reaction of phthalaldehydic acid with amino alcohols may provide interesting opportunities in organic synthesis. For example, the amino acid IV upon dehydration with benzoyl chloride in pyridine yielded the spiro lactam V. This lactam has a strong γ-lactam carbonyl band in the infrared (at 1691 cm.$^{-1}$ in Nujol) and no NH stretching absorption. The model compound, phthalimidine, has a strong carbonyl band at 1700 cm.$^{-1}$ in carbon tetrachloride.[13] The lactam (V) is resistant to alkaline hydrolysis in aqueous ethanol.

In contrast to the mixture of isomers obtained with benzaldehyde, and the pure oxazolidine obtained with *p*-nitrobenzaldehyde, cinnamaldehyde gave the Schiff base, (1-cinnamalaminocyclohexyl)-methanol (VI), as the only crystalline product. The infrared spectrum in Nujol is in good agreement with the Schiff base structure (VI). The ultraviolet spectrum in ethanol is also in good agreement, since its long wave length maximum

(8) E. D. Bergmann, Y. Hirshberg, S. Pinchas, and E. Zimkin, *Rec. trav. chim.*, **71**, 192 (1952).

(9) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951).

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(12) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).

(13) W. Theilacker and W. Schmidt, *Ann.*, **597**, 95 (1955).

occurs at 287 (log ϵ 4.40), whereas that of the dicinnamyl derivative of ethylenediamine occurs at 282 mμ (log ϵ/2 4.44).[14] In contrast, the high intensity band of β-methylstyrene, a model compound for the oxazolidine structure, occurs at 251 mμ (log ϵ 4.21).[15] The formation of the Schiff base from cinnamaldehyde is consistent with the generalization that increased conjugation with the C=N group, such as that in the products from α,β-unsaturated aldehydes,[2,4] tends to favor the Schiff base form.

Water collected rapidly in the trap during all of the condensations with aldehydes; the reactions were probably complete within an hour, although refluxing was usually continued for a longer time. In contrast, the condensation with the ketone, cyclohexanone, was much slower and required several hours for all of the water to be collected. The liquid product from cyclohexanone has the dispiro oxazolidine structure VIIIa. The only previous report of a dispiro oxazolidine prepared by a similar method is that from (1-aminoethyl)-cyclohexanol and cyclohexanone.[2,4] Our dispiro oxazolidine (VIIa) has a molecular refraction of 60.346 at 32°. This value is in excellent agreement with that for the oxazolidine, of 60.379 at 30°, calculated from the Eisenlohr atomic refractions[4,16] and taking into account the average depression of 0.50 for the oxazolidine ring.[4,7] The Schiff base structure is excluded because of the lack of a C=N band in the infrared spectrum and because the calculated molecular refraction of 62.359 at 30° is too high. Oxazolidine structures for the acetyl (VIIb) and *p*-nitrobenzoyl (VIIc) derivatives of the dispiro oxazolidine are confirmed by the presence of amide carbonyl bands in the infrared.

The reaction of (1-aminocyclohexyl)methanol with ketones appears to be restricted to the relatively unhindered cyclic ketones and, possibly, to reactive ketones such as pyruvic acid. Acetone does not appear to react; when an equimolar solution of acetone and (1-aminocyclohexyl)methanol in benzene was refluxed for eighteen hours before removal of the benzene, the residual oil yielded a single benzoyl derivative, (1-benzamidocyclohexyl)methanol, derived from the starting material. Likewise, acetophenone and diethyl ketone do not react; only negligible amounts of water were collected by azeotropic removal with benzene.

During the course of this work several other new derivatives of (1-aminocyclohexyl)methanol were prepared. Included among these, besides the benzamide, are the di-*p*-nitrobenzoyl derivative, and the benzoate and carbonate salts. (1-Aminocyclohexyl)-methanol is notably "carbodioxiphilic";[17] it absorbs carbon dioxide readily, both in the presence and absence of water.

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

1-Aza-3-oxaspiro[4.5]decane (IIa). A mixture of (1-aminocyclohexyl)methanol[5] (3.20 g., 0.0248 mole), aqueous 37% formalin (10 cc., 0.12 mole formaldehyde), and benzene (50 cc.) was refluxed for 9 hr. A calibrated constant water separator (Dean and Stark trap) was then attached and refluxing was continued. The water (about 13.5 cc.) came over during the first hour but refluxing was continued for a total of 6 more hr. The benzene was then distilled and a large relatively volatile fraction was removed at 75–82° (5 mm.), leaving a light yellow residual oil (1.73 g., 0.0123 mole, 50%). This oil was converted to its benzoyl derivative without distillation or further purification.

1-Benzoaza-3-oxaspiro[4.5]decane (IIb; *benzamide of* IIa). By the Schotten-Baumann method, to a mixture of crude 1-aza-3-oxaspiro[4.5]decane (0.8 g., 0.0057 mole), benzoyl chloride (0.8 g., 0.0057 mole), and water (10 cc.) was added aqueous 20% sodium hydroxide (7 cc.). The mixture was shaken and a white crystalline solid (1.23 g., 0.0050 mole, 88%), m.p. 115–130°, formed rapidly. Four recrystallizations from ethanol-water yielded colorless flakes, m.p. 127–129°; $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1639 in CS_2, 1634 in CCl_4, 1622 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{19}NO_2$ (245.31): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.27; H, 7.72; N, 5.64.

Mixture of (1-benzalaminocyclohexyl)methanol and 1-aza-2-phenyl-3-oxaspiro[4.5]decane (IIIa). A solution of (1-aminocyclohexyl)methanol[5] (10.0 g., 0.0774 mole) and benzaldehyde (16.4 g., 0.154 mole) in undried benzene (75 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; after 30 min. 1.0 cc. (72%) had collected and at the end of the 5-hr. reflux period a total of 1.6 cc. (115%) had collected in the trap. The benzene was distilled and the excess benzaldehyde was removed at 50–55° (4 mm.). The residual light yellow oil (88%) was distilled, giving a pale yellow fraction (12.34 g., 0.0569 mole, 74%), b.p. 127–132° (2 mm.), n_D^{25} 1.5413. Redistillation yielded a very pale yellow analytical sample, b.p. 128–129° (2 mm.), n_D^{25} 1.5415. The odor of the sample, as well as the infrared spectrum, indicated contamination by both starting materials, which were not successfully separated by repeated distillation; ν_{OH} 3430 (shoulder); ν_{NH} 3310; $\nu_{C=O}$ 1704 (benzaldehyde); $\nu_{C=N}$ 1645 cm.$^{-1}$ on the liquid. The C=N band, of medium intensity, indicated the presence of the open form of the product, (1-benzalaminocyclohexyl)methanol.

Anal. Calcd. for $C_{14}H_{19}NO$ (217.30): C, 77.38; H, 8.81. Found: C, 76.78; H, 8.85.

The benzaldehyde contaminant in the sample appears to undergo air oxidation to benzoic acid, as evidenced by precipitation of 1-(hydroxymethyl)cyclohexylammonium benzoate in the samples fairly soon after distillation and analysis. The melting point of the precipitate was undepressed upon admixture with an authentic sample of this benzoate salt.

The crude oil resulting from removal of the benzene and excess benzaldehyde was used for the preparation of crystalline derivatives without distillation or other purification. It was shown, however, that the same benzoyl derivative was

(14) L. N. Ferguson and G. E. K. Branch, *J. Am. Chem. Soc.*, 66, 1467 (1944).

(15) American Petroleum Institute Research Project 44. Carnegie Institute of Technology. Catalog of Ultraviolet Spectral Data. Serial No. 122, contributed by The Dow Chemical Co., Dec. 31, 1945.

(16) K. Fajans in A. Weissberger, *Physical Methods of Organic Chemistry*, Vol. 1, Part 2, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1163.

(17) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, 73, 5068 (1951).

obtained from a distilled sample of the oil; after two recrystallizations from ethanol-water, the benzoyl derivative melted at 134–136°, which was undepressed upon admixture of the sample with that prepared as described in the following section.

The oil was immiscible with water and surprisingly resistant to hydrolysis. A sample which had been overlaid with water for 2 weeks had the odor of benzaldehyde, but readily gave the benzoyl derivative under the conditions of the Schotten-Baumann reaction. After two recrystallizations from ethanol-water, the benzoyl derivative melted at 133–136°, which was undepressed upon admixture of the sample with that prepared as described in the following section.

1-Benzoaza-2-phenyl-3-oxaspiro[4.5]decane (IIIb; *benzamide of* IIIa). By the Schotten-Baumann method, to a mixture of crude (1-benzalaminocyclohexyl)methanol and 1-aza-2-phenyl-3-oxaspiro[4,5]decane (1.0 g., 0.0046 mole), benzoyl chloride (0.8 g., 0.006 mole), and water (10 cc.) was added aqueous 20% sodium hydroxide (7 cc.) over a period of 5 min., with vigorous shaking. The mixture was intermittently warmed gently on the steam bath and shaken for 5 more min. The coagulated yellowish mass was then crystallized from ethanol-water, giving light yellowish plates (0.54 g., 0.0017 mole, 37%), m.p. 126–136°. Three recrystallizations from ethanol-water yielded colorless plates, m.p. 134–136.5°. The ultraviolet spectrum in 95% ethanol shows only rising end absorption (at 220 mμ, log ε is 3.99 and at 215, 4.05); $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1640 in CS_2, 1645 in CCl_4, 1628 in $CHCl_3$, 1629 in a KBr disk, 1627 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{23}NO_2$ (321.40): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.56; H, 7.32; N, 4.25.

1-(Phenylcarbamoaza)-2-phenyl-3-oxaspiro[4.5]decane (IIIc; *phenylurea derivative of* IIIa) was obtained after five recrystallizations from light petroleum (b.p. 60–68°) as colorless, chunky crystals, m.p. 124–127°; λ_{max} in 95% C_2H_5OH: 239 mμ (log ε 4.31), with inflections at 268 (3.23), 272 (3.17), 281 (3.10); ν_{NH} 3390 in CS_2 and CCl_4, 3400 in $CHCl_3$, 3380 in Nujol; $\nu_{C=O}$ 1672 in CS_2, 1682 in CCl_4, ~1667 in $CHCl_3$, 1675 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$ (336.42): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.14; H, 7.19; N, 8.46.

1-Aza-2-(4-nitrophenyl)-3-oxaspiro[4.5]decane (IIId). A solution of (1-aminocyclohexyl)methanol[4] (4.00 g., 0.0310 mole) and *p*-nitrobenzaldehyde (4.70 g., 0.0311 mole) in undried benzene (75 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; at the end of the 2.5-hr. reflux period 0.62 cc. (111%) had collected. The benzene was distilled and the residue was dried at aspirator pressure, leaving a brown powder (8.20 g.). Crystallization from ethanol-water gave light yellowish flakes (5.41 g., 0.0206 mole, 66%), m.p. 73–77°. Four recrystallizations from ethanol-water yielded 1-aza-2-(4-nitrophenyl)-3-oxaspiro-[4,5]decane as colorless flakes, m.p. 77–79°; λ_{max} in 95% C_2H_5OH: 267 mμ (log ε 4.04); ν_{NH} 3270 in CS_2, 3280 in CCl_4, 3270 in Nujol; ν_{NO_2} 1347 in CS_2, 1528, 1349 in CCl_4, 1516, 1348 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$ (262.30): C, 64.10; H, 6.92; N, 10.68. Found: mol. wt. (Rast), 293; C, 63.88; H, 7.13; N, 10.73.

1-Benzoaza-2-(4-nitrophenyl)-3-oxaspiro[4.5]decane (IIIe; *benzamide of* IIId) was obtained by the Schotten-Baumann reaction in 23% yield, m.p. 163–166°, after two recrystallizations. A final recrystallization from ethanol-water yielded colorless, shiny plates, m.p. 163–165°; λ_{max} in 95% C_2H_5OH: 265 mμ (log ε 3.96). $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1625; ν_{NO_2} 1520, 1350 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{22}N_2O_4$ (366.40): C, 68.83; H, 6.05; N, 7.65. Found: C, 68.94; H, 6.01; N, 7.35.

Zwitterion form of (1-(2-carboxybenzal)aminocyclohexyl)-methanol (IV). A solution of (1-aminocyclohexyl)methanol[5] (6.40 g., 0.0495 mole) and phthalaldehydic acid (7.50 g., 0.0499 mole) in undried benzene (100 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Within 20 min. 1.0 cc. of water had collected; at the end of the 7.5-hr. reflux period 1.20 cc. (134%) had collected. After the solution had been set aside overnight, a white precipitate was present, which did not redissolve when the benzene was warmed for distillation. The benzene was distilled under aspirator vacuum. The residual solid (~12 g., 0.046 mole, 93%) dissolved slowly in chloroform. Five recrystallizations from chloroform–light petroleum (b.p. 60–68°), yielded white crystals, m.p. 133–136°; λ_{max} in 95% C_2H_5OH: 237 mμ (log ε 3.92), 294 (3.15); $\nu_{OH\ or\ NH}$ 3100; $\nu_{C=N}$ 1634; $\nu_{C=O}$ 1560 cm.$^{-1}$ in Nujol; in $CHCl_3$: $\nu_{C=O}$ 1754 cm.$^{-1}$; $\nu_{C=N}$ none.

Anal. Calcd. for $C_{15}H_{19}NO_3$ (261.31): C, 68.94; H, 7.33; N, 5.36. Found: acid neut. equiv. 267, 275, 273, av. 272; C, 69.19; H, 7.70; N, 5.46.

The compound was also obtained from the same solvent pair in admixture with, or wholly in a higher melting dimorphic form, m.p. 147–150°.

Anal. Found: C, 68.94; H, 7.35; N, 5.26.

The two dimorphic forms had identical infrared spectra in Nujol and were shown to be interconvertible.

Spiro[2,3-oxazolo(2,3-a)isoindol-5-one-3,1'-hexane] (V). Benzoyl chloride (1.08 g., 0.0077 mole) was added to a solution of (1-(2-carboxybenzal)aminocyclohexyl)methanol (1.00 g., 0.00382 mole) in pyridine (15 cc.). The resulting solution was warmed at about 75° for 45 min. and then poured into ice water, causing the separation of a light yellow oil. The mixture was stirred and crystals (0.69 g., 0.00284 mole, 74%), m.p. 88–100°, formed over a period of an hour. The compound can be recrystallized, if desired, from ethanol-water. From separate solutions of water containing a small amount of pyridine, the compound was obtained in two forms, m.p. 80.5–82°, and m.p. 98–100°. The lower melting form was converted to the higher melting form after heating *in vacuo* at 56°; λ_{max} in 95% C_2H_5OH: 225 mμ (log ε 3.94), 230 inflection (3.89), 245 (3.69), 280 inflection (3.17). ν_{NH} none; $\nu_{C=O}$ 1691 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{17}NO_2$ (243.29): C, 74.05; H, 7.04; N, 5.76. Found: lower melting form (after heating), C, 74.11; H, 7.15; N, 5.67; higher melting form, mol. wt. (Rast), 246; C, 73.58; H, 7.25; N, 5.54.

(1-Cinnamalaminocyclohexyl)methanol (VI). A solution of (1-aminocyclohexyl)methanol[5] (3.20 g., 0.0247 mole) and cinnamaldehyde (9.00 g., 0.0680 mole) in undried benzene (60 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; at the end of the 2.5-hr. reflux period 0.60 cc. (135%) had collected. The dark yellow solution turned strawberry red upon being set aside overnight. Excess benzene was removed at aspirator pressure and cinnamaldehyde was removed at 95–105° (3 mm.). The viscous, dark red residue was dissolved in benzene (15 cc.), causing immediate separation of crystals. These crystals were washed with a little benzene to remove contaminating red oil, and recrystallized from benzene–light petroleum (b.p. 60–68°), giving light yellowish needles (1.10 g., 0.00453 mole, 18%), m.p. 90–93°. Three more recrystallizations from benzene–light petroleum (b.p. 60–68°) yielded (1-cinnamalaminocyclohexyl)methanol as colorless needles, m.p. 96–98°; λ_{max} in 95% C_2H_5OH: 220 mμ (log (ε 4.07), 225 (4.06), 287 (4.40); ν_{OH} 3160 in Nujol; $\nu_{C=N}$ 1631 in CS_2, 1633 in CCl_4, 1634 in Nujol. $\nu_{C=C}$ 1617 in CCl_4, 1615 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{16}H_{21}NO$ (243.34): C, 78.97; H, 8.70; N, 5.76. Found: C, 79.24; H, 8.75; N, 5.76.

An attempt to prepare a benzoyl derivative by the Schotten-Baumann method gave no crystalline product.

7-Oxa-15-azadispiro[5.2.5.1]pentadecane (VIIa). A solution of (1-aminocyclohexyl)methanol[5] (20.0 g., 0.155 mole) and cyclohexanone (30.4 g., 0.310 mole) in undried benzene (100 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water collected slowly; at the end of the 9-hr. reflux period 3.7 cc. (132%) of water had collected. The benzene was distilled,

the excess cyclohexanone was removed at 35–38° (2 mm.), and then the main fraction distilled as a light yellow oil (28.92 g., 0.138 mole, 89%), b.p. 98–104° (2 mm.), $n_D^{27.4}$ 1.4913. Redistillation yielded 7-oxa-15-azadispiro-[5.2,5,1]-pentadecane as a colorless oil, b.p. 97–99° (2 mm.), $n_D^{27.4}$ 1.4915, n_D^{32} 1.4893, d_4^{32} 1.0002; ν_{NH} 3310 (very faint) cm.$^{-1}$, $\nu_{C=N}$ none; on the oil.

Anal. Calcd. for $C_{13}H_{23}NO$ (209.32): C, 74.59; H, 11.08; N, 6.69. Found: C, 74.85; H, 11.56; N, 7.08.

The benzoyl derivative tended to oil out of ethanol-water solution and did not crystallize well.

7-Oxa-15-azadispiro[5.2.5.1]pentadecane hydrochloride (*hydrochloride of* VIIa). Hydrogen chloride gas was passed into a solution of 7-oxa-15-azadispiro[5,2,5,1]pentadecane (2.00 g., 0.0096 mole) in dry ether (50 cc.), causing precipitation of fine, colorless platelets (1.88 g., 0.0077 mole, 80%). These crystals appear to change form at 180–190° and melt with sublimation at 204–207°; $\nu_{NH_2^+}$ 2740, 2590, 2460, 2370, 2090, 1586 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{13}H_{23}NO{\cdot}HCl$ (245.79): Cl, 14.42. Found: Cl, 14.62, 14.66, 14.56, 14.65, av. 14.62.

7-Oxa-15-acetoazadispiro[5.2.5.1]pentadecane (VIIb, *acetamide of* VIIa). A solution of 7-oxa-15-azadispiro[5,2,5,1]-pentadecane (2.00 g., 0.00957 mole) in acetic anhydride (18.5 g., 0.181 mole) was warmed for 3.25 hr. and then the yellow solution was poured into ice water (50 cc.). The resulting mixture was stirred occasionally, causing the yellow oil to crystallize slowly as colorless plates (1.01 g., 0.00402 mole, 42%), m.p. 119–124°. Five recrystallizations from acetone-water yielded colorless plates, m.p. 122–124°; $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1634 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{25}NO_2$ (251.36): C, 71.67; H, 10.03; N, 5.57. Found: C, 71.76; H, 9.96; N, 5.39.

(7-Oxa-15-(4-nitrobenzoaza)dispiro[5.2.5.1]pentadecane (VIIc; *p-nitrobenzamide of* VIIa). A solution of 7-oxa-15-azadispiro[5,2,5,1]pentadecane (2.00 g., 0.0096 mole) and *p*-nitrobenzoyl chloride (1.76 g., 0.0095 mole) in pyridine (15 cc.) was warmed on a steam bath for 60 min. The deep red solution was poured into ice water, causing precipitation of a light brown solid (2.80 g.), m.p. 100–120°. Five recrystallizations alternately from ethanol-water and acetone-water yielded colorless, rectangular crystals, m.p. 175–178°; $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1630; ν_{NO_2} 1524, 1349 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{20}H_{26}N_2O_4$ (358.42): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.94; H, 7.45; N, 8.01.

(1-Benzamidocyclohexyl)methanol (*benzamide of* I). By the Schotten-Baumann method, to a mixture of (1-aminocyclohexyl)methanol[5] (1.0 g., 0.0077 mole), benzoyl chloride (1.1 g., 0.0078 mole) and water (10 cc.) was added aqueous 20% sodium hydroxide as needed to keep the mixture basic to litmus. The resulting precipitate was dissolved in methylene chloride and reprecipitated by the addition of light petroleum (b.p. 60–68°). The precipitate (1.26 g., 0.0054 mole, 70%), m.p. 110–120° was recrystallized five times from methylene chloride–light petroleum (b.p. 60–68°), yielding colorless needles, m.p. 118–122°; $\nu_{NH,OH}$ 3420, 3320, in $CHCl_3$, 3260, 3050, 1554 in Nujol; $\nu_{C=O}$ 1640 cm.$^{-1}$ in $CHCl_3$ and in Nujol.

Anal. Calcd. for $C_{14}H_{19}NO_2$ (233.30): C, 72.07; H, 8.21; N, 6.00. Found: C, 72.19; H, 8.35; N, 6.05.

(1-p-Nitrobenzamidocyclohexyl)methyl p-nitrobenzoate di-p-nitrobenzoyl derivative of I) was obtained by the Schotten-Baumann reaction, after recrystallization from acetone-ethanol as colorless crystals, m.p. 193–195.5°; ν_{NH} 3380; $\nu_{C=O}$ 1714, 1663; ν_{NO_2} 1523, 1353 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{21}N_3O_7$ (427.40): C, 59.01; H, 4.95; N, 9.83. Found: C, 59.16; H, 4.97; N, 9.98.

1-(Hydroxymethyl)cyclohexylammonium benzoate (*benzoate salt of* I) was obtained after recrystallization from methylene chloride as colorless needles, m.p. 159–160°; ν_{OH} 3310; $\nu_{NH_3^+}$ 2330, 2120, 1645; $\nu_{C=O}$ 1564 (shoulder), 1550, 1400 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{21}NO_3$ (251.32): C, 66.90; H, 8.42; N, 5.57. Found: C, 66.50; H, 8.24; N, 5.51.

Bis[1-(hydroxymethyl)cyclohexylammonium]carbonate (*carbonate salt of* I). Carbon dioxide gas was passed through a solution of (1-aminocyclohexyl)methanol[5] (2.00 g., 0.0155 mole) in water (5 cc.) for 30 min., forming a white powder (1.85 g.), m.p. 78–103°. Two washings with benzene yielded a sample (1.00 g., 0.0031 mole, 40%), m.p. 90–96°; $\nu_{NH_3^+}$ 2140, 1618; $\nu_{C=O}$ 1576, 1378 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{32}N_2O_5$ (320.42): C, 56.22; H, 10.07; N, 8.74. Found: C, 56.83; H, 10.05; N, 8.55.

Addition of a saturated solution of barium hydroxide to an aqueous solution of the sample resulted in immediate formation of a white precipitate.

When carbon dioxide gas was passed through a solution of (1-aminocyclohexyl)methanol[5] (2.00 g., 0.0155 mole) in dry benzene (10 cc.) for 20 min., a white powder (1.60 g.), m.p. ~67–69° precipitated. This precipitate had an elemental composition resembling a mixture of the carbamide and carbamate, $RNHCONHR{\cdot}RNHCOO^-H_3\overset{+}{N}R$, where R = $C_7H_{13}O$.

Anal. Calcd. for $C_{30}H_{58}N_4O_7$ (596.80): C, 60.37; H, 9.80; N, 9.39. Found: C, 61.14; H, 10.42; N, 9.49.

In contrast to the immediate formation of a precipitate with the carbonate, addition of a saturated solution of barium hydroxide to a freshly prepared aqueous solution of the mixture prepared in the absence of water resulted in formation of a heavy flocculent white precipitate within 2–3 min.

MINNEAPOLIS 14, MINN.

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

5-Phenyl-2-isoxazoline-3-carboxylic Acid[1]

WYMAN R. VAUGHAN AND JOHN L. SPENCER[2]

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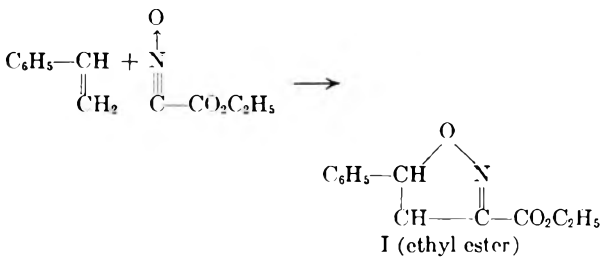
The preparation of 5-phenyl-2-isoxazoline-3-carboxylic acid by the reaction between styrene and carbethoxyformonitrile oxide, followed by hydrolysis, is described. The chemistry of this compound is discussed, and a number of derivatives are described. In addition the analogous preparation of 4-[3-hydrazido-5-phenyl-2-isoxazolinyl] carbamate from methyl styrylcarbamate and carbethoxyformonitrile oxide, followed by hydrazinolysis, is also described, and certain of its reactions are considered. The use of carbethoxyformonitrile oxide in this manner affords a useful synthetic route to various 3-substituted 2-isoxazolines.

The failure of benzylidenepyruvic acid oxime to cyclize, either to 3-hydroxylamino-5-phenyl-2-(5H)furanone by the lactoenoic tautomeric process common to imino derivatives of benzylidenepyruvic acid,[3] or to 5-phenyl-2-isoxazoline-3-carboxylic acid (I) in common with chalcone oximes,[4] has been commented upon elsewhere.[5] In view of the decided reluctance of this oxime and its derivatives to produce I, it seemed desirable to prepare I by another route and investigate its stability with respect to ring-opening as well as its general characteristics.

The reaction between benzonitrile oxide and various olefins[6] suggested that the only known nonaromatic nitrile oxide, carbethoxyformonitrile oxide,[7] might be expected to add to styrene to give the ethyl ester of I:



I (ethyl ester)

Since nitrile oxides are prone to polymerization it seemed desirable to use very mild conditions for the reaction and to generate the nitrile oxide *in situ* and slowly. The nitrile oxide is usually made by treating ethyl chlorooximinoacetate with a base,[7] and when sodium hydroxide at 0° proved unsatisfactory, sodium carbonate at room temperature was tried. Thus a solution of styrene and ethyl chlorooximinoacetate in ether was vigorously stirred while a solution of aqueous sodium carbonate was added very slowly, and a 50% yield of the desired ester was obtained. Hydrolysis by 10% sodium hydroxide, followed by acidification afforded I. Tentative assignment of the desired structure was made by analogy with the reaction between benzonitrile oxide and styrene.[6e-k] Confirmation of this assignment was obtained by oxidation of I to the known 5-phenyl-isoxazole-3-carboxylic acid,[8] with additional support from decyclization studies. The treatment of I with concentrated sulfuric acid for twenty-four hours at room temperature converted it into benzylidenepyruvic acid oxime, which had previously been shown to be stable to sulfuric acid for long periods of time.[5] Accordingly it is clear that the acyclic form is the stable one in sulfuric acid solution. Similarly treatment of the amine derived

(1) Abstracted from a portion of the Ph.D. Dissertation of John L. Spencer, University of Michigan, 1958.

(2) National Science Foundation predoctoral fellow 1956–58.

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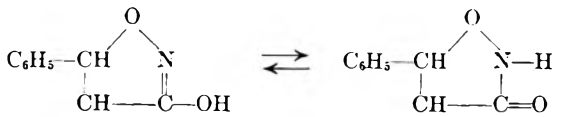
(7) G. S. Skinner, *J. Am. Chem. Soc.*, **46**, 731 (1924).

(8) A. Quilico and M. Simonetta, *Gazz. chim. ital.*, **77**, 586 (1947); *Chem. Abstr.*, **42**, 5904 (1948).

from I *via* the Curtius rearrangement (see below) with dilute hydrochloric acid afforded cinnamic acid, presumably *via* the amide oxime,[9] which also fails to cyclize in acidic media.

With a comparatively simple synthesis for I at hand it was of interest to determine whether 3-amino-5-phenyl-2-isoxazoline (II) accessible from derivatives of I through the Curtius rearrangement could be converted to 3-hydroxy-5-phenyl-2-isoxazoline, which should be tautomeric with 5-phenyl-3-isoxazolidinone:



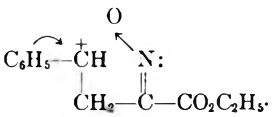
The latter substance is the 4-deamino analog of 5-phenylcycloserine,[10-12] which has been shown to possess some antibiotic activity.

To this end the hydrazide of I was prepared, converted to the azide with nitrous acid and rearranged to both the urethan (III) and the amine (II). While II may partake of the same type of tautomerism pictured for the hydroxy analog, its general behavior suggests that it exists primarily as the 2-isoxazoline rather than the 3-imino-5-phenylisoxazolidine. Thus, its acetyl derivative is base-soluble; and while II cannot be titrated potentiometrically, it is soluble in 5% aqueous hydrochloric acid, and it forms a stable hydrochloride in alcohol or ether. However, nitrous acid, nitrosyl chloride, and nitrogen tetroxide under a variety of reaction conditions afforded only untractable oils possessing none of the expected characteristics of the desired substance. Likewise attempts to hydrolyze the potential imino or amino group by conventional and unconventional (*e.g.* Bucherer, reverse Sommelet[13]) procedures afforded only starting material, cinnamic acid, or unidentifiable tars. The only clean reactions involved acetylation, which occurs readily on warming with acetic acid and even to some extent with 50% aqueous acetic acid, and exchange with hydrazine in glacial acetic acid, which affords the 3-β-acetylhydrazino analog of II; this, like the acetyl derivative of II, is base-soluble.

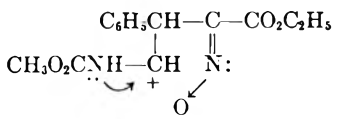
Several other potential preparations of 5-phenyl-3-isoxazolidinone from I and its derivatives were investigated. The Hunsdiecker silver salt reaction failed to afford the desired 3-bromo-5-phenyl-2-isoxazoline, and various oxidative reactions (*e.g.* periodic acid, lead tetraacetate on I or the carbinol derived from I by treatment with methyl Grignard) were entirely unsuccessful, only starting material being recovered. With a stronger oxidizing agent, permanganate, I was oxidized to the isoxazole.

In the expectation that a 4-substituent might alter the characteristics of I, the addition of carbethoxyformonitrile to several β-substituted styrenes was investigated. Cinnamic acid, methyl cinnamate, and cinnamonitrile failed to afford products, but no exhaustive study of reaction conditions was made because it was found that methyl styrylcarbamate reacted well.

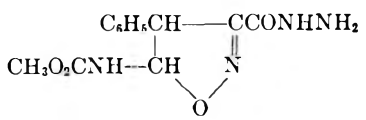
The exact nature of the reaction between styrene and a nitrile oxide is unknown, but the failure to observe reactions with methyl cinnamate and cinnamonitrile under conditions which are satisfactory for styrene suggests that the attack of the nitrile oxide is more electrophilic than nucleophilic in character, and the comparably good reaction of methyl styrylcarbamate would seem to substantiate this hypothesis. Thus in spite of one's inclination to picture the charge distribution in a nitrile oxide as $R-C\equiv N\rightarrow O$, it would seem that $R-\overset{+}{C}=\ddot{N}\rightarrow O$ is the more significant for the addition reaction. The initial reaction intermediate with styrene is accordingly



With methyl styrylcarbamate, however, the inherently greater polarizability of the *p*-electrons of nitrogen (compared with the π-electrons of phenyl) should provide greater stabilization of a transition state leading to



On this basis, then, the hydrazide derived from the adduct of methyl styrylcarbamate and carbethoxyformonitrile oxide is formulated as methyl 5-[3-hydrazido-4-phenyl-2-isoxazolinyl)carbamate:



IV

This is in keeping with the observation that the addition of nitrile oxides to olefins is similar to that of aliphatic diazo compounds and azides and orientation follows the Markownikoff rule.[6c]

The initial product of this reaction was not purified, but by analogy with the hydrazinolysis of the ethyl ester of I, which could be very readily converted to the hydrazide, which was more tractable, the crude product was at once converted to the above hydrazide (IV). Since the ethyl group, and

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(10) F. A. Kuehl, Jr., *et al.*, *J. Am. Chem. Soc.*, **77**, 2344 (1955).

(11) P. H. Hidy, *et al.*, *J. Am. Chem. Soc.*, **77**, 2345 (1955).

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not the methyl, was hydrazinolyzed, there can be no doubt as to the structure.

The hydrazide was converted to the azide, which then was rearranged in ethanol to give a bis-urethane, which unfortunately resisted hydrolysis under mild conditions; and under more vigorous conditions it afforded only uncharacterizable products. Consequently it would appear that introduction of a 4-substituent consisting of a functional group renders the system less tractable than without it.

The present work constitutes an introductory survey of the applicability of the nitrile oxide synthesis to 3-functionally substituted 2-isoxazolines. The method is a convenient one and should be satisfactory for the preparation of any 2-isoxazoline-3-carboxylic acid to the extent that any given olefin has been shown to react with aromatic nitrile oxides. From the work herein described it further appears that one can readily prepare derivatives of such acids and that the amines available *via* the Curtius rearrangement should also be readily accessible. However, the transformation of such amines into 3-isoxazolidinones is not at present feasible.

EXPERIMENTAL[14-16]

Ethyl chlorooximinoacetate. Ethyl chlorooximinoacetate was prepared by the action of 2 moles of nitrous acid on ethyl glycinate hydrochloride according to the procedure of Skinner.[7]

Ethyl 5-phenyl-2-isoxazoline-3-carboxylate. Carbethoxyformonitrile oxide was generated *in situ* with styrene to give the addition product. The following procedure was found to give the best yield. To a solution of 15.1 g. (0.10 mole) of ethyl chlorooximinoacetate in 220 ml. of ether was added 12.5 g. (0.12 mole) of styrene. The solution was vigorously stirred with a Hershberg stirrer while a solution of 10.6 g. (0.10 mole) of sodium carbonate in 150 ml. of water was added dropwise over a 4-hr. period at room temperature.

The layers were separated and the ether layer washed with water. Ether extraction of the aqueous layer gave essentially no ester. Evaporation of the original ether layer gave about 17 g. of crude ester. This was distilled under vacuum to yield 11.0 g. (50%) of slightly yellow colored ester, b.p. 162–163°/2.5 mm.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.02; H, 6.02; N, 6.44.

5-Phenyl-2-isoxazoline-3-carboxylic acid (I). In a separate run the 17.0 g. of crude ester was hydrolyzed to the acid. A mixture of the ester and 100 ml. of 10% sodium hydroxide was stirred until a white solid formed (about 4 hr.). This was dissolved by adding 150 ml. of water and the hydrolysis was completed by an additional 20 hr. of stirring. Nonacidic impurities were removed by ether extraction, and polymeric material was removed by filtration.

The solution of the sodium salt was acidified by dropwise addition of 10% hydrochloric acid. This yielded, after cooling, 11.0 g. of crude acid, m.p. 90–103°. Recrystallization from benzene yielded 9.5 g. (49%) of white product, m.p. 104–106°; neut. equiv. calcd.: 191, found: 190.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.89; H, 4.83; N, 7.31.

Treatment of the acid with ethereal diazomethane and, after evaporation, hydrazine in ethanol gave the same hydrazide (see below) as the original crude ester. The identity of these two compounds was shown by undepressed mixture melting point and superimposable infrared spectra.

5-Phenyl-2-isoxazoline-3-carboxylic acid hydrazide. The hydrazide was prepared from the crude ester by reaction with hydrazine in ethanol. The crude ester in ethanol, 1 g. per 10 ml., was slowly added to a 10% ethanolic solution of hydrazine with swirling and cooling in an ice bath. (One milliliter of hydrazine was used per g. of ester.) After the addition the solution was allowed to warm to room temperature and filtered from an orange tar. Evaporation of the alcohol left an orange semisolid which upon trituration with water yielded the crude hydrazide, m.p. 107–114°. Recrystallization from alcohol raised the melting point to 112.5–115.5°. When 17.0 g. of crude ester was used, 100 ml. of water was used for the trituration and 40 ml. of alcohol for the recrystallization to give 10.0 g. (49% based on ethyl chlorooximinoacetate) of hydrazide, m.p. 113–115°. The analytical sample was recrystallized twice from water, m.p. 113.5–115.5°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.33; H, 5.49; N, 20.57.

5-Phenyl-2-isoxazoline-3-carboxylic acid azide. To a solution of 50 ml. of acetone and 50 ml. of 10% hydrochloric acid was added 3.0 g. (0.015 mole) of the above hydrazide. This solution was cooled in an ice bath while a solution of 1.5 g. (0.022 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. An additional 50 ml. of water was added to yield 2.8 g. (88%) of analytically pure shiny white plates, m.p. 82–83° vigorous dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.62; H, 3.82; N, 25.96.

Ethyl 3-[5-phenyl-2-isoxazolinyl]carbamate. The above azide was dissolved in ethanol, 1 g. per 100 ml., and the solution refluxed for 2 hr. Evaporation of the alcohol left a white solid. This was recrystallized from ethanol-water, m.p. 123.5–127°. When 1.3 g. of azide was used 1.2 g. (86%) of urethan was obtained. Two further recrystallizations from the same solvent pair gave the analytical sample, m.p. 126.0–127.5°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.67; H, 6.17; N, 11.93.

Hydrolysis of the urethan. (a) *In base:* A solution of 1.9 g. (0.0081 mole) of the urethan in 25 ml. of 10% sodium hydroxide was heated at 110° for 36 hr. The resulting mixture was cooled and the precipitate collected and washed with water. This was found to be 3-amino-5-phenyl-2-isoxazoline, II, m.p. 128–132°; yield 0.75 g. (56%). This product has an infrared spectrum identical with that obtained by direct rearrangement of the azide (see below) and no depression of melting point was obtained on mixing the two samples.

(b) *In water:* The urethan (100 mg., 0.00043 mole) was refluxed in 25 ml. of water for 65 hr. The resulting solution was filtered and concentrated to approximately 5 ml. Cooling yielded 45 mg. (65%) of 3-amino-5-phenyl-2-isoxazoline (II), m.p. 125–133°, as shown by identical infrared spectra and undepressed mixture melting point.

(c) *In acid:* The urethan (526 mg., 0.002 mole) was refluxed in 25 ml. of 5% hydrochloric acid for 16 hr. Cooling yielded 230 mg. (69%) of solid, m.p. 120–132°, which was shown to be *trans*-cinnamic acid by its neutral equivalent (calcd., 148; found, 148) and its infrared spectrum and failure to depress the melting point of an authentic sample of *trans*-cinnamic acid.

3-Amino-5-phenyl-2-isoxazoline (II). The above azide, (3.5 g., 0.16 mole) was slowly added to a solution of 70 ml. of trifluoroacetic acid and 17.5 ml. of water. The azide dissolved during the addition and the resulting solution was heated on a steam bath for 30 min. after the bubbling had

(14) Boiling points and melting points are uncorrected.

(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) Infrared spectra obtained from Nujol mulls or thin films by means of a Perkin-Elmer model 21 infrared spectrophotometer.

ceased. Evaporation of the solvents left a waxy solid which was dissolved in 50 ml. of 10% hydrochloric acid. The solution was filtered and made basic with 25% sodium hydroxide. After cooling, the solid, m.p. 127–130°, was collected, 2.2 g. (84%). An analytical sample was prepared by recrystallization from benzene and twice from water, m.p. 129.5–131.5°, in which it is less soluble than in 5% hydrochloric acid.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.66; H, 6.40; N, 17.29.

Amine hydrochloride. The above amine (II) (1.0 g., 0.0062 mole) was added to 25 ml. of absolute ethanol saturated with hydrogen chloride. The amine dissolved slowly and no amine salt precipitated upon standing. Evaporation of the solvent left a white solid, m.p. 163–170° dec. The melting point was very dependent on the rate of heating. Recrystallization from methanol-ether gave an analytical sample.

Anal. Calcd. for $C_9H_{11}N_2OCl$: C, 54.41; H, 5.58; N, 14.11. Found: C, 54.37; H, 5.57; N, 14.03.

The same amine hydrochloride as shown by identical infrared spectra and undepressed mixture melting point was obtained by dissolving the amine in ether, bubbling in hydrogen chloride, and collecting the precipitate.

Hydrolysis of the amine (II). (a) *In hydrochloric acid:* The amine was dissolved in 5% hydrochloric acid and heated on a steam bath for 12 hr. Cooling yielded a solid, m.p. 126–132° which had an infrared spectrum identical with *trans*-cinnamic acid and showed no depression of melting point on mixing.

(b) *In glacial acetic acid:* The amine (300 mg.) was dissolved in 7.5 ml. of acetic acid and refluxed 24 hr. The solvent was evaporated leaving a semisolid which was recrystallized from water, m.p. 95–135°. Recrystallization from water twice more gave an analytical sample of acetyl derivative, m.p. 146.5–147.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.68; H, 6.01; N, 13.80.

(c) *In 50% acetic acid:* Refluxing the amine in 50% acetic acid gave a mixture of starting material, *trans*-cinnamic acid and the acetylation product obtained from glacial acetic acid.

Attempted deamination of the amine (II). (a) *With nitrous acid:* The amine (162 mg., 0.0001 mole) was dissolved in 10 ml. of 0.1023*N* hydrochloric acid by warming. The solution was cooled in an ice bath and a solution of 69 mg. (0.001 mole) sodium nitrite in 5 ml. of water was added dropwise with swirling and continued cooling. An orange oil separated and was extracted with chloroform. The oil remaining after evaporation of the chloroform could not be crystallized. The same results were obtained when two and three times the quantity of hydrochloric acid was used, when acetic acid buffered with sodium acetate was used, and when the sodium nitrite solution was added over a 2-day period. The oil was insoluble in 5% sodium hydroxide. Its infrared spectrum had an adsorption band at 2150 $cm.^{-1}$

(b) *With nitrosyl chloride:* The amine suspended in carbon tetrachloride was treated with an equivalent amount of nitrosyl chloride dissolved in the same solvent. The mixture was warmed on a steam bath during which time an oil separated. Evaporation of the solvent left the same oil as above as shown by identity of infrared spectra. Treating the amine dissolved in chloroform and cooled in an ice bath with excess nitrosyl chloride solution gave the same results.

(c) *With nitrogen tetroxide:* A solution of 0.5 g. of nitrogen tetroxide in 20 ml. of carbon tetrachloride was cooled to 0°. Sodium acetate, 738 mg., and 486 mg. of amine were added. After standing 30 min. the mixture was poured on ice and the layers separated. The aqueous layer was extracted with ether and the combined organic layers were evaporated leaving the same oil as obtained with nitrous acid.

Nitrosation of the urethan. The procedures of White[17] for the nitrosation of amides were used.

(17) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

(a) *With nitrogen tetroxide:* Using nitrogen tetroxide, sodium acetate, and urethan, 702 mg., nothing but unchanged urethan could be obtained.

(b) *With acetic anhydride, acetic acid, and sodium nitrite:* Using 1.17 g. of urethan, 5 ml. of acetic acid, 25 ml. of acetic anhydride, and 7.5 g. of sodium nitrite gave a mixture of starting material and the same oil that was obtained by the nitrosation of the amine (II) as indicated by the infrared spectrum.

Reaction of amine (II) *with hydrazine in acetic acid.* The solution formed by adding 2.0 ml. of hydrazine to a solution of 2.0 g. of II in 20 ml. of acetic acid was allowed to stand 48 hr. The solution developed a slight yellow color after approximately half this time. The solvent was evaporated leaving an orange colored semisolid. This was treated with 20 ml. of 10% hydrochloric acid. The orange precipitate which formed was collected and washed with 10% hydrochloric acid. Trituration of this orange solid with benzene gave 0.6 g. of white solid, m.p. 152–155° dec. with great dependence on rate of heating. It was insoluble in sodium hydroxide as well as hydrochloric acid, but was not further identified.

The aqueous acid filtrate from above was made neutral with 10% sodium hydroxide. This yielded a light tan solid which was recrystallized from water. It was then heated in *ca.* 60 ml. of benzene and the mixture was cooled. This yielded 0.5 g. of white solid, m.p. 145–150°. It was found to be soluble in both 5% hydrochloric acid and 5% sodium hydroxide, but insoluble in sodium bicarbonate. An analytical sample, m.p. 155–157°, was prepared by recrystallization from benzene.

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.49; H, 5.93; N, 19.40.

5-Phenylisoxazole-3-carboxylic acid. 5-Phenyl-2-isoxazoline-3-carboxylic acid (I) was oxidized with permanganate to the corresponding aromatic isoxazole. To a solution of 4 ml. of concd. sulfuric acid in 40 ml. of water was added 1.9 g. (0.01 mole) of 5-phenyl-2-isoxazoline-3-carboxylic acid (I). With mechanical stirring 3.0 g. (0.02 mole) of potassium permanganate was added in small portions. After the addition 4 g. of sodium bisulfite was added to reduce any manganese dioxide formed. The mixture was cooled in an ice bath and yielded 1.0 g. of light tan solid. This was recrystallized from benzene to give 0.8 g. (43%) of white solid, m.p. 153–161° dec. The analytical sample was prepared by recrystallization from water andaga in from benzene, 156–161° dec. The reported[8] m.p. is 162°. Neut. equiv.: Calcd., 189. Found, 191.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.52; H, 3.65; N, 7.51.

Decyclization of 5-phenyl-2-isoxazoline-3-carboxylic acid (I). 5-Phenyl-2-isoxazoline-3-carboxylic acid (100 mg.) was dissolved in 1 ml. of concd. sulfuric acid. After standing 24 hr. the solution was poured onto 5 g. of ice to yield 100 mg. of slightly yellow solid, m.p. 125–135° dec. Recrystallization from ethanol-water gave 65 mg. of white solid, m.p. 156–158° dec. There was no depression of the melting point when mixed with a sample of benzylidenepyruvic acid oxime[5] and the two samples had identical infrared spectra.

Dimethyl-3-[5-phenyl-2-isoxazoline]-methanol. Methylmagnesium iodide was prepared from 2.4 g. (0.1 g.-atom) of magnesium and 14.1 g. (0.1 mole) of methyl iodide, and a solution of 5.5 g. (0.025 mole) of ethyl 5-phenyl-2-isoxazoline-3-carboxylate in 100 ml. of ether was added in small portions, the reaction being allowed to subside after each addition. A brownish oil separated and the mixture was stirred an additional hour.

The complex was decomposed with saturated ammonium chloride, approximately 15 ml. being required. With continued stirring the ammonium chloride solution was added dropwise at such a rate as to maintain reflux and in amount necessary to change the cloudy mixture to a clear solution with precipitated solid. The ether layer was decanted and

the ether evaporated leaving an oil which solidified on prolonged cooling. Recrystallization from a small quantity of carbon tetrachloride gave 2.4 g. (46%) of white solid, m.p. 58–60°. Further recrystallizations from the same solvent gave an analytical sample, m.p. 59–61°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.29; H, 7.38; N, 6.93.

Methyl styrylcarbamate. Methyl styrylcarbamate was prepared by a Hofmann rearrangement on cinnamamide according to the procedure of Weermann.[18]

Methyl 5-[3-carbethoxy-4-phenyl-2-isoxazolinyl]carbamate. A solution of 17.7 g. (0.10 mole) of methyl styrylcarbamate in 400 ml. of ether was added to a solution of 18.2 g. (0.12 mole) of ethyl chlorooximinoacetate[7] in 100 ml. of ether. With vigorous mechanical stirring 12.7 g. (0.12 mole) of sodium carbonate in 180 ml. of water was added dropwise over a 7-hr. period at room temperature. After the addition the mixture was stirred an additional hour. The layers were separated; the ether layer was washed with water and dried over magnesium sulfate. Filtration and evaporation of the ether left a semisolid residue, 31 g. The ester was not purified but converted directly to the hydrazide.

Methyl 5-[3-hydrazido-4-phenyl-2-isoxazolinyl]carbamate (IV). The above 31 g. of crude ester in 250 ml. of ethanol was slowly added to a solution of 25 ml. of hydrazine in 250 ml. of ethanol cooled in an ice bath. After the addition the solution was allowed to warm to room temperature over a 30-min. period. The solution was filtered from the reddish solid and tars and the solvent evaporated, leaving a solid.

The residual solid was dissolved in 100 ml. of chloroform and extracted with 100 ml. of 5% hydrochloric acid. The acid extract was washed twice with 50 ml. of chloroform, partially neutralized with 50 ml. of 10% sodium hydroxide, and made basic with 50 ml. of 5% sodium bicarbonate. This yielded, after cooling, 13 g. [47% based on methyl styrylcarbamate] of light tan solid, m.p. 127–137° sl. dec. Two recrystallizations from methanol only raised the melting point slightly, 130–140° sl. dec. Further recrystallizations from methanol-water did not raise the melting point further.

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot 1/2H_2O$: C, 50.18; H, 5.25; N, 19.49. Found: C, 50.27, 50.17; H, 5.22, 5.29; N, 19.48, 19.59.

The analytical sample was recrystallized from benzene-cyclohexane and dried at 0.03 mm. for 48 hr. without change. However, drying at 100° and atmospheric pressure removed the water.

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.73; H, 5.07; N, 20.11.

Methyl 5-[3-carbazido-4-phenyl-2-isoxazolinyl]carbamate. A solution of 0.50 g. (0.0072 mole) of sodium nitrite was added dropwise to a solution of 1.0 g. (0.0036 mole) of the above hydrazide (IV) in 50 ml. of 5% hydrochloric acid cooled in an ice bath. This yielded 0.94 g. (90%) of white solid, m.p. 115° vigorous dec.

A sample for analysis was prepared by dissolving in ethanol, filtering and reprecipitating with water, m.p. 120° vigorous dec.

Anal. Calcd. for $C_{12}H_{11}N_5O_4$: C, 49.83; H, 3.83; N, 24.21. Found: C, 50.10; H, 4.16; N, 24.11.

Ethyl methyl 3,5-[4-phenyl-2-isoxazolinyl]dicarbamate. The above azide (0.90 g., 0.0030 mole) was dissolved in 50 ml. of ethanol and the solution refluxed for 30 min. The solution was decolorized with Norit and evaporated to dryness. The residue was triturated with a very small amount of ether to give 0.60 g. (65%) of white solid, m.p. 173–183°. Recrystallization from ethanol-water gave an analytical sample, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.68; H, 5.59; N, 13.82.

ANN ARBOR, MICH.

(18) R. A. Weerman, *Ann.*, **401**, 1 (1913).

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

2,6-Disubstituted 3,5-Thiomorpholinediones and Related Compounds[1]

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Methods suitable for the synthesis of α,α'-dialkylthiodiacetamic acids including those with unlike radicals and their conversion to 2,6-dialkyl-3,5-thiomorpholinediones are described. The diacetamic acids could be separated into racemates but attempts to resolve the racemates to their optical isomers were unsuccessful. In the synthesis of 2,2-dialkyl-3-thiomorpholones by a previously unreported process, the intermediate dialkyl(2-aminoethylmercapto)acetic acids were isolated.

Previous workers have reported the synthesis of unsubstituted 3,5-thiomorpholinedione,[2] symmetrical 2,6-di- and 2,2,6,6-tetrasubstituted analogs,[3,4] unsymmetrical 2,2-disubstituted analogs[4–7] and unsymmetrical 2,2,6-trisubstituted analogs.[7,8]

The present series of 2,6-disubstituted 3,5-thiomorpholinediones was prepared by the scheme outlined in Fig. 1, which is equally well suited for the synthesis of compounds with unlike radicals.

5-Monoalkyl-2-imino-thiazolidinones (Series I) were prepared in yields of 80–90% which is about twice that obtained for the geminal dialkyl compounds. One previously unreported member of Series I, 5-(2-secpentyl)-2-imino-4-thiazolidinone, was prepared from its hydrobromide salt and hydrolyzed to its 2-keto derivative.

(1) Based on the Ph.D. thesis of Richard N. Macnair.

(2) Schulze, *Zeitschrift fur Chemie*, **2**, 182 (1866), through Beilstein's *Handbuch der Organischen Chemie*, ed. 4, von Julius Springer, Berlin, 1921, Vol. 27, p. 249.

(3) P. R. Rasanen and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **38**, 599 (1949).

(4) C. Barkenbus and P. Panzera, *J. Org. Chem.*, **20**, 237 (1955).

(5) G. S. Skinner and J. B. Bicking, *J. Am. Chem. Soc.*, **76**, 2776 (1954).

(6) J. R. Lovett, M.S. thesis, University of Delaware, 1955.

(7) J. R. Lovett, Ph.D. thesis, University of Delaware, 1957.

(8) G. S. Skinner and J. S. Elmslie, *J. Org. Chem.*, **24**, 1702 (1959).

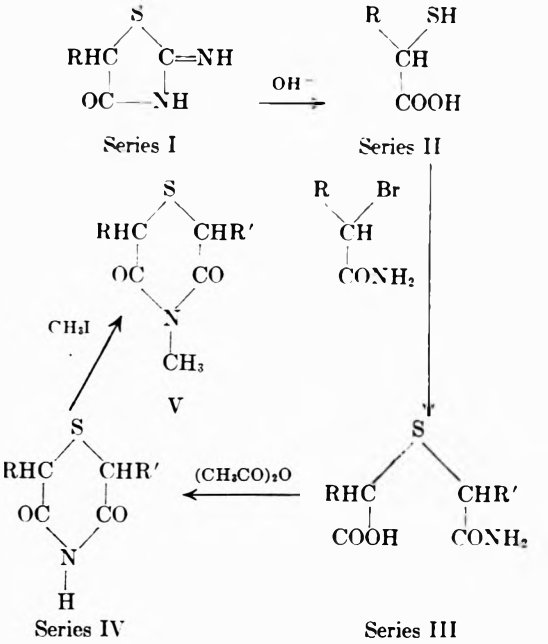


Fig. 1. Preparation of 2,6-disubstituted 3,5-thiomorpholinediones

Compounds of Series I were hydrolyzed in dilute sodium hydroxide to obtain the monosubstituted mercaptoacetic acids (Series II) in virtually 100% yield. Neither unchanged starting material nor products of partial hydrolysis were recovered. This is in direct contrast to the behavior of geminal disubstituted derivatives which gave mixtures of mercapto acid, mercapto amide, thiazolidinedione and unreacted iminothiazolidinone. The acids of Series II were very susceptible to oxidation in contrast to the disubstituted mercaptoacetic acids and amides which were readily distilled under diminished pressure. The special precaution of hydrolysis and extraction in a nitrogen atmosphere had to be adopted and purification at this stage was abandoned.

Substituted thiodiacetamic acids (Series III, Table I) were prepared by the action of an α-bromoamide with an alkylmercaptoacetic acid in ether solution in the presence of alcoholic sodium ethoxide under nitrogen. Series III compounds, having two asymmetric centers, may exist in stereoisomeric forms. Separation of these into what appeared to be and what we shall refer to as two racemates (A and B) was accomplished by fractional recrystallization in all cases except III-4 III-5, and III-7. Each pair of racemates gave identical analyses. The 2-*sec*-pentyl group in III-4 and III-5 provides an additional asymmetric center causing four possible racemates. Only one of these racemates was obtained pure in each case but a residue of each which melted over a range was analyzed showing identical composition to the respective pure racemate. No second form of III-7 was observed.

2,6-Disubstituted 3,5-thiomorpholinediones (Series IV, Table II) were obtained by refluxing the corresponding thiodiacetamic acids of Series III with acetic anhydride. Where two asymmetric centers exist in the molecule, only one pure crystalline form was isolated. Where three asymmetric centers exist, one being in the side chain as in IV-4 and IV-5, two pure crystalline forms were obtained.

Representative members of Series III and IV were shown to have no optical activity, as expected. The infrared spectra of the amic acids including all of the isomeric pairs showed characteristic absorption bands for OH at 2.9–3.0, NH at 3.05–3.15, CH at 3.3–3.5, COOH carbonyl at 5.85–5.95 and $CONH_2$ carbonyl at 6.1–6.2 μ. The absorption curve of the isomeric amic acid A and B pairs between 6.2 and 16 μ were largely different. Both pure III A and III B forms and mixtures thereof were used to prepare Series IV compounds but only one form was obtained as stated above.

The infrared spectra of the thiomorpholinediones including the isomeric pairs of IV-4 and IV-5 showed characteristic absorption bands for NH at 3.1, CH at 3.4, and CONHR carbonyl at 5.8–6.1 μ. The absorption curve of the isomeric thiomorpholinedione A and B pairs between 6.2 and 16 μ were also largely different.

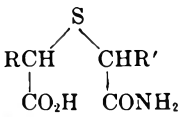
N-Methyl-2,6-disubstituted 3,5-thiomorpholinediones (Series V, Table II) were prepared by modification of the method of Loudon and Ogg for acyclic and cyclic amides.[9] The most important modifications were a decrease in the reaction temperature to room temperature and a decrease of methyl iodide to an equimolecular amount. Proof that the nitrogen was methylated lay in the absence of the NH band at 3.1 μ.

3-Thiomorpholone has been prepared unsubstituted[10] and substituted[11,12] in various positions including 2-, 4-, 5- and 6-. The 3-thiomorpholones (Series VII, Table III) prepared in this work were 2,2-disubstituted. Both 2,2-diethyl- and 2-*n*-butyl-2-ethyl-3-thiomorpholone have been prepared previously, the former by Goldberg and Lehr[11] and the latter by Gabbert.[12] Goldberg and Lehr treated ethyleneimine with the ethyl ester of mercaptodiethylacetic acid and heated the product to close the ring. Gabbert heated the product from *n*-butylethylmercaptoacetic acid and 2-bromoethylamine hydrobromide. The latter method was repeated successfully for 2-*n*-butyl-2-ethyl-3-thiomorpholone (VII-IV). This method also proved successful in the preparation of 2,2-diethyl-3-thiomorpholone (VII-2) so the procedure may very well be a general one for all compounds of this type. Another method was developed for the prepara-

(9) J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 739 (1955).
(10) Herbert Bestian, *Ann.*, **566**, 210 (1950).
(11) Moses Wolf Goldberg and Hanna H. Lehr, U. S. Patent **421,680**, April 7, 1954.
(12) J. D. Gabbert, M.S. thesis, University of Delaware, 1956.

TABLE I

2,6-DISUBSTITUTED THIODIACETAMIC ACIDS

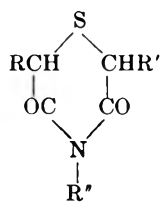


No.[a]	R	R′	M.P., °	C		H		N		Solvent
				Calcd.	Found[b]	Calcd.	Found	Calcd.	Found	
III-1A	C_2H_5	CH_3	144	43.96	44.18	6.85	6.62	7.32	7.31	Nitromethane
III-1B	C_2H_5	CH_3	101–102	43.96	44.20	6.85	7.18	7.32	7.23	*n*-Hexane
III-2A	*n*-C_4H_9	CH_3	143–144	49.29	49.15	7.81	7.94	6.38	6.40[c]	Ethanol/water (1:1)
III-2B	*n*-C_4H_9	CH_3	82–83	49.29	49.52	7.81	7.90	6.38	6.25[d]	Cyclohexane
III-3A	*n*-C_4H_9	C_2H_5	151–152	51.48	51.13	8.21	8.04	6.00	5.96	Ethanol/water (1:1)
III-3B	*n*-C_4H_9	C_2H_5	95–96	51.48	52.03	8.21	8.32	6.00	5.94	Cyclohexane
III-4A	2-*sec*-C_5H_{11}	CH_3	162–163	51.48	51.51	8.21	8.16	6.00	5.96	Ethanol/water (1:1)
III-4B	2-*sec*-C_5H_{11}	CH_3	88–94	51.48	51.61	8.21	8.49	6.00	5.88[e]	*n*-Hexane
III-5A	2-*sec*-C_5H_{11}	C_2H_5	144–145	53.41	53.54	8.56	8.44	5.66	5.62	Ethanol/water (1:1)
III-5B	2-*sec*-C_5H_{11}	C_2H_5	83–88	53.41	53.54	8.56	8.98	5.66	5.70	*n*-Hexane
III-6A	C_6H_5	C_2H_5	182–183	56.90	56.90	5.97	6.20	—	—	Ethanol
III-6B	C_6H_5	C_2H_5	153–154	56.90	56.96	5.97	6.31	5.53	5.40	Acetone
III-7	C_6H_5	CH_3	160–161	55.21	55.56	5.48	5.47	5.85	5.95	Isopropyl alcohol

[a] The letters A and B designate racemates of the same composition. [b] These and all subsequent analyses were performed by Sharp and Dohme Division of Merck, Inc. [c] S Calcd. 14.62; found 14.49. [d] S Calcd. 14.62, found 14.81. [e] S Calcd. 13.74, found 13.54.

TABLE II

2,6-DISUBSTITUTED AND 2,4,6-TRISUBSTITUTED 3,5-THIOMORPHOLINEDIONES



No.	R	R,	R″	M.P., ° or B.P., ° (mm.)	Yield, %	C		H		N		Solvent
						Calcd.	Found	Calcd.	Found	Calcd.	Found	
IV-1	C_2H_5	CH_3	H	97–98	81	48.53	48.34	6.40	6.27	8.08	8.05	Isopropyl alcohol
IV-2	*n*-C_4H_9	CH_3	H	85–86 117/0.25	88.4	53.70	53.66	7.51	7.46	6.96	6.89	*n*-Hexane distilled
IV-3	*n*-C_4H_9	C_2H_5	H	93–94	49	55.78	55.49	7.96	7.92	6.50	6.48	Isopropyl alcohol
IV-4A	2-*sec*-C_5H_{11}	CH_3	H	100–101	68.5[a]	55.78	55.78	7.96	8.31	6.50	6.29	*n*-Hexane
IV-4B	2-*sec*-C_5H_{11}	CH_3	H	109–111 (0.15)		55.78	55.54	7.96	8.16	6.50	6.36	Distilled
IV-5A	2-*sec*-C_5H_{11}	C_2H_5	H	120–121	63.6[b]	57.61	57.51	8.35	8.60	6.10	6.08	*n*-Hexane
IV-5B	2-*sec*-C_5H_{11}	C_2H_5	H	116 (0.14)		57.61	57.49	8.35	8.58	6.10	6.09	Distilled
IV-5C	2-*sec*-C_5H_{11}	C_2H_5	H	94–95		57.61	57.73	8.35	8.78	6.10	5.97	*n*-Hexane
IV-6	C_6H_5	C_2H_5	H	123–124	78.3	61.25	61.21	5.57	5.69	5.95	5.88	Ethanol
IV-7	C_6H_5	CH_3	H	114–115	65.8	59.71	59.89	5.01	5.17	6.33	6.34	Isopropyl alcohol
V-1	*n*-C_4H_9	C_2H_5	CH_3	101–102[c] (0.23)		57.61	57.35	8.35	8.93	6.10	5.85	Distilled
V-2	C_6H_5	C_2H_5	CH_3	129–131[d] (0.10)	75.3	62.62	61.87	6.06	6.14	5.62	5.61	Distilled

[a] Includes A and B. [b] Includes A, B, and C. [c] n_D^{25} 1.4990. [d] n_D^{25} 1.5666.

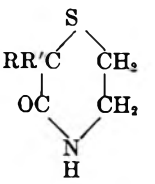
tion of Series VII compounds which consisted in treating a mercaptoacetamide with 2-bromoethylamine hydrobromide and subsequently pyrolyzing the intermediate amino amide. 2-*n*-Butyl-2-ethyl-3-thiomorpholone (VII-IZ) was prepared in this manner and was identical with VII-IY by comparison of boiling points, refractive indices, and infrared spectra. The previously uncharacterized intermediate dialkyl(2-aminoethylmercapto)acetic acids (Series VI) were isolated.

Pharmacological screening tests performed on members of Series IV, V, and VII showed no promise of anticonvulsant activity.[13] Thus it ap-

(13) These tests were performed by Sharp and Dohme Division of Merck, Inc., West Point, Pa.

TABLE III

2,2-DIALKYL 3-THIOMORPHOLONES



No.	R	R′	M.P., ° or B.P., °/mm.	n_D^{25}	Yield, %
VII-1Y	*n*-C_4H_9	C_2H_5	143/0.85	1.5148[a]	78.4
VII-1Z	*n*-C_4H_9	C_2H_5	143–145/1.1	1.5138[a]	60.1
VII-2	C_2H_5	C_2H_5	57–58[b,c]		60.0

[a] J. D. Gabbert, M.S. thesis, University of Delaware, 1956; found b.p. 155°/5.5 mm., n_D^{26} 1.5148. [b] M. W. Goldberg and H. H. Lehr, U. S. Patent 421,680. [c] $C_8H_{15}NOS$: C, 55.47; H, 8.73; N, 8.09; S, 18.51. Found: C, 55.62; H, 8.48; N, 8.01, 8.03; S, 18.46.

pears that the same groups in the 2,6- positions are less effective than they are in the 2,2- position. In addition to this comparison it is interesting to note that where the same two groups are concerned, geminally substituted 3,5-thiomorpholinediones melt lower than their 2,6-disubstituted analogs.[5,7]

EXPERIMENTAL

5-(2-sec-Pentyl)-2-imino-4-thiazolidinone hydrobromide. This compound separated in a crude yield of 46.8% by application of the procedure previously used for the preparation of 5,5-dialkyl-2-imino-4-thiazolidines.[6] It was washed with ether and recrystallized from isopropyl alcohol, m.p. 211–212°.

Anal. Calcd. for $C_8H_{15}BrN_2OS$: C, 35.96; H, 5.65; Br, 29.91; N, 10.48. Found: C, 35.96; H, 5.65; Br, 29.58; N, 10.41.

5-(2-sec-Pentyl)-2-imino-4-thiazolidinone. This substance was prepared by dissolving 2 g. of the hydrobromide salt in an excess of hot water and treating this solution immediately with an excess of solid sodium bicarbonate. The product precipitated quantitatively and was recrystallized from ethyl alcohol, m.p. 202–203°.

Anal. Calcd. for $C_8H_{14}N_2OS$: C, 51.61; H, 7.58; N, 15.04. Found: C, 52.00; H, 7.50; N, 15.01.

5-(2-sec-Pentyl)-2,4-thiazolidinedione. This product was prepared by refluxing 5.0 g. (0.027 mole) of the above hydrobromide with 48 cc. of 2*N* hydrochloride acid for 8 hr. The insoluble oil was extracted with ether and this solution was washed with water and saturated sodium bicarbonate solution. The ether was evaporated to yield 2.7 g. (54%) of an oil which was distilled under diminished pressure to give 1.6 g. of a liquid, b.p. 103°/0.15 mm., n_D^{25} 1.5155.

Anal. Calcd. for $C_8H_{13}NO_2S$: C, 51.32; H, 6.99; N, 7.48. Found: C, 51.34; H, 7.10; N, 7.35.

Mercaptoacetic acids of series II. A substituted 2-imino-4-thiazolidinone, 0.2 mole, in a stainless steel flask with a 10% solution containing 0.9 mole of sodium hydroxide was refluxed for at least 1 hr. while nitrogen was passed through the vessel. The product was obtained quantitatively by acidification of the mixture with concd. hydrochloric acid followed by ether extraction. No bicarbonate-insoluble products were obtained. A nitrogen atmosphere was maintained as much as possible during the acidification and ether extraction and the ether solution of the product was continuously bathed with nitrogen while being dried over magnesium sulfate before use.

Substituted thiodiacetamic acids of series III. A freshly prepared mercaptoacetic acid, 0.2 mole, in a dry ether solution was placed in a three necked flask through which nitrogen was passed continuously. To this was added 0.2 mole of an α-bromoamide. The mixture was stirred while a dry sodium ethoxide solution containing 9.2 g. (0.40 mole) of sodium in 160 cc. of absolute ethanol was added dropwise during approximately 1 hr. The mixture was transferred to a beaker and the solvent allowed to evaporate to about 1/8 its volume. The residue was diluted with up to 500 cc. of water and acidified stepwise with concd. hydrochloric acid. The precipitated fractions were filtered and dried under vacuum to constant weight. The yields in these preparations ranged from 74–100% before separation into racemates.

Separation of series III *compounds into racemates.* In general, two or more fractions of impure product were obtained from the above preparation. The mixtures were fractionally recrystallized from appropriate solvent pairs which are noted in Table I. Two racemates, A and B, were obtained. The higher melting A was obtained first from one solvent. This solvent was then removed from the mother liquor and a second solvent was used on the residue to obtain the lower melting B. This procedure was repeated with alternation of the solvents until the separation was effected.

2,6-Disubstituted 3,5-thiomorpholinediones of series IV. These were prepared by refluxing 0.02 mole of a Series III amic acid with 60 cc. (64.8 g.) of freshly distilled acetic anhydride for 45 min. The product was precipitated by decomposing the excess acetic anhydride in iced water. The mixture was diluted with water as necessary to precipitate the product completely. If the product was crystalline, it was filtered. If it was oily, the acid was neutralized with solid sodium bicarbonate and the product was extracted with ether. The average yield of crude product was 74%. Purification was effected by recrystallization from the solvent stated in Table II or by distillation.

In two specific examples of this procedure using pure amic acids III-3A, m.p. 151–152°, and III-3B, m.p. 95–96°, a single 3,5-thiomorpholinedione (IV-3) was obtained, m.p. 93–94°, and a mixture of the product from III-3A with that from III-3B also melted at 93–94°.

Racemates of IV-4. Separation was effected by first recrystallizing 20.6 g. of the crude product from *n*-hexane to give 0.45 g. of a solid which was recrystallized once more to yield a small amount of solid, m.p. 100–101° (IV-4A). The residue was an oil which was distilled under diminished pressure, b.p. 109–111°/0.15 mm., n_D^{25} 1.5143 (IV-4B). This oil solidified while standing for a month.

Racemates of IV-5. Separation was effected by first recrystallizing 32.7 g. of crude material above from *n*-hexane yielding 2.5 g. of a solid which was recrystallized several times from 150-cc. portions of *n*-hexane, to give 1.25 g. of white plates, m.p. 120–121° (IV-5A). The oily residue (30.2

g.) was distilled under diminished pressure into fractions which completely solidified within a few days. The purest fractions were redistilled, b.p. 116°/0.14 mm., n_D^{25} 1.5101, (IV-5B) which resolidified. A representative portion of the solidified product, 4.3 g., was readily soluble in warm *n*-hexane and was purified by fractional precipitation of high melting material by cooling until the melting point range narrowed to 1°. At this point it was recrystallized once to yield 0.15 g. of a white solid, m.p. 94–95° (IV-5C). Infrared spectra indicated that the liquid, B, was probably a mixture of the two solids, A and C. IV-5C was thought to predominate in this mixture due to the solubility difference in *n*-hexane between IV-5A and IV-5C and the solubility similarity in *n*-hexane between IV-5B and IV-5C.

N-Methyl-2,6-disubstituted 3,5-thiomorpholinediones. Series V). These were most conveniently prepared by treating 0.02 mole of the corresponding Series IV thiomorpholinedione with 0.05 mole (2.8 g.) of potassium hydroxide in 90 cc. of acetone while stirring at 0°. To this was added 1.25 cc. (2.84 g., 0.02 mole) of methyl iodide. The stirred mixture was allowed to warm to room temperature. After 1 hr. the liquid was decanted from the solid and the acetone was evaporated. The residue was diluted with water and the oil was extracted with ether yielding 2.0 g. of the cyclic imide after evaporation of the ether. This oil was insoluble in sodium bicarbonate solution.

The aqueous solution from above was acidified with concd. hydrochloric acid and the oil thus precipitated was extracted with ether and washed with sodium bicarbonate solution. This aqueous solution was washed with ether and then acidified to reprecipitate the oil which was extracted once more with ether, 4.7 g. after the ether was removed. Distillation of this acid portion under diminished pressure gave the identical cyclic imide.

n-Butylethyl(2-aminoethylmercapto)acetic acid (VI-2). This compound was prepared from 8.28 g. (0.047 mole) of *n*-butylethylmercaptoacetic acid dissolved in a cold 10% solution containing an equimolecular amount of sodium hydroxide (1.88 g., 0.047 mole). To this cold solution were added simultaneously an aqueous solution of 9.6 g. (0.047 mole) of 2-bromoethylamine hydrobromide and a 10% solution containing 3.76 g. (0.047 mole) of sodium hydroxide. The addition took place during a period of 45 min. with constant stirring which was continued for 1 hr. The solution was neutralized with glacial acetic acid and evaporated under diminished pressure to precipitate 7.6 g. (73.8%) of a crystalline product which was recrystallized from a 1/1 mixture of ethanol and water, m.p. 180–181° dec.

Anal. Calcd. for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.38. Found: C, 54.75; H, 9.43; N, 6.34.

Diethyl(2-aminoethylmercapto)acetic acid (VI-1). This was prepared similarly in a 97.7% yield and was recrystallized from 95% ethanol, m.p. 233–234° dec.

Anal. Calcd. for $C_8H_{17}NO_2S$: C, 50.22; H, 8.96; N, 7.32. Found: C, 50.17; H, 9.10; N, 7.23.

2-n-Butyl-2-ethyl- and 2,2-diethyl-3-thiomorpholone (VII-1Y *and* VII-2). These were prepared from 2-bromoethylamine hydrobromide[12] with the results as shown in Table III.

2-n-Butyl-2-ethyl-3-thiomorpholone (VII-2Z). In a manner similar to that described above, 5.19 g. (0.029 mole) of *n*-butylethylmercaptoacetamide was treated with 6.0 g. (0.029 mole) of 2-bromoethylamine hydrobromide. The reaction mixture was made strongly basic with sodium hydroxide to precipitate the product which acted like an extremely deliquescent solid and was not purified but was immediately pyrolyzed to produce 3.58 g. (60.1%) of VII-1Z which was redistilled, b.p. 143–145°/1.1 mm., n_D^{25} 1.5138. Infrared spectra showed this to be identical with VII-1Y.

NEWARK, DEL.

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND THE RESEARCH LABORATORIES, THE UPJOHN CO.]

Investigations on Steroids. XXXI. Preparation of 19-Hydroxycorticosterone[1,2]

G. WINSTON BARBER,[3] DUREY H. PETERSON,[4] AND MAXIMILIAN EHRENSTEIN[3]

Received February 9, 1960

By the action of the fungus *Cunninghamella blakesleeana*, 19-hydroxycortexone (II) has been converted into a crystalline compound interpreted to be 19-hydroxycorticosterone (III). Contrary to expectations, acetylation of III gave a mixture of products, from which as main component the crystalline 11β,19,21-triacetate (VI B) was isolated. Benzoylation of III gave the crystalline 19,21-dibenzoate (V). III possesses little, if any, glucocorticoid activity and is devoid of mineralocorticoid action. Although there appears to be no doubt that III and its benzoylation product are identical with compounds described in the literature,[9] discrepancies exist regarding the acetylation and the physiological activity of III.

The syntheses of 19-hydroxy analogs of a number of steroid hormones were done at the University of Pennsylvania.[5a-d] The preparation of 19-hydroxycortexone[5a,6] (II) coincided with the elucidation of the structure of aldosterone by the combined efforts of a Swiss-British team.[7] II was subsequently found to occur in adrenal tissue.[8,9] We immediately considered it desirable to synthesize

(1) This investigation was supported by research grants (C757-C3, C757-C4, CY757-C5, and CY757-C6) from the National Cancer Institute of the National Institutes of Health, Public Health Service. A part of the K-Strophanthin used in this investigation was kindly donated by S. B. Penick & Co., New York, N. Y.

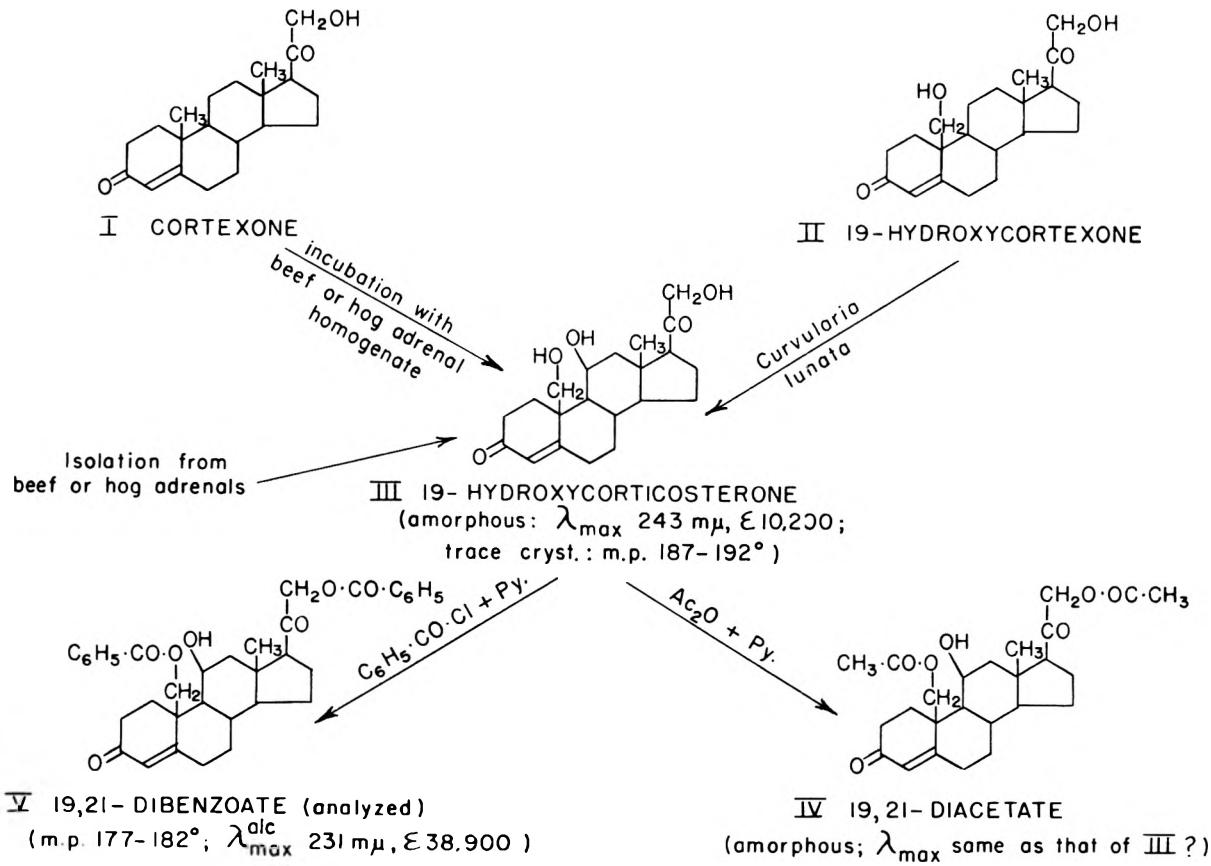
(2) The findings of this paper were presented on September 5, 1958, at the 4th International Congress of Biochemistry in Vienna {*cf.* Maximilian Ehrenstein: Biochemistry of the Corticoids, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 [Symposium: Biochemistry of Steroids], Pergamon Press, p. 259 (1959)}.

(3) University of Pennsylvania.

(4) The Upjohn Co.

(5) (a) G. W. Barber and M. Ehrenstein, *J. Am. Chem. Soc.*, **76**, 2026 (1954); G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954). (b) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 774 (1956). (c) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 783 (1956) (d) M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959).

R. Neher and A. Wettstein, Helv. Chim. Acta, 39, 2062 (1956).



a structural isomer of aldosterone in which carbon atom 19 rather than carbon atom 18 is linked with carbon atom 11 by way of a hemiacetal bridge. As the first step in this direction, we aimed at preparing 19-hydroxycorticosterone (III).

The microbiological hydroxylation[10] of 19-hydroxycortexone (II) appeared to us as the method of choice. The microbiological procedure was carried out in the Research Laboratories of the Upjohn Co., whereas the isolation and identification of the reaction product were done at the University of Pennsylvania. Hydroxylation of II was achieved by applying the fungus *Cunninghamella blakesleeana Lendner* which is known to hydroxylate in the 11β- position.[11] In two out of three major experiments, using in each case as starting material several hundred milligrams of II, we were able to secure a yield of 25–30% of a hydroxylation product which crystallized after repeated chromatography. In the third fermentation experiment, for unexplained reasons neither the starting material nor a conversion product could be isolated. In this instance, apparently extensive enzymatic degradation took place which was perhaps facilitated by the presence of the 19-hydroxyl group. Obviously, the conditions for the microbiological hydroxylation of II have to be studied further.[12] On the basis of the analysis and also in view of the molecular rotation,[13] the crystalline reaction product was tentatively assigned the structure of 19-hydroxy-

(6) In agreement with the proposals of Fieser, the previous name 19-hydroxy-11-desoxycorticosterone is replaced by 19-hydroxycortexone. *Cf.* "Steroids" by Louis F. Fieser and Mary Fieser, Reinhold Publishing Corp., New York, N. Y., 1959; see pp. 602, 706.

(7) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. v. Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1200 (1954).

(8) V. R. Mattox, Proc. Staff Meetings Mayo Clinic, **30**, 180 (1955).

(9) R. Neher and A. Wettstein, *Helv. Chim. Acta*, **39**, 2062 (1956).

(10) For the pertinent literature *cf.* the following reviews: (a) A. Wettstein: Conversion of Steroids by Microorganisms, *Experientia*, 11, 465–479 (1955). (b) S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson: Microbiological Transformations of Steroids and Their Applications to the Synthesis of Hormones, *Vitamins and Hormones*, **14**, 359–432, Academic Press, New York (1956). (c) D. H. Peterson: Microbiological Transformation of Steroids and Their Application to the Synthesis of Hormones, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 [Symposium: Biochemistry of Steroids], Pergamon Press, 83–119 (1959).

(11) For specific literature, *cf.* references: 10a, pp. 474, 475; 10b, p. 390; 10c, p. 87.

(12) The 21-monoacetate of II[5a] was screened with *Cunninghamella blakesleeana*. The reaction product contained only traces of steroidal material (papergram analysis). In the same fashion, discouraging results were obtained on screening 19-oxocortexone.[23]

corticosterone (III). The infrared spectrum, determined in March 1955 in the laboratory of Dr. T. F. Gallagher at the Sloan-Kettering Institute for Cancer Research, was in agreement with this assumption. Acetylation yielded an amorphous product which initially resisted all attempts at crystallization, even after repeated column chromatography. The analysis of the chromatographed, yet amorphous material was in good agreement with a triacetate. This was difficult to explain in view of the normally unreactive 11β-hydroxyl group. On the other hand, the infrared spectrum showed hydroxyl absorption. Paper chromatography of the amorphous acetate indicated that it consisted of one major and at least two minor components. Further purification was temporarily suspended.

In December 1956 Neher and Wettstein[9] published a comprehensive paper on the isolation of new pregnane compounds from adrenal glands. Among the new products was an amorphous substance, λ_{max} 243 mμ, ϵ_{max}, 10,200 (only traces were obtained in crystalline form; m.p. 187–192°) also considered to be 19-hydroxycorticosterone (III), which was isolated in small amounts from various sources, namely: (1) from beef and hog adrenal glands; (2) from experiments in which cortexone had been incubated with homogenates obtained from beef or hog adrenal glands; (3) from experiments in which 19-hydroxycortexone (II) had been aerobically incubated with the fungus *Curvularia lunata (Wakker) Boedijn.* The identity of the products obtained from these different sources was established by comparison of the crystalline dibenzoates (V) (mixture melting points; paper chromatography; infrared spectra). For comparison with our crystalline III, a sample of amorphous III was kindly supplied by the laboratory of Dr. Wettstein. The infrared spectrum of each of these products was examined in the Sloan-Kettering Institute for Cancer Research through the courtesy of Dr. T. F. Gallagher. The spectra were measured in chloroform solution on a Model 21 Perkin-Elmer double beam infrared spectrometer and the spectra were identical[14] in all respects in the regions of 4000 to 2750; 1800 to 1600; 1500 to 1280; and 1150 to 800 cm.$^{-1}$ (*cf.* also Experimental). On acetylating their amorphous compound, the CIBA group obtained a product which remained amorphous after chromatography over alumina. Apparently it was considered to be uniform. Largely based on paper chromatographic data, this material was assigned the structure of the 19,21-diacetate (IV). Surprisingly this acetate is reported to possess the same ultraviolet characteristics as the free compound. On acetylating a 19-hydroxyl group in Δ^4-3-keto steroids, normally a distinct hypsochromic shift of the absorption maximum is observed.[15]

In view of the nonuniformity of our amorphous acetate, more recently a renewed effort at purification was made. By subjecting it to partition chromatography, the major component was finally obtained in crystalline form. According to the infrared spectrum no hydroxyl group is present. This is in agreement with the analysis of the amorphous acetate which had indicated a triacetate (see above). In our opinion several possibilities exist for the formation of an 11β,19,21-triacetate (VI B) from a 19,21-diacetate (IV). This probably involves the shift of an acetyl group from the 19-position to the vicinal 11β- position, possibly through the intermediary stage of an orthoacetate (VII). In accordance with expectations, the crystalline triacetate and also the minor acetylation products showed the typical hypsochromic shift of the ultraviolet absorption maxima connected with the acetylation of 19-hydroxyl[15] and 11β-hydroxyl[16] groups in Δ^4-3-keto steroids. On the other hand, the molecular rotation of the crystalline triacetate wholly disagrees with the calculated value.[17] This may be due to vicinal effects which do not become manifest in the free compound. If the triacetate contains a 19,11-bridge, as depicted by formula VIII, the presence of the additional asymmetric carbon atom (*) would prohibit a prediction of the molecular rotation. The various acetylation products of III pose an attractive stereochemical problem which will be investigated further.

Neher and Wettstein[9] characterized their amorphous 19-hydroxycorticosterone (III) by the crystalline 19,21-dibenzoate (V). On benzoylating our crystalline (III), a crystalline product also resulted. Since the supplies of the CIBA compound were exhausted, a direct comparison of the two substances was not possible. The recorded infrared spectrum, kindly supplied by Dr. Wettstein, was very similar to that of our compound. This criterion alone does not necessarily establish the identity of

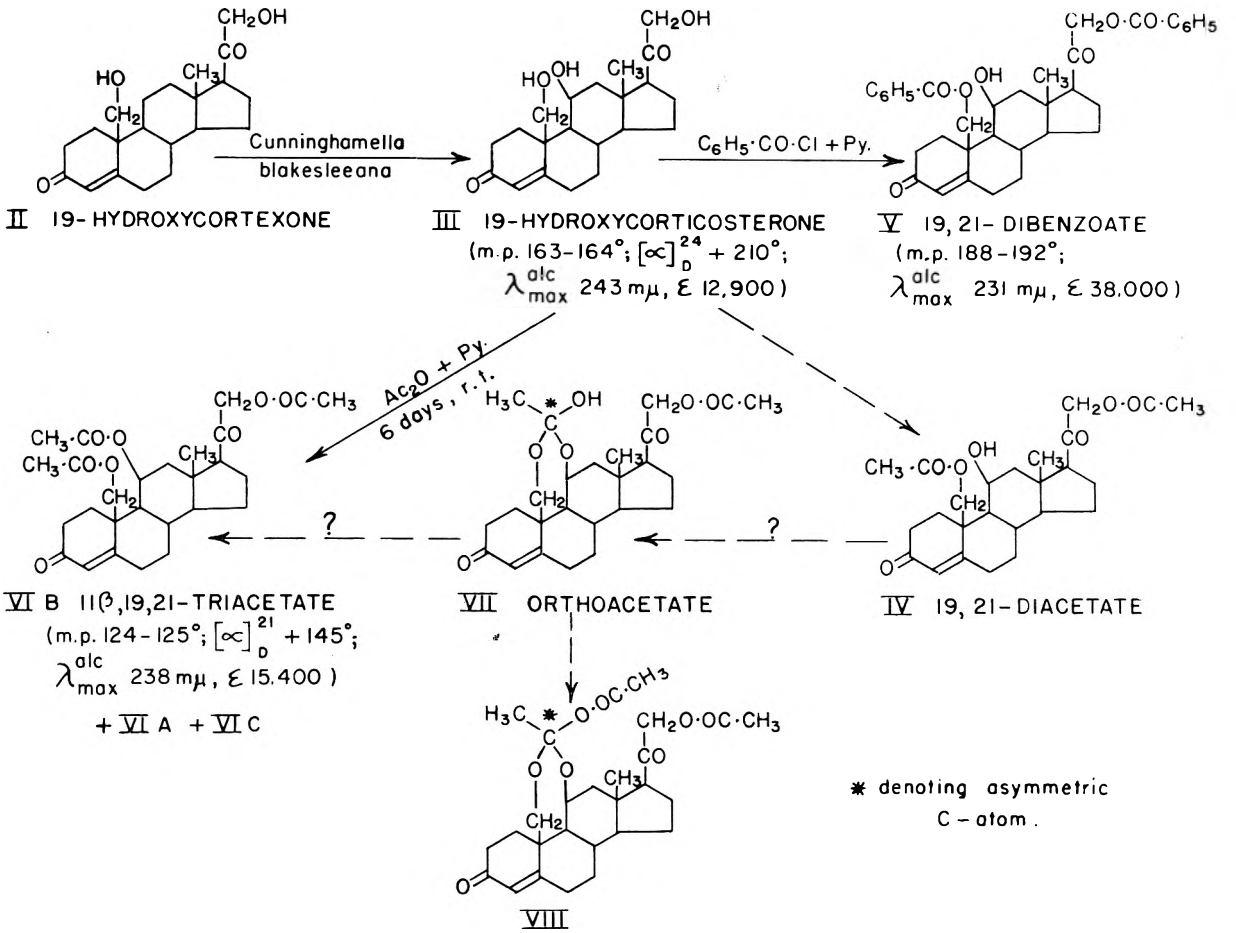
(13) Molecular rotation reported for 19-hydroxycortexone: +640° (Ref. 5a, second paper, see p. 1761). Increment for the introduction of an 11β-hydroxyl group: +110° (average of eight cases of Δ^4-3-oxo steroids; range +41° to +181°; the rotation values recorded in the literature were utilized without regard to certain differences of solvents). Calcd. for 19-hydroxycorticosterone (III): M_D +750°. Found: M_D +761° ± 7°.

(14) February 1957.

(15) Lit. *cf.* E. J. Becker and M. Ehrenstein, *Liebigs Ann. Chem.*, **608**, 54 (1957), see p. 59.

(16) A moderate hypsochromic shift of the absorption maximum has been observed on acetylating 11β-hydroxy-Δ^4-3-keto steroids; *cf.* E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen, R. Rausser, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 5486 (1953).

(17) Molecular rotation reported for 19-hydroxycorticosterone 19,21-diacetate: +902° (Ref. 5a, second paper, see p. 1761). Increment for the introduction of an 11β-acetoxyl group: +189° (value obtained by utilizing pertinent data of the paper cited in ref. 16). Calcd. for 19-hydroxycorticosterone 11β,19,21-triacetate (VI B): M_D +1091°. Found: M_D +708° ± 35°.



the two products, because benzoxy groups impart similar characteristics to the spectrum anyway. However, in view of the similarity of the other constants (melting point, ultraviolet absorption spectrum), there appears to be little doubt regarding their identity.

Physiological activity. The amorphous 19-hydroxycorticosterone (III) described by the CIBA group is claimed to possess notable physiological activity. "Das neue 19-Hydroxycorticosteron besitzt sowohl mineral - als auch glucocorticoide Wirkungen, jedoch schwächere als diejenigen von Aldosteron bzw. Cortison."[9] ("It has both glycogen-deposition and mineralocorticoid activity, but weaker than cortisone in the first property and weaker than aldosterone in the second.")[18]

The crystalline 19-hydroxycorticosterone (III) was subjected to various bioassays.

A. Glucocorticoid acitivity. Two different tests were applied. (1) In the Ingle work test (4 rats), performed by Dr. E. H. Morley in the Research Laboratories of the Upjohn Co., this compound was considerably less active than corticosterone. (2) In the eosinophil depletion assay, conducted through the courtesy of Dr. Ralph I. Dorfman at the Worcester Foundation for Experimental Biology, the substance was less than one third as active as corticosterone. Broadly speaking, the findings in these two assays parallel those in the liver glycogen deposition test which was not done with III. One may conclude, therefore, that III possesses little, if any, glucocorticoid activity.

B. Mineralcorticoid activity. Crystalline (III) was tested by two different groups. (1) In bioassays performed by Dr. Robert H. Curtis in the laboratory of Dr. John A. Luetscher, Jr., at Stanford University School of Medicine, III was not sodium-retaining in a dose of 10 μg. Since rats are usually sensitive to as little as one microgram of cortexone or cortexone acetate,[19] these bioassays show that the mineralocorticoid activity of III, if any, is probably less than one tenth that of cortexone acetate. (2) In assays carried out at the Worcester Foundation for Experimental Biology through the courtesy of Dr. Ralph I. Dorfman III in doses of 6 to 50 μg. had no significant effect on the excretion of sodium or potassium in salt loaded adrenalectomized rats. One must conclude, therefore, that III is devoid of mineralocorticoid activity.

(18) English translation quoted from book mentioned in ref. 6; see p. 706.

(19) *Cf.* John A. Luetscher, Jr., and Quentin B. Deming: "Bioassay of sodium-retaining corticoids and some changes in excretion of these substances in disease" in "Renal Function," Transactions of the Second Conference, 155–178, Josiah Macy, Jr. Foundation, New York, 1951, see p. 59.

EXPERIMENTAL

Melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected. *Ultraviolet* spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer. The *infrared* studies pertaining to this paper were carried out on a Perkin-Elmer Model 21 double beam spectrometer in the Division of Steroid Metabolism of the Sloan-Kettering Institute for Cancer Research in New York through the courtesy of Dr. Thomas F. Gallagher. The correlations are based upon those summarized in the publication of Jones and Herling.[20] Only those bands are mentioned which appear to have a direct bearing upon the structure of the particular compound. Details of other correlations between spectrum and structure will be summarized at a later time by the group at the Sloan-Kettering Institute.

Unless stated otherwise, the *microanalyses* were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide; 80°) according to Milner and Sherman.[21] The percentage loss of weight on drying is recorded; there was in no instance a gain of weight on exposure of the dried sample to the atmosphere. For *optical rotations* no correction for crystal solvent has been made. The sample was dissolved in chloroform to make 2 cc. of solution and the rotation was determined in a 2-dm. semimicro tube. The *adsorbents* alumina,[22] silica gel,[22] and Florisil[23] used for chromatography have been described.

Conversion of 19-hydroxycortexone (II) *into 19-hydroxycorticosterone* (III). *A. Fermentation procedure.*[24] In trial runs, batches of 5 mg., 10 mg., 15 mg., and 15 mg. of II, m.p. 169–172°, were incubated with the mold *Cunninghamella blakesleeana* for a period of 24 hr. The procedure is described in detail in the main experiment (see below). Examination of the isolated extracts by paper chromatography indicated, respectively, the presence of 50, 50, 50, and 30% of starting material (II) and 8, 8, 8, and 38% of a more polar compound. In all instances there was present about 1 to 2% of a second transformation product which moved slower than the starting material.

On the basis of these trial runs, the first experiment on a larger scale was performed (November 1954). Ten 250 cc. flasks, each containing 100 cc. of a medium (composition: 10 g. of technical dextrose, 20 g. of corn steep liquor solids, and 1000 cc. of tap water; *p*H 5.6–5.8),[25] were inoculated with spores of *Cunninghamella blakesleeana* and incubated (25°) with shaking for 24 hr. Thereafter 10 mg. of II, m.p. 169–172°, was added in 1.0 cc. of ethanol to each flask and the aerobic incubation (25°) was continued for 48 hr. The beer and mycelium from each flask were combined and extracted by the procedure of Peterson *et al.*[26] The extract was examined by paper chromatography using the Bush B-5 system[27] and was estimated to contain 18% of starting material (II) and 45% of a newly formed more polar compound showing similar maximum ultraviolet absorption.

B. Isolation of the reaction product.[28] Except for small amounts of material withdrawn for paper chromatographic studies, all extracts resulting from the trial runs and the main experiment (see A) were combined. The brownish resinous residue (180.1 mg.), originating from a total of 145 mg. of II and estimated to contain 37.5 mg. of unchanged II and 53.1 mg. of the main reaction product, was chromatographed over 10 g. of silica gel (16 × 75 mm.). The following eluates were collected: (a) benzene (200 cc.), benzene-chloroform, 1:1 (200 cc.), and chloroform (400 cc.); 18.8 mg. of yellow oil; (b) chloroform-ether, 9:1 (200 cc.), and 3:1 (200 cc.); 15.9 mg. of semicrystalline material; (c) chloroform-ether, 1:1 (200 cc.) and ether (1200 cc.); 48.1 mg. of crystalline fractions, m.p.'s between 159 and 165°, considered to be starting material (II); (d) ether-methanol, 199:1 (200 cc.); 5.9 mg. of semicrystalline residue; (e) ether-methanol, 99:1, 197:3, 39:1, 19:1, 9:1, 3:1, and 1:1 (200 cc. each); 74.0 mg. of yellow resin, representing the crude reaction product (III). The latter was rechromatographed over 20 g. of silica gel (16 × 140 mm.). The material eluted with ether-methanol, 39:1 (600 cc.) and 19:1 (1000 cc.) was a colorless resin; total wt.: 58.8 mg. This was chromatographed over 20 g. of Florisil (16 × 180 mm.). The first twenty eluates (200 cc. each of chloroform-acetone; ratios gradually changing from 199:1 to 7:3) gave a total of 8.5 mg. of resin. The following ten eluates (200 cc. each of chloroform-acetone; ratios gradually changing from 13:7 to 1:3) yielded exclusively crystalline residues; total: 33.9 mg. of crude 19-hydroxycorticosterone (III). The fractions eluted subsequently with chloroform-acetone, 3:17, acetone, acetone-methanol and methanol (total vol., 1200 cc.) gave 10.6 mg. of resin. Total recovery in this chromatogram was 53.0 mg.

Recrystallization of the crude crystalline III (33.9 mg.) from acetone-hexane gave 31.6 mg. of globular clusters of minute needles, m.p. 161–162°. Additional recrystallization from acetone-water (m.p. 97–100°; resolidification about 130°; remelting at 160–161°) and acetone-hexane yielded 20.9 mg. of colorless rods, m.p. 163–164°. $[\alpha]_D^{24}$ +210° ± 2°; $[M]_D^{24}$ +761° ± 7° (10.45 mg.; α + 2.20° ± 0.02°). λ_{max}^{alc} 243 mμ; ε12,900.

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.38; H, 8.55. Residue, 0.34. (Corr. for residue: C, 69.62; H, 8.58).

The infrared spectrum of III was determined[29] in chloroform solution. There is strong associated hydroxyl absorption. The carbonyl region shows a band at 1708 cm.$^{-1}$ which is due to the C=O stretching vibration of the 20-ketone group. There is weak absorption at 1688 cm.$^{-1}$ which suggests the presence of a small amount of impurity. Bands at 1666 and 1618 cm.$^{-1}$ are due to the Δ^4-3-ketone system.

A second incubation experiment on a larger scale was performed (May 1955) in identical fashion with a total of 248 mg. of 19-hydroxycortexone (II).[30] In this instance, extraction of the beer and mycelium gave as much as 2.18 g. of a dark brown oil. Papergram analysis of the crude extract indicated the presence of approximately 75 mg. of III (~30% conversion) and 25 mg. (~10%) of unchanged II. Chromatography over 25 g. of silica gel (18 × 150 mm.); benzene, benzene-chloroform and chloroform eluted a total of 1.71 g. of waxy and oily material, probably of nonsteroid nature; elution with chloroform-ether and ether gave 153.6 mg. of yellow resin, probably containing some starting material (II); ether-methanol mixtures eluted 238.4 mg. of yellow resin. Two chromatograms of the latter material on Florisil (25 g., 18 × 240 mm.; 10 g., 18 × 85 mm.)

(20) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(21) R. T. Milner and M. S. Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).

(22) Ref. 5a, second paper.

(23) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **20**, 1253 (1955).

(24) In collaboration with H. C. Murray (microbiology) and L. M. Reineke (paper chromatography), Research Laboratories, The Upjohn Co.

(25) *Cf.* ref. 10b, p. 422.

(26) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(27) I. E. Bush, *Nature*, **166**, 445 (1950); *Biochem. J.*, **50**, 370 (1952).

(28) Experiments by G. Winston Barber.

(29) March 1955. Interpretation by Friederike Herling. The fingerprint region is different from any spectrum in the collection of the Sloan-Kettering Institute.

(30) Pooled material; m.p.'s between 160 and 173°. Papergram analysis indicated the presence of approximately 5% of a second component which was not affected by the bioconversion.

finally led, by eluting with chloroform-acetone, to a total of 89.9 mg. of twelve consecutive crystalline fractions whose melting points indicated uniformity throughout. Recrystallization of this material from acetone-hexane (75.1 mg.; rosettes of colorless needles; m.p. 101–103°, no resolidification) and acetone-water yielded 33.7 mg. of fan-like clusters of flat needles representing 19-hydroxycorticosterone (III); m.p. 100–105°, resolidification about 130°, final melting at 159–160°; no depression of melting point when mixed with the analytical sample of III (see above), λ_{max}^{alc} 243 mμ; ε14,000. The infrared spectrum of this product was determined[31] in chloroform solution and was found to be identical in all respects with that of the reference compound (see above) in the regions of 4000 to 2750, 1800 to 1600, 1500 to 1280, and 1150 to 800 cm.$^{-1}$ Surprisingly, no additional crystalline material could be secured from the mother liquors of the crystallizates, even after chromatography.

A third large scale incubation experiment was carried out in analogous fashion (April-May 1957) with 540 mg. of 19-hydroxycortexone (II), m.p. 158–160°. Papergram analysis of the extracted material indicated the following composition: starting material (II), 45%; 19-hydroxycorticosterone (III), 10%; two additional products, showing greater polarity than the starting material, 14% and 10%, respectively. The crude extracted material (solids, 1.62 g.) was refermented with the result that, in addition to traces of the starting material (II) and of several products more polar than II, only very small amounts (1–3%) of III could be detected by paper chromatography. Subsequent chromatography (solid, 1.51 g.) once over silica gel and twice over Florisil failed to yield any crystalline product.

Acetylation of 19-hydroxycorticosterone (III). *First experiment* (*February 1955*).[28] A solution of 10 mg. of pure crystalline (III), m.p. 163–165° (analytical sample), in 2 cc. of pyridine and 1 cc. of acetic anhydride was kept at room temperature for 16 hr. After evaporating most of the pyridine *in vacuo*, the residue was taken up in 25 cc. of 1*N* hydrochloric acid and, after standing for 5 min., the mixture was extracted with ether. After washing with 1*N* hydrochloric acid, 1*N* sodium carbonate, and water, the ether phase was dried over sodium sulfate and evaporated to dryness leaving 11.3 mg. of a white brittle foam. Attempts to crystallize this product failed and hence it was chromatographed over 2 g. of alumina (activity I-II; 6 × 85 mm.); petroleum ether, petroleum ether–benzene, benzene, benzene-ether, and ether eluted nothing; 50 cc. of ether plus 0.2 cc. of methanol, 50 cc. of ether plus 0.5 cc. of methanol, and 49 cc. of ether plus 1 cc. of methanol eluted, respectively, 2.7 mg., 4.0 mg., and 2.1 mg. of colorless resin. Attempts to crystallize the combined material (VI) were unsuccessful. It was finally dissolved in 1 cc. of benzene, and the solution was evaporated to dryness from the frozen state *in vacuo*. The resulting powdery amorphous residue was triturated with 1 cc. of petroleum ether, yielding after decanting and drying 8.0 mg. of powdery material. $[\alpha]_D^{22}$ + 201° ± 4° (5.07 mg.; α + 1.02° ± 0.02°). λ_{max}^{alc} 239 mμ.

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52) (diacetate): C, 67.24; H, 7.68. Calcd. for $C_{27}H_{36}O_8$ (488.56) (triacetate): C, 66.37; H, 7.43. Found[32]: C, 66.43; H, 7.97. Weight loss, 3.74 (Did not melt on drying at 70°).

The infrared spectrum of this product was determined[33] in carbon disulfide and in carbon tetrachloride solution. It shows associated hydroxyl absorption which can be tentatively interpreted as indicative of the presence of a hydroxyl group at C-11β associated with the 19-acetate. Carbonyl absorption at 1754 and 1732 cm.$^{-1}$ (carbon tetrachloride) is evidence for a 21-acetoxy-20-ketone group and at 1744 cm.$^{-1}$ suggests the presence of the 19-acetoxy group. Bands at 1678 and 1624 cm.$^{-1}$ (carbon tetrachloride) are due to the Δ^4-3-ketone system. There is a broad band at 1421–1416 cm.$^{-1}$ (carbon tetrachloride) which is due to the C—H scissoring vibrations of the unsubstituted methylene groups at C-2 adjoining the 3-ketone group and at C-21 in 21-acetoxy-20-ketones, and probably at C-19 in 19-acetates. A broad band at 1375 cm.$^{-1}$ (carbon tetrachloride) is due to C—H bending vibrations of the acetate methyl groups. C—O stretching vibration at 1231 cm.$^{-1}$ (carbon disulfide) confirms the presence of acetate groups.

Papergram analysis of this material[34] was conducted using Carbitol (diethylene glycol monoethyl ether) as stationary phase and methylcyclohexane saturated with Carbitol as mobile phase (development time: 12 to 20 hr.). A separation into three spots (ultraviolet scanner) was observed: The middle spot (about 9 cm. from the starting point) represents about 70% of the total steroid; the more polar spot (about 6 cm. from the starting point) about 20%; and the rapid moving component (about 16 cm. from the starting point) about 5–10%.

Second experiment (*July 1955 and February 1958*).[28] A solution of 20 mg. of crystalline III, double m.p. 100–105° and 159–160°, in 2 cc. of dry pyridine and 1 cc. of acetic anhydride was allowed to stand at room temperature for 6 days. The reaction mixture was evaporated *in vacuo* at room temperature and the residue was taken up in ether. After washing with 1*N* hydrochloric acid, 1*N* sodium carbonate, and water, the ether was dried and evaporated, and the residual colorless resin (30.6 mg.) was chromatographed over 10 g. of Florisil (10 × 230 mm.). Chloroform containing 6–10% of acetone eluted 28.7 mg. of colorless resin as a single peak (VI).

The composition of this material was investigated by chromatographing 0.1 mg. on a 1/2-inch strip of Whatman No. 1 filter paper in the system propylene glycol-methylcyclohexane. For comparison, 0.05-mg. samples of 19-hydroxycorticosterone (III), 19-hydroxycortexone (II), and the 21-monoacetate and 19,21-diacetate of II were chromatographed on parallel 1/2-inch strips (length: 26 cm.) at the same time. Development was continued for 10 days, 5 cc. of eluate being collected per strip.

The dried strips were scanned in a model DU Beckman spectrophotometer at 240 mμ. The quantities were estimated from the areas under the peaks when the extinction values are plotted against the distance along the paper strip. In this way, three ultraviolet absorbing components of VI were detected and the composition of VI was estimated as approximately 10% of VI A, a rapidly moving component found in the eluate;[35] approximately 60% of VI B, which had moved about 7.5 cm. from the starting point; and approximately 25% of VI C, which had moved hardly at all. Of the comparison compounds, III, II, and the 21-monoacetate of II had not moved at all, whereas the 19,21-diacetate of II had moved 21 cm. from the starting point.

The acetylation product (VI) was now chromatographed[36] on an intimate mixture of 100 g. of Florisil and 50 g. of redistilled propylene glycol (26 × 190 mm.) with redistilled methylcyclohexane as the mobile phase. Substance VI A was apparently eluted by the first 500 cc. (residue: 2.6 mg.) and was not investigated. The next 4500 cc. of methylcyclohexane eluted nothing, so the methylcyclohexane was gradually replaced by benzene, the following fractions being collected and evaporated to dryness *in vacuo:* (1) 400 cc. of

(31) April 1958. Interpretation by Beatrice S. Gallagher.

(32) The sample (2.104 mg.) was blocked between two samples of known composition and of the same size. The error should be within ±0.3%.

(33) March 1955. Interpretation by Friederike Herling.

(34) Courtesy of L. M. Reineke, Research Laboratories, The Upjohn Co.

(35) The eluate was evaporated to dryness and the residue was subjected to another papergram analysis (shorter time of development).

(36) To a solution of the acetylation product VI in a few drops of acetone was added a pinch of Florisil. The dried mixture was placed on top of the column. All eluents of this chromatogram were saturated with propylene glycol.

methylcyclohexane plus 100 cc. of benzene, residue: 2.6 mg.; (2) 300 cc. of methylcyclohexane plus 200 cc. of benzene, residue: 4.0 mg.; (3) 200 cc. of methylcyclohexane plus 300 cc. of benzene, residue: 2.3 mg.; (4) 100 cc. of methylcyclohexane plus 400 cc. of benzene, residue: 4.7 mg.; (5) 500 cc. of benzene, residue: 3.0 mg.

These five fractions were subjected to paper chromatographic investigation as described above, 0.06 mg. portions of the residues being run simultaneously on parallel $^1/_2$-inch strips (length: 26 cm.; time: 6 days; total eluent: 43 cc.). Fractions (1) and (2) were found to contain only substance VI B and were therefore combined and briefly chromatographed over 2 g. of Florisil (8 × 100 mm.). Chloroform containing 2–6% of acetone eluted 5.3 mg. of colorless resin, representing the triacetate of 19-hydroxycorticosterone [$C_{27}H_{36}O_8$ (488.6)] (VI B). Crystallization from acetone-water gave 3.0 mg. of cubic crystals, m.p. 124–125°. $[\alpha]_D^{21}$ +145° ± 7°; M_D^{21} +708° ± 35° (2.41 mg.; α + 0.35° ± 0.01°). λ_{max}^{alc} 238 mμ; ε 15,400.

The infrared spectrum of the crystalline triacetate (VI B) was determined[37] in carbon disulfide and in carbon tetrachloride solution. It is similar to but not identical with that of the amorphous acetylation product (*cf.* first experiment). There is *no hydroxyl absorption* and a relatively more intense acetate-carbonyl band at 1744 cm.$^{-1}$ Because of the resemblance in the "fingerprint" region (1400–650 cm.$^{-1}$) of the crystalline (second experiment) and amorphous product (first experiment) and because the carbonyl region (1800–1600 cm.$^{-1}$) of both products differs only in band intensities and not band positions, the spectra are interpreted to mean that the amorphous material (first experiment) is a mixture which contains the crystalline compound (second experiment). Assuming that the latter is pure, the bands that characterize it in the region 1800–1600 cm.$^{-1}$ are as follows: 1754 cm.$^{-1}$ (shoulder) 20-ketone–21-acetate (a-band);[38] 1744 cm.$^{-1}$ acetate-carbonyl; 1736 cm.$^{-1}$ (shoulder) 20-ketone–21-acetate (b-band);[38] 1686 cm.$^{-1}$ (shoulder); 1679 cm.$^{-1}$ 3-ketone in Δ^4-3-ketone; 1627 cm.$^{-1}$ C=C stretching vibration in Δ^4-3-ketone (this value is higher than average, probably due to the influence of the adjacent acetate group at C-19).

Fractions 3 and 4 of the above chromatogram were found to be mixtures of VI B and VI C, whereas fraction 5 contained only substance VI C. On these papergrams, VI C was itself found to be resolved into three components, each of which, on elution from the paper and examination of the ultraviolet absorption spectrum had maximum absorption at 240 mμ, thus suggesting the hypsochromic shift of the absorption maximum which has been generally observed on acetylating 19-hydroxy-Δ^4-3-keto steroids.[15,16] Each of these components also reduced triphenyltetrazolium chloride after a short delay, indicating the presence of the ketol acetate grouping at position 17. When compared with II and III by paper chromatography in the system toluene propylene glycol, all three components of VI C ran considerably faster than either II or III.

Benzoylation of 19-hydroxycorticosterone (III).[28] The mother liquor residues from the recrystallization of III (microbiological hydroxylation of II, first experiment, see above) were combined and chromatographed over 10 g. of Florisil. The fractions eluted by chloroform containing 25–60% of acetone were combined (12 mg.) and dissolved in 0.6 cc. of dry pyridine. To this was added 0.8 cc. of a 10% solution of benzoyl chloride in dry benzene. After standing for 40 hr. and subsequently adding 1 cc. of water, the reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in ethyl acetate and the solution was shaken with 3*N* hydrochloric acid and 1*N* sodium carbonate, dried and evaporated, leaving 22.1 mg. of colorless resin. This was chromatographed over 2 g. of alumina (activity I–II; 8 × 55 mm.); petroleum ether and petroleum ether–benzene eluted nothing; the fractions eluted by benzene and by benzene containing 5–30% of ether were combined (5.3 mg.). Crystallization from benzene–petroleum ether gave 1.6 mg. of yellowish granular crystals, m.p. 188–192°. λ_{max}^{alc} 231 mμ; ε (for mol. wt. 570.6) 38,000. The infrared spectrum was determined[31] in methylene chloride solution and showed the following absorption bands: (1) 3680 and 3600 cm.$^{-1}$ (hydroxyl absorption); (2) 1718 (20-ketone and benzoate), 1667, (1620, 1602, 1583 cm.$^{-1}$ obscured by solvent absorption); (3) 1179, 1115, 1098, 1073, 1042, 1028, 875 cm.$^{-1}$

The corresponding data obtained by Neher and Wettstein[39] on a compound interpreted to be the 19,21-dibenzoate of 19-hydroxycorticosterone (V) are given for comparison purposes: m.p. 177–182°; λ_{max}^{alc} 231 mμ; ε 38,900. The infrared spectrum, as recorded in the CIBA laboratories, showed the following absorption bands (in CH_2Cl_2): (1) 3690 and 3610 cm.$^{-1}$; (2) 1721, 1672, 1626, 1605, 1587 cm.$^{-1}$; (3) 1172, 1114, 1093, 1070, 1039, 1026, 879 cm.$^{-1}$

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(37) April 1958. Interpretation by Beatrice S. Gallagher.

(38) *Cf.* footnote in table, p. 37 of Glyn Roberts, Beatrice S. Gallagher and R. Norman Jones: "Infrared Absorption Spectra of Steroids. An Atlas. Volume II." Interscience Publishers, Inc., New York, 1958.

(39) Ref. 9, see p. 2085.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE CITY COLLEGE OF NEW YORK, COLUMBIA UNIVERSITY, AND THE UNIVERSITY OF MICHIGAN]

Amino Derivatives of Strophanthidin. I. Reactions of Primary and Secondary Amines with the Butenolide Side Chain of Strophanthidin[1]

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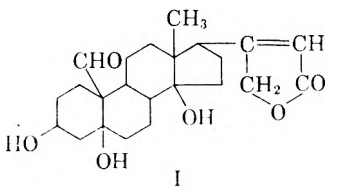
Strophanthidin undergoes aminolysis of the butenolide side-chain when heated with primary amines to give $\Delta^{\alpha,\beta}$-unsaturated γ-lactams. Further reaction with additional amine leads to more complicated products. With secondary amines, the butenolide side-chain of strophanthidin apparently is converted to an eneamine-amide. The structures of these substances are discussed and the reaction of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide with amines has been investigated.

During the attempted preparation of certain 3-(*N*,*N*-dialkyl)glycyl esters of strophanthidin[3] by the reaction of chloroacetylstrophanthidin with secondary amines, nitrogenous products which were evidently mixtures of several bases were obtained. This introduced the possibility that these substances may have arisen from the reaction of the amines with other reactive parts of the strophanthidin molecule (I) possibly not involving the chloroacetyl group at all. As in the preparation of the piperidylglycyl ester of strophanthidin the most complicated mixture of bases was obtained, the direct reaction of strophanthidin with piperidine was investigated. Strophanthidin does indeed react with piperidine to give a mixture of nitrogenous bases. Further, nitrogenous compounds result from the reaction of strophanthidin with primary amines.

The products of the reaction of strophanthidin with amines present interesting possibilities from the standpoint of physiological action.[4] Therefore, an investigation of the nature of the reaction and



I

of the structures of the products was undertaken. In the present paper we present the results of a study of the reaction of strophanthidin with a number of amines both primary and secondary.

The compounds produced by the reaction of one equivalent of strophanthidin with one equivalent of various primary amines are listed in Table I. In general the reactions involved condensation of one equivalent of each of the reactants with elimination of one mole of water. All of the substances gave positive Legal (nitroprusside) tests indicating that the side-chain double bond was still intact. There was strong evidence that the reaction proceeded further with involvement of a second equivalent of amine possibly at other reactive sites of the strophanthidin molecule as mixtures of compounds of higher nitrogen content were found among the reaction products. However, as all attempts to separate these mixtures into pure constituents have failed so far, a discussion of them will be postponed for a later communication. In addition to the amines listed in Table I, the reaction was attempted with ethanolamine, aniline, and tetrahydroisoquinoline. However, the products were too unstable to permit isolation and characterization.

In considering possible structures for the products of the reaction of strophanthidin with one equivalent of a primary amine certain observations have been made. As indicated above all the compounds gave a positive Legal test. Although it was impossible to demonstrate the presence either of the C-10 aldehyde group by formation of carbonyl derivatives of the amine condensation products or the C-3 hydroxyl group by preparation of acyl derivatives, the presence of these functions was indicated indirectly. Strophanthidin benzoate and strophanthidin oxime both reacted with *n*-propylamine in a manner exactly analogous to the reaction of strophanthidin itself with *n*-propylamine. The conclusion appears to be justified that the reaction of strophanthidin with primary amines does not involve either the C-3 hydroxyl group or the C-10 aldehyde group and must be concerned with the butenolide side-chain. From the evidence at hand we believe that the course of this reaction may be represented by I–XI. Further reaction of X with a second equivalent of amine may involve isomerization of X to XII under the influence of the basic amine[5] followed by reaction of the isomerized prod-

(1) This investigation was aided in part by a grant from Eli Lilly and Company to whom we express our appreciation.

(2) Present address: Department of Chemistry, University of Michigan, Ann Arbor, Michigan.

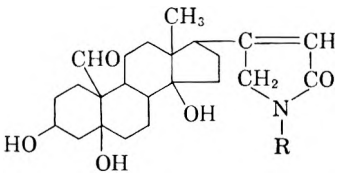
(3) W. Küssner, U.S. patent 2,296,677 (Sept. 22, 1942).

(4) H. L. Otto, T. Greiner, H. Gold, F. Palumbo, L. Warshaw, N. T. Kwit, and K. K. Chen., *J. Pharmacol. and Exp. Therap.*, **107**, 225 (1953). In this paper the structure of the tryptamine derivative of strophanthidin, which was highly uncertain at the time, is erroneously pictured as involving the C-10 aldehyde group.

(5) W. D. Paist, E. R. Blout, F. C. Uhle, and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941).

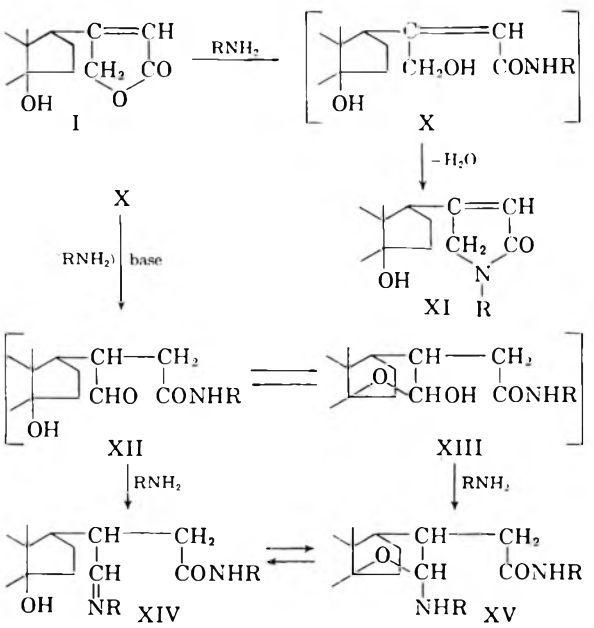
TABLE I

PRODUCTS FROM THE REACTION OF ONE MOLE OF PRIMARY AMINES WITH STROPHANTHIDIN



Reacting Amine		R	Formula	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
n-Propyl	II	*n*-Propyl	$C_{26}H_{39}NO_5$	70.1	8.8	3.1	69.9	9.0	3.1
n-Butyl	III	*n*-Butyl	$C_{27}H_{41}NO_5 \cdot H_2O$	68.8	9.1	3.0	68.6	9.2	2.9
n-Butyl	IV	*n*-Butyl	$C_{27}H_{41}NO_5$[a]	70.6	9.0	3.1	70.9	9.3	3.5
Tryptamine	V	2-(3′-Indolyl)ethyl	$C_{33}H_{42}N_2O_5$	72.5	7.8	5.1	72.5	7.8	5.5
1-Diethylamino-4-aminopentane	VI	4-Diethylamino-1-methylbutyl	$C_{32}H_{52}N_2O_5$	70.6	9.5	5.1	70.6	9.2	4.8
Glycine ethyl ester	VII	Carboethoxymethyl	$C_{27}H_{39}NO_7$	66.5	8.0	2.9	66.4	8.3	2.8
dl-Alanine ethyl ester	VIII	Carboethoxyethyl	$C_{28}H_{41}NO_7$	66.8	8.1	2.8	67.1	8.1	2.9
Tryptophan methyl ester	IX	1-Carbethoxy-2-(3′-indolyl)ethyl	$C_{35}H_{44}N_2O_7$	69.5	7.3	4.6	69.6	7.2	4.5

[a] Anhydrous compound.



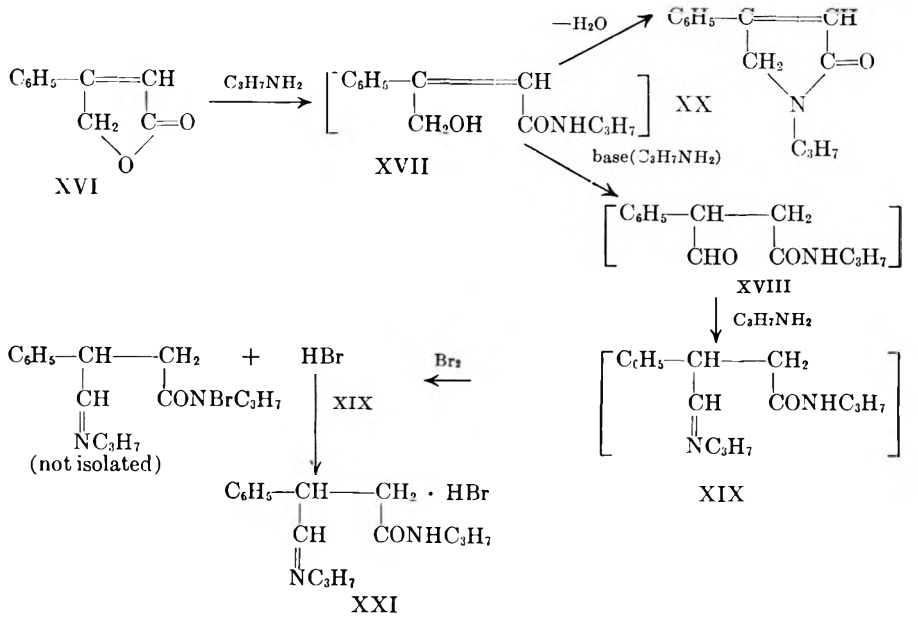
uct with a second equivalent of amine *via* either XII or XIII to yield XIV or XV. As indicated below in connection with the reaction of strophanthidin with secondary amines, we prefer the XII–XIV sequence. In conformity with structure XI the product of the reaction of strophanthidin with *n*-propylamine showed strong infrared absorption characteristic of an *N,N*-disubstituted amide. The compounds were all soluble in dilute hydrochloric acid, a property characteristic of *N,N*-disubstituted amides of sufficiently high molecular weight.[6]

In order to provide confirmation for the above interpretation attention was directed to the reaction of *n*-propylamine with the model compound, β-phenyl-$\Delta^{\alpha,\beta}$-butenolide[7,8] (XVI). This differs from strophanthidin in lacking the C-14 hydroxyl group, the presence of which may play a role in the reactions under consideration, particularly those of strophanthidin with secondary amines (see below). When XVI was allowed to react with *n*-propylamine the reaction took a course which paralleled that of strophanthidin. The initial product of the reaction was the unsaturated alcohol amide (XVII) formed by aminolysis of the butenolide. The greater portion of XVII was isomerized under the influence of the amine to the aldehyde amide (XVIII) which then reacted with a second equivalent of amine to give the imine (XIX), as no hydroxyl group corresponding to the C-14 hydroxyl of strophanthidin was present. A smaller amount of XVII apparently underwent ring closure to give the unsaturated lactam (XX) which was too unstable for purification. However, the crude material gave a positive Legal test. The imine (XIX) was isolated as its hydrobromide when an ethereal solution of it was treated with bromine. Apparently the amide hydrogen was replaced by bromine initially (the analogous amide derived from morpholine which carries no amide hydrogen was inert to bromine) and the hydrogen bromide liberated formed a salt with the unbrominated imine to give the stable hydrobromide (XXI) which was isolated.

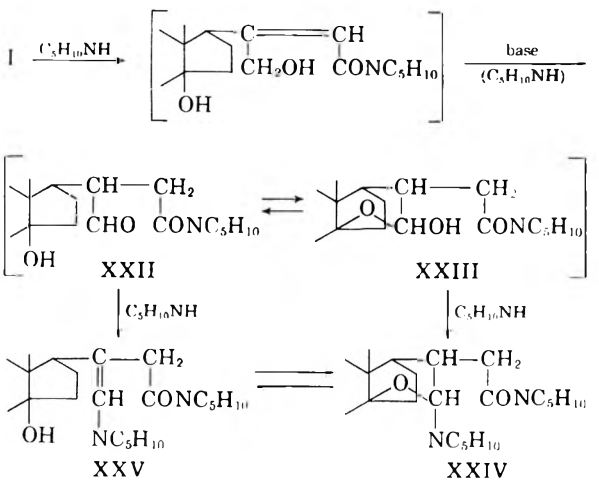
(6) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, New York, 1956, p. 80.

(7) M. Rubin, W. D. Paist, and R. C. Elderfield, *J. Org. Chem.*, **6**, 260 (1941).

(8) R. G. Linville and R. C. Elderfield, *J. Org. Chem.*, **6**, 270 (1941).



The reaction of strophanthidin with two equivalents of a secondary amine—*e.g.*, piperidine or morpholine—paralleled the course suggested above for the reaction with primary amines. However, it was not possible to isolate the product of the reaction of one equivalent of a secondary amine with strophanthidin in pure form. The reaction is formulated as shown in I-XXIV-XXV. In this case



the carbinolamide is incapable of cyclizing through loss of water to give an unsaturated lactam. Hence, it can only undergo isomerization under the influence of the basic amine to give the aldehyde amide (XXII) or its tautomer (XXIII). Reaction of XXII with a second equivalent of secondary amine would then lead to the eneamine (XXV),[9] whereas reaction of XXIII with a second equivalent of secondary amine would lead to XXIV. It is also entirely possible that XXIV and XXV may be in equilibrium.

(9) C. Mannich and H. Davidson, *Ber.*, **69**, 2106 (1936).

Of the above possibilities we favor structure XXV as the most likely possibility based on the infrared spectrum of the substance. Strong absorption bands were present at 1720, 1650, and 1603 cm.$^{-1}$ Of these the band at 1650 cm.$^{-1}$ is the most significant, as Leonard and Gash[10] have shown that such absorption is characteristic of eneamines. Further, the infrared spectrum of the strophanthidin-piperidine product is clear in the region 1000–1200 cm.$^{-1}$ where absorption due to a carbinolamine ether would be expected.[11]

Substantiation of this interpretation was again obtained from a study of the reaction of XVI with morpholine (the products from the reaction with piperidine was exceedingly difficult to manipulate). When XVI was refluxed with morpholine in benzene solution, the product initially obtained was completely soluble in cold dilute hydrochloric acid. Although the substance could not be isolated in pure form, this acid solubility is consistent with either the carbinolamine (XXVI) or eneamine (XXVII) structure both of which would be expected to be reasonably unstable. This assignment was corroborated by conversion of the product to the oxime (XXVIII) during which the nitrogen function was destroyed.

EXPERIMENTAL[12,13]

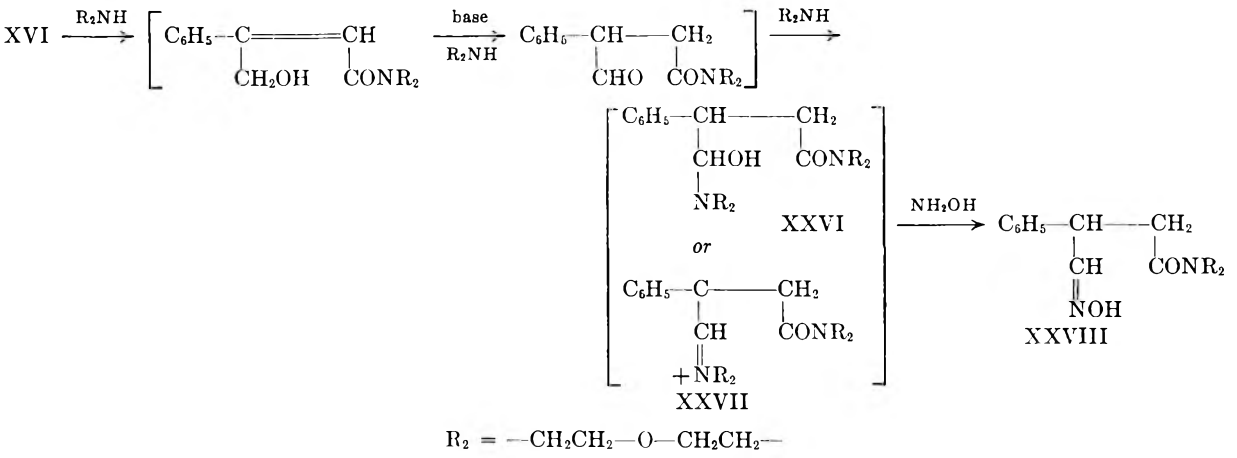
Reaction of strophanthidin with amines. With n-propylamine (II). A mixture of 1 g. of strophanthidin and 10 ml. of redistilled *n*-propylamine was swirled until a clear solution

(10) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(11) Private communication from Dr. O. E. Edwards, National Research Council of Canada, Ottawa, Canada.

(12) All melting points are uncorrected for stem exposure.

(13) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.



resulted. The solution was boiled in an open flask on the steam bath for 15 min., after which residual traces of the amine were removed at the water pump. The frothy white residue was dissolved in 15 ml. of 3% hydrochloric acid. On addition of 10% sodium carbonate solution a white solid precipitated which was collected, air dried, and taken up in boiling benzene. After filtering from a little insoluble material, addition of pentane to the cooled solution gave a heavy white amorphous precipitate. This was collected, taken up in cold benzene, and chromatographed over an alumina column with 20-ml. portions of 3:1 benzene-absolute methanol as eluent. The material collected in the first three fractions was combined and weighed 499 mg. It contracted at 75°, softened to a glass at 85–90°, and decomposed at 112°. The Legal test was positive. Analytical data for this and other products are given in Table I.

Later fractions from the chromatogram contained more nitrogen, gave dubious Legal tests, and probably were the result of partial reaction with a second equivalent of amine.

With n-butylamine (III, IV). This was obtained in almost quantitative yield by the same procedure. After recrystallization from benzene-petroleum ether, a monohydrate which softened at 90° and decomposed at 105–107° was obtained. When dried at 100° over phosphorus pentoxide *in vacuo* the compound melted to a glass which gave satisfactory analytical figures for the anhydrous lactam.

With tryptamine (V). Equimolar portions of strophanthidin (404 mg.) and tryptamine (160 mg.) were intimately mixed and dissolved in 15 ml. of absolute ethanol. The solution was refluxed in the steam bath for 2 hr., after which half the volume of solvent was removed by distillation. Crystallization occurred in the hot solution and, after cooling, the white material was collected, washed twice with absolute ethanol, and air dried. It gave a positive Legal test and melted with decomposition at 200–220°. On treatment with 3% hydrochloric acid, it partially dissolved. After filtering, the filtrate was neutralized with sodium carbonate solution and the precipitate was collected, dried, and taken up in boiling absolute ethanol. Pentane was added to the filtered alcohol solution to the appearance of turbidity. On refrigeration white rosettes of needles, m.p. 217–220°, appeared.

In a subsequent preparation, the product crystallized directly from the alcoholic reaction mixture without treatment with hydrochloric acid. A second crop was obtained by addition of pentane to the mother liquor. Elimination of the hydrochloric acid treatment is desirable as some decomposition of the product attends its use.

With 1-diethylamino-4-aminopentane (VI). *Procedure A.* To a solution of 1 g. of strophanthidin in 7 ml. of 1-diethylamino-4-aminopentane purified over the dithiocarbamate[14] a mixture of 25 ml. of benzene and 25 ml. of toluene was added and the clear solution was refluxed overnight. After removal of most of the solvent at the water pump, addition of petroleum ether precipitated the product as an oily mass. After decanting the solvents, the oily residue was taken up in dilute hydrochloric acid, filtered from insoluble material, and the lactam was precipitated as an oily mass by addition of potassium carbonate solution. This was lifted from the liquid and, after air drying, the substance solidified. It was further purified by precipitation from benzene by petroleum ether, a second precipitation from dilute hydrochloric acid by potassium carbonate, and final crystallization from benzene-petroleum ether. The yield of material, m.p. 92–95° dec. after softening at 80°, was 100 mg. It gave a positive Legal test. For analysis it was dried *in vacuo* at 56°.

Procedure B. To a solution of 1 g. of strophanthidin in 10 ml. of hot cyclohexanone was added 3 ml. of 1-diethylamino-4-aminopentane.[14] After heating the mixture at 140–150° in an oil bath for 15 min. and cooling, the product was precipitated by addition of petroleum ether. After purification by the hydrochloric acid procedure described above, 500 mg. of product was obtained.

With glycine ethyl ester (VII). A mixture of 0.44 g. of freshly prepared glycine ethyl ester and 2 g. of strophanthidin was warmed on the steam bath in a flask provided with a calcium chloride tube for 20 min. About half of the strophanthidin went into solution and the reaction product appeared as a thick viscous liquid mixed with unchanged strophanthidin. The mixture was extracted twice with ether to remove unchanged glycine ester and then with cold dilute hydrochloric acid to remove the product from unchanged strophanthidin. After precipitation of the product by slowly adding solid potassium carbonate to the acid extract, the oily material was removed and air dried, on which it solidified. It was taken up in boiling benzene and filtered. On cooling and addition of petroleum ether an oil separated. The benzene-petroleum ether purification was repeated three times and finally a crystalline product was obtained. The yield was 1 g. The substance gave a positive Legal test, softened at 100°, and melted with decomposition at 115–119°. For analysis it was dried *in vacuo* at 65°.

With dl-alanine ethyl ester (VIII). The procedure was the same as that used with glycine ethyl ester. The product, obtained in 55% yield with complete recovery of starting material, formed a crystalline mass, m.p. 118–122° dec. with softening at 100°. For analysis it was dried *in vacuo* at 65°.

With dl-tryptophan methyl ester (IX). This was prepared in the same manner as was the product from glycine ethyl ester except that a 30-min. heating period gave a product of highest purity in maximum yield. The yield was 52% with complete recovery of starting materials. The substance decomposed at 155–160° with softening at 120°. For analysis it was dried *in vacuo* at 80°.

(14) R. G. Jones, *Ind. Eng. Chem., Anal. Ed.*, 16, 431 (1944).

With piperidine (XXV). *Procedure A*. To a solution of 1 g. of strophanthidin in 10 ml. of warm cyclohexanone was added 2 ml. of dry and freshly distilled piperidine. The mixture was heated at 150° in an oil bath for 15 min. After cooling, addition of three volumes of pentane precipitated a semisolid mass. After chilling for 2 hr., the supernatant liquid was decanted and the residual oil was extracted with 3% hydrochloric acid which left 577 mg. of crude insoluble unreacted strophanthidin. The product was precipitated from the acid solution by addition of dilute sodium carbonate solution. Precipitation from benzene by pentane gave an amorphous off-white powder which was chromatographed in benzene solution over alumina. Elution with benzene-methanol gave 110 mg. of crystalline material, m.p. 195–197°, from 350 mg. of crude product. The Legal test was negative. This is the product of the reaction of strophanthidin with two equivalents of piperidine with elimination of one water. This material contains methanol of crystallization. Solvent free material can be obtained from benzene as described below. For analysis it was dried *in vacuo* at 100°, which gave a solvent free product.

Anal. Calcd. for $C_{33}H_{52}N_2O_6$: C, 71.1; H, 9.4; N, 5.0. Found: C, 70.9; H, 9.4; N, 5.1.

The later fractions from the chromatogram gave material which displayed a positive Legal test and which gave analytical figures for nitrogen corresponding to reaction of strophanthidin with one equivalent of piperidine. However, the carbon and hydrogen figures did not agree with this interpretation. The compound is under further investigation.

Procedure B. A solution of 1 g. of strophanthidin in 10 ml. of cyclohexanone was diluted with 50 ml. of a 1:1 mixture of benzene and toluene. After refluxing for 48 hr. on the steam bath, the solvents were removed at the water pump and the residue was worked up as in Procedure A without chromatography. The product formed white prisms after several crystallizations from benzene-petroleum ether and finally from benzene. It contracts at 170°, begins to darken at 250°, and decomposes at 255°. The yield was 800 mg.

Anal. Found: C, 70.8; H, 9.6; N, 5.0.

With morpholine. The product of the reaction of strophanthidin with two equivalents of morpholine was obtained in almost quantitative yield by Procedure A as given for the piperidine compound. It softened at 158–160° and melted with decomposition at 180°. The Legal test was negative.

Anal. Calcd. for $C_{31}H_{48}N_2O_7$: C, 66.4; H, 8.6; N, 4.9. Found: C, 66.1; H, 8.5; N, 4.6.

Reaction of strophanthidin benzoate with n-propylamine. A solution of 1 g. of strophanthidin benzoate in 5 ml. of *n*-propylamine was warmed in an open flask on the steam bath for 10 min., during which the amine evaporated leaving a brown gum. Last traces of the amine were removed at the water pump and the residue was extracted with dilute hydrochloric acid. About one-fourth of the residue went into solution leaving unchanged strophanthidin benzoate. The acid extract was made alkaline with potassium carbonate solution and the precipitate was recrystallized from benzene-petroleum ether to give 0.3 g. of material which softened at 100°, melted at 118–120°, resolidified, and finally melted with decomposition at 195°. The Legal test was positive.

Anal. Calcd. for $C_{33}H_{43}NO_6$: C, 72.1; H, 7.8; N, 2.6. Found: C, 71.9; H, 7.9; N, 2.8.

Reaction of strophanthidin oxime with n-propylamine. A solution of 1 g. of strophanthidin oxime in 10 ml. of *n*-propylamine was warmed under an air condenser on the steam bath for 30 min. The condenser was removed and the amine was evaporated completely. Extraction of the residue with dilute hydrochloric acid left 0.5 g. of insoluble unchanged oxime. The acid filtrate was made alkaline with potassium carbonate solution and the white precipitate was collected. As this did not give a positive Legal test, it was put aside for future investigation. The alkaline filtrate was almost saturated with solid potassium carbonate with cooling and the solid which was salted out was collected, dried, and extracted with boiling benzene to remove traces of the material giving the negative Legal test. It was finally extracted with boiling chloroform, the chloroform solution was filtered from inorganic salts, and pentane was added. The oxime which separated as white crystals underwent a transition at 130–140° and the new solid melted at 200° with decomposition. The yield was 0.1 g. and the Legal test was positive.

Anal. Calcd. for $C_{26}H_{40}N_2O_5$: C, 67.8; H, 8.7; N, 6.0. Found: C, 67.7; H, 8.7; N, 5.6.

Reaction of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide with n-propylamine (XXI). A solution of 1 g. of the butenolide and 5 ml. of *n*-propylamine in 50 ml. of dry benzene was refluxed on the steam bath for 12 hr. and the benzene was removed under reduced pressure. The oily residue was taken up in 5% hydrochloric acid leaving 0.2 g. of undissolved material. The insoluble material gave a positive Legal test which, in contrast to the negative test displayed by the acid insoluble fraction, was obtained when the butenoide was heated directly with propylamine without the use of benzene as solvent. In the latter instance a portion of the butenolide may have been altered in a different manner. The acid solution was repeatedly extracted with ether to remove non-nitrogenous material and made alkaline with ammonia. The alkaline solution was extracted with ether and the alkaline solution put aside. The combined ether extracts were dried over anhydrous sodium sulfate. Removal of the solvent left 0.6 g. of a viscous transparent liquid which did not crystallize and gave a negative Legal test. The oil was taken up in 15 ml. of absolute ether and a dilute ethereal solution of bromine was added until the color of bromine persisted. Reaction with bromine was instantaneous. Removal of the ether under reduced pressure left a viscous residue which was taken up in 3 ml. of benzene. Dry ether was added until precipitation was complete. The supernatant liquid was decanted and the precipitation repeated twice. On stirring, the sticky residue crystallized. Further recrystallization from benzene-ether and finally from benzene gave 0.3 g. of white crystals, m.p. 138°. For analysis it was dried at 78° *in vacuo*.

Anal. Calcd. for $C_{16}H_{25}BrN_2O$: C, 56.3; H, 7.3; N, 8.2; Br, 23.5. Found: C, 56.5; H, 7.6; N, 7.8; Br, 23.6.

The alkaline water layer from the above ether extraction was taken to dryness and the residue was extracted with chloroform. From the chloroform extracts 0.1 g. of material, m.p. 160°, which gave a positive Legal test was obtained. On attempted purification the substance was changed to one with which the Legal test was negative and which was not investigated further.

Reaction of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide with morpholine. (XXVIII, R = $-CH_2CH_2OCH_2CH_2-$) The procedure was the same as in the reaction of the butenolide with *n*-propylamine. The residue from removal of the benzene was completely soluble in dilute hydrochloric acid. The solid residue was extracted several times with warm acetone leaving 0.5 g. of acetone insoluble material, m.p. 105–106°. Attempted purification resulted in a deep-seated change. The substance was therefore converted to the oxime which formed white prisms, m.p. 140–141°, from ethanol. Analyses corresponded to the oxime of β-phenyl-β-formylpropionylmorpholine.

Anal. Calcd. for $C_{14}H_{17}N_2O_3$: C, 64.4; H, 6.5; N, 10.7. Found: C, 64.4; H, 6.8; N, 10.4.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Action of Grignard Reagents on Heterocyclic Compounds. I. Action of Grignard Reagents on Unsaturated Azlactones

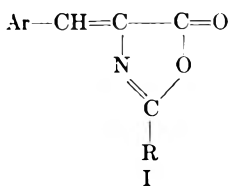
WILLIAM IBRAHIM AWAD AND MOHAMED SHAWKEY HAFEZ

Received October 14, 1959

Phenylmagnesium bromide reacts with unsaturated azlactones (I) to give carbinols (II), and in some cases the corresponding oxazoline (III) has been isolated. The oxazolines have also been obtained from the corresponding carbinol by the action of an acetic anhydride–sodium acetate mixture. Both the carbinols (II) and the oxazolines (III) have been transformed by the action of a hydrochloric acid–acetic acid mixture to give compounds of structure (V). The constitution of the products is discussed.

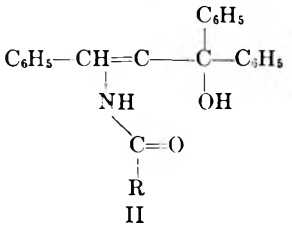
Recently Pourrat,[1] Mustafa and Harhash,[2] and Filler and Wismar,[3] have investigated the action of some Grignard reagents on unsaturated azlactones. The results of these investigators differed in several instances. We have now reinvestigated the whole problem.

Phenylmagnesium bromide reacts with 2-phenyl-4-benzylidene-5(4H)-oxazolone (Ia), to give mainly 1,1-diphenyl-2-benzamidocinnamyl alcohol (IIa) as described by Mustafa and Harhash[2] (the melting point of IIa is similar to that described by Filler and Wismar[3]). Contrary to the relative yields reported by Filler and Wismar,[3] only a small quantity of 2,5,5-triphenyl-4-benzylidene-2-oxazoline (IIIa)(m.p. 176°, Filler and Wismar[3] 161–163°; Pourrat[1] 151°) was isolated together with IIa on working with high concentrations.



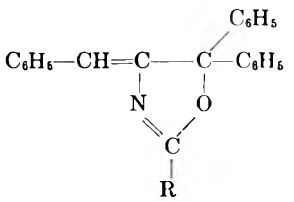
I

Ia. Ar = R = C_6H_5
Ib. Ar = C_6H_5, R = CH_3



II

IIa. R = C_6H_5
IIb. R = CH_3



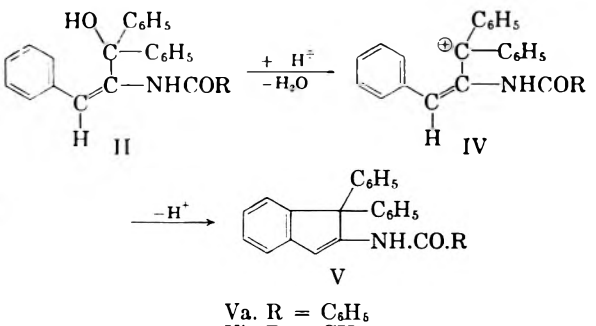
III

IIIa. R = C_6H_5
IIIb. R = CH_3

Mustafa and Harhash[2] reported that refluxing IIa with an acetic acid–hydrochloric acid mixture gave a compound (m.p. 186°) to which they erroneously gave structure IIIa. Filler and Wismar[3] failed to reproduce this experiment. These authors attributed the difference between Mustafa and Harhash[2] and Pourrat[1] regarding this compound to stereochemical factors.

Attempts to prepare the above compound, m.p. 186°, under the conditions mentioned by Mustafa and Harhash[2] were not successful. However, when the experiment was repeated in the cold or by mere warming the compound was obtained in almost quantitative yield.

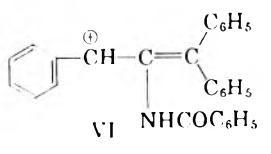
The constitution of this product is believed to be 1,1-diphenyl-2-benzamidoindene, Va, formed according to the following scheme.



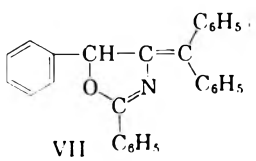
II IV V

Va. R = C_6H_5
Vb. R = CH_3

It was thought at the beginning of this study that the carbonium ion (IV) isomerized to VI, which readily cyclized to give VII.



VI



VII

Ozonolysis of the product did not give any benzophenone but mainly a high melting pale yellow compound.

The constitution of V is mainly based on: 1) oxidation with concentrated sulfuric acid and mercuric sulfate[4] to give phthalic anhydride, thus definitely excluding structure (VII); 2) the infrared spectrum of the product in carbon tetrachloride, showing an —NH stretching frequency at 3472

(1) Pourrat, *Bull. Soc. chim. France*, 828 (1955).
(2) Mustafa and Harhash, *J. Org. Chem.*, **21**, 575 (1956).
(3) Rober Filler and James D. Wismar, *J. Org. Chem.*, **22**, 853 (1957).
(4) A. Schönberg, W. I. Awad, and G. A. Mousa, *J. Am. Chem. Soc.*, **77**, 3850 (1955).

cm.$^{-1}$, amide I at 1694 cm.$^{-1}$, and amide II at 1618 cm.$^{-1}$; 3) its colorlessness; and 4) the compounds being insoluble in hydrochloric acid (*i.e.*, it is not basic).

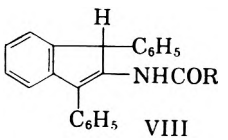
Compounds of structure III have been transformed to compounds of structure V by the action of a hydrochloric acid–acetic acid mixture.

$$\begin{matrix}\text{IIIa. R} = \text{C}_6\text{H}_5 \\ \text{IIIb. R} = \text{CH}_3\end{matrix} \xrightarrow{\text{H}^+} \text{IV} \longrightarrow \text{V}$$

This reaction is in favor of the formation of the carbonium ion IV. The same product was obtained by boiling II in benzene in the presence of phosphorus pentoxide or by refluxing this carbinol in glacial acetic acid or formic acid.

A Fischer model of the *cis* form of that carbinol (II) shows that the hydroxylated carbon is vicinal to the phenyl group on which the ring closure takes place. This cannot be taken as a criterion for the stereochemical configuration of that carbinol, as the formation of the carbonium ion IV and its possible canonical structure VI may cause a free rotation around the carbon atom attached to the phenyl group on which the ring closure has taken place.

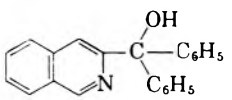
The authors are in favor of structure V and not of structure VIII (by cyclization of the carbonium ion VI), because of the relative stability of the carbonium ion IV when attached to two phenyl



VIII

groups (+E) as compared with the carbonium ion VI which is attached to one phenyl group.

One might argue that the ring closure results in an isoquinoline structure IX, which, in reality on oxidation can give phthalic anhydride. This



IX

structure is excluded on the following basis: 1) such a structure is basic in nature, a fact which is not present in the compound, and 2) infrared spectrum (*inter alia*).

Trials to hydrolyze V by 70% sulfuric acid gave only a high melting compound which may be a polymer, as indenes are known to be easily polymerized.

The action of acetic anhydride and sodium acetate on IIa, which gave a yellow-brown product with a melting range (140–160°) as described by Filler and Wismar,[3] was reinvestigated. We have isolated from that product by elution chromatography on alumina, two compounds, a yellow product IIIa and a colorless product in a good yield, which proved to be Vb by melting point and mixture melting point.

Phenylmagnesium bromide was also allowed to react with 2-methyl-4-benzylidene-5(4H)-oxazolone (Ib) to give mainly 1,1-diphenyl-2-acetamidocinnamyl alcohol (IIb). When this compound was allowed to react with an acetic anhydride–sodium acetate mixture, only one product was obtained having structure IIIb, according to Filler and Wismar.[3]

When the carbinol IIb or the oxazoline IIIb is treated with a hydrochloric acid–acetic acid mixture, one and the same compound is obtained which is believed to be 1,1-diphenyl-2-acetamido-indene, Vb. This structure is deduced by analogy with Va and the infrared spectrum (an —NH stretching frequency at 3472 cm.$^{-1}$, amide I at 1697 cm.$^{-1}$, and amide II at 1623 cm.$^{-1}$).

EXPERIMENTAL

Microanalyses were carried out by Alfred Bernhardt, im Max Planck Institut, Mülheim (Rühr) Germany. The melting points are not corrected.

The infrared measurements are carried out in Perkin-Elmer infracord model 137 in carbon tetrachloride solution. Cell thickness 0.5 mm.

Reaction of 2-phenyl-4-benzylidene-5(4H)-oxazolone (Ia) *with phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide [prepared from 3.65 g. (0.15 g.-atom) magnesium turnings and 23.6 g. (0.15 mole) bromobenzene in 50 ml. ether], was added a fine suspension of 2-phenyl-4-benzylidene-5(4H)-oxazolone (12.5 g.) in 70 ml. ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath until nearly all the ether was driven off. The oily residue thus obtained was triturated with 50 ml. alcohol and allowed to cool. A colorless substance (IIa) separated, which was filtered (yield 11.95 g.), m.p. 165°. The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 83.23; H, 5.71; N, 3.34.

The mother-liquor was treated with a little water and left overnight. A yellow substance separated (IIIa) which was filtered and crystallized from ethyl alcohol in yellow crystals, m.p. 176° (yield 1.35 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{21}N$ O: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.18; H, 5.71; N, 3.82.

Action of a hydrochloric acid-acetic acid mixture on carbinol IIa. To a fine suspension of IIa (1.0 g.) in acetic acid (20 ml.) was added hydrochloric acid (10 ml.) (sp. gr. 1.18). The substance went gradually into solution (yellow color). The reaction mixture was warmed on a water bath for 2 min. and left at room temperature for 30 min. A colorless substance separated: it was filtered, washed with water, and crystallized from benzene-petroleum ether (b.p. 40–60°) in colorless needles, m.p. 186° (yield 0.9 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{21}N$ O: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.56; H, 5.48; N, 3.54.

Action of acetic acid or formic acid on IIa. IIa (1.0 g.) was refluxed with acetic acid or formic acid (50 ml.) for 30 min. The acid was distilled and the volume was reduced to 10 ml. and allowed to cool. A colorless substance separated which was filtered, washed with water, and crystallized from benzene-petroleum ether (b.p. 40–60°) (yield 0.81 g.

in the case of acetic acid and 0.88 g. in the case of formic acid). The substance proved to be Va (melting point and mixture melting point).

Action of phosphorus pentoxide on IIa *in benzene.* To a solution of IIa (1.0 g.) in anhydrous benzene (50 ml.) was added phosphorus pentoxide (2 g.). The color changed immediately (orange-yellow). The reaction mixture was refluxed for 30 min., filtered, and concentrated; a colorless product separated. It was filtered and crystallized from benzene-petroleum ether (b.p. 40–60°) as colorless needles, (yield 0.84 g.). This product proved to be Va (melting point and mixture melting point).

Action of acetic anhydride and sodium acetate on IIa. IIa (4 g.) was refluxed with acetic anhydride (200 ml.) and fused sodium acetate (2.0 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. The yellowish-brown substance thus obtained (m.p. 140–160°) was treated with 50 ml. of ethyl alcohol and warmed on a water bath. A yellow substance separated which was filtered and crystallized from ethyl alcohol as yellow flakes [m.p. 176°, undepressed on admixture with IIIa (yield 0.45 g.)]. The mother-liquor was treated with little water and left overnight. A colorless substance separated, m.p. 140–145° (yield 2.7 g.). Elution chromatography of this substance over alumina using ether as eluent gave a colorless substance which was crystallized from petroleum ether (b.p. 60–80°) as colorless fluffy needles, m.p. 185° (undepressed on admixture with Vb).

The acidic aqueous layer was extracted with ether several times. The combined ethereal extract was washed with a little water, dried over anhydrous sodium sulfate, and evaporated on a water bath. A colorless substance separated (0.9 g.), which was shown to be benzoic acid (melting point and mixture melting point).

Action of a hydrochloric acid–acetic acid mixture on oxazoline (IIIa). The experiment was carried out as described before for the carbinol IIa. The product was shown to be Va (melting point and mixture melting point).

Ozonolysis of Va.[5] A stream of ozonized oxygen was allowed to pass through a solution of Va (2 g.) in chloroform (100 ml.) for 15 min. The reaction mixture was hydrolyzed with water. The chloroform solution was then extracted with a dilute solution of sodium carbonate, then washed with water. The chloroform layer was separated and concentrated: a solid separated which melted above 300°. Acidification of the carbonate solution gave a colorless substance which was filtered and crystallized from water and proved to be benzoic acid (melting point and mixture melting point).

Oxidation of Va *to phthalic anhydride.* A mixture of Va (0.5 g.), mercuric sulfate (0.3 g.), and concd. sulphuric acid (4 ml.) was placed in a glass retort (100 ml. capacity). The mixture was then heated in a metal bath for 10 min. at 250° (bath temperature), then for 50 min. at 300–310° (bath temperature), after which colorless needles were observed on the colder part of the retort tube. The crystals were scratched out of the tube and sublimed to give the characteristic needles of phthalic anhydride (melting point and mixture melting point and positive fluorescein test).

Reaction of 2-methyl-4-benzylidene-5(4H)oxazolone (Ib) *with phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide [prepared from 3.65 g., (0.15 g.-atom) of magnesium turnings and 23.6 g. (0.15 mole) of bromobenzene in 50 ml. ether], was added a fine suspension of 2-methyl-4-benzylidene-5(4H)oxazolone (9.35 g.) in 70 ml. of ether. The reaction mixture was treated as in the case of Ia. The oily residue thus obtained was triturated with petroleum ether (b.p. 60–80°) and allowed to cool. A colorless substance separated which was filtered and crystallized from benzene as colorless needles, m.p. 147° (yield 10.5 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.35; H, 6.06; N, 4.31.

Action of a hydrochloric acid–acetic acid mixture on IIb. To a fine suspension of IIb (1.0 g.) in acetic acid (20 ml.) was added hydrochloric acid (10 ml.) (sp. gr. 1.18). The substance went gradually into solution (yellow color). The reaction mixture was treated as in the case of IIa. The product was crystallized from petroleum ether (b.p. 60–80°) in colorless needles, m.p. 185° (yield 0.91 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.82; H, 6.16; N, 4.24.

Action of acetic anhydride and sodium acetate on IIb. IIb (1.0 g.) was refluxed with acetic anhydride (50 ml.) and fused sodium acetate (0.5 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. A pale-yellow substance (Vb) separated which was filtered, washed with water, and crystallized from ethyl alcohol as very pale yellow needles, m.p. 97° (yield 0.85 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.70; H, 6.12; N, 4.32.

Action of a hydrochloric acid–acetic acid mixture on oxazoline (IIIb). The experiment was carried out as described before for IIb. The product proved to be Vb (melting point and mixture melting point).

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(5) The authors wish to express their thanks to Professor G. Soliman, Alexandria University, for allowing them to use the ozonizer at his disposal.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Action of Grignard Reagents on Heterocyclic Compounds. II. Action of Grignard Reagents on Some Substituted Unsaturated Azlactones

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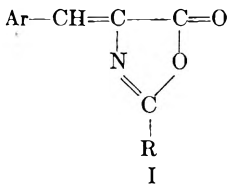
Various Grignard reagents were allowed to react with some substituted unsaturated azlactones (I) to give carbinols (II) and in some cases the corresponding oxazolines (III). The carbinols and the oxazolines were transformed to indene derivatives (IV) by the action of a hydrochloric acid–acetic acid mixture.

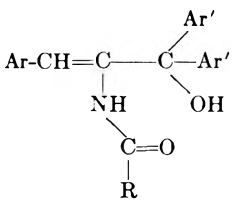
Recently, it has been shown[1,2,3,4] that 2-phenyl-4-benzylidene-5(4H)oxazolone (Ia) reacts with phenylmagnesium bromide to give mainly 1,1-diphenyl-2-benzamidocinnamyl alcohol (IIa); when this carbinol was treated with acetic anhydride and sodium acetate, 2,5,5-triphenyl-4-benzylidene-2-oxazoline (IIIa) was obtained. IIIa was also obtained from the Grignard reaction together with IIa when working under high concentrations. It was also shown[1] that when the carbinol (IIa) was treated with a hydrochloric acid–acetic acid mixture, boiling acetic or formic acid or boiling benzene in the presence of phosphorus pentoxide, 1,1-diphenyl-2-benzamido-indene (IVa) was formed.

This study is now extended to show the effect of substitution in the benzylidene radical, in the Grignard reagent used, or in the group attached in position 2 of the oxazolone ring, on the course of the reaction as it is assigned for each formula (*inter alia*). In all cases the carbinol (II) or the oxazoline (III) has been transformed to the corresponding indene derivative (IV) by the action of the hydrochloric acid–acetic acid mixture either cold or by mere warming.[1] The constitution of the products discussed here is based on the analogy with the products discussed in part I.[1]



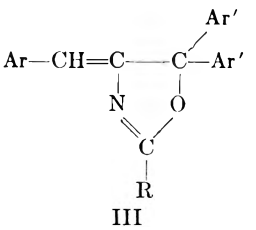
I

Ia. Ar = R = C_6H_5
Ib. Ar = p-$CH_3OC_6H_4$; R = C_6H_5
Ic. Ar = o-ClC_6H_4; R = C_6H_5
Id. Ar = C_6H_5; R = CH_3



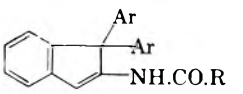
II

IIa. Ar = R = Ar′ = C_6H_5
IIb. Ar = R = C_6H_5; Ar′ = p-ClC_6H_4
IIc. Ar = R = C_6H_5; Ar′ = o-$CH_3OC_6H_4$
IId. Ar = p-$CH_3OC_6H_4$; R = Ar′ = C_6H_5
IIe. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = p-ClC_6H_4
IIf. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = o-$CH_3OC_6H_4$
IIg. Ar = o-ClC_6H_4; R = Ar′ = C_6H_5
IIh. Ar = o-ClC_6H_4; R = C_6H_5; Ar′ = p-ClC_6H_4
IIi. Ar = C_6H_5; R = CH_3; Ar′ = C_6H_5
IIj. Ar = C_6H_5; R = CH_3; Ar′ = p-ClC_6H_4
IIk. Ar = C_6H_5; R = CH_3; Ar′ = o-$CH_3OC_6H_4$



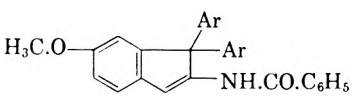
III

IIIa. Ar = R = Ar′ = C_6H_5
IIIb. Ar = R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIIc. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIId. Ar = o-ClC_6H_4; R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIIe. Ar = C_6H_5; R = CH_3; Ar′ = p-ClC_6H_4
IIIf. Ar = C_6H_5; R = CH_3; Ar′ = o-$CH_3OC_6H_4$



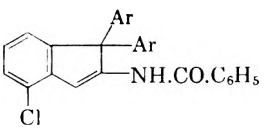
IV

IVa. Ar = C_6H_5; R = C_6H_5
IVb. Ar = p-ClC_6H_4; R = C_6H_5
IVc. Ar = o-$CH_3OC_6H_4$; R = C_6H_5
IVd. Ar = p-$CH_3OC_6H_4$; R = C_6H_5
IVe. Ar = C_6H_5; R = C_6H_5
IVf. Ar = p-ClC_6H_4; R = CH_3
IVg. Ar = o-$CH_3OC_6H_4$; R = CH_3



IV

IVh. Ar = C_6H_5
IVi. Ar = p-ClC_6H_4
IVj. Ar = p-$CH_3OC_6H_4$



IV

IVk. Ar = C_6H_5
IVl. Ar = p-ClC_6H_4
IVm. Ar = p-$CH_3OC_6H_4$

As far as the nature of the Grignard product is concerned, whether it is of type II or type III, Filler and Wismar[4] concluded from their experiments that the nature of the product depends upon

(1) W. I. Awad and M. S. Hafez, *J. Org. Chem.*, in press.
(2) Mustafa and Harhash, *J. Org. Chem.*, **21**, 575 (1956).
(3) Pourrat, *Bull. Soc. chim. France*, 828 (1955).
(4) Robert Filler and James D. Wismar, *J. Org. Chem.*, **22**, 853 (1957).

TABLE I

COMPOUNDS OF STRUCTURE II

Compound	Solvent of Crystln.	M.P.°	Yield,[d] %	Formula[e]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Color with Concd. H_2SO_4
IIb		193	65	$C_{28}H_{21}NO_2Cl_2$[f]	70.88	70.61	4.43	4.68	2.95	2.82	Orange-red
IIc	[c]	180	68	$C_{35}H_{27}NO_4$	77.40	77.59	5.85	5.86	3.01	3.16	Violet
IId	[c]	149	72	$C_{29}H_{25}NO_3$					3.21	3.06	Orange
IIe	[b]	175	64	$C_{29}H_{23}NO_3Cl_2$	69.04	69.35	4.56	4.74	2.73	2.45	Orange
IIf	[a]	176	65	$C_{31}H_{29}NO_5$	75.13	75.26	5.90	5.96	2.83	2.99	Violet
IIg	[a]	142	67	$C_{28}H_{22}NO_2Cl$	76.39	76.35	5.01	5.07	3.19	3.34	Orange
IIh	[a]	172	65	$C_{28}H_{20}NO_2Cl_3$	66.10	66.66	3.93	3.99	2.75	2.39	Orange-yellow
IIj	[b]	178	68	$C_{23}H_{19}NO_2Cl_2$[g]	67.77	67.93	4.50	4.73	3.31	3.52	Orange-red
IIk	[a]	170	66	$C_{25}H_{25}NO_4$	74.44	73.80	6.20	6.06	3.47	3.34	Violet

[a] Benzene-petroleum ether (b.p. 40–60°). [b] Petroleum ether (b.p. 60–80°). [c] Benzene. [d] Yield is calculated as pure material. [e] All crystals were colorless. [f] Calcd.: Cl, 14.97. Found: Cl, 14.68. [g] Calcd.: Cl, 16.82. Found: Cl, 16.76.

TABLE II

COMPOUNDS OF STRUCTURE III

Compound	Method of Preparation	Solvent of Crystln.	M.P.°	Yield,[g] %	Formula[f]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Color with Concd. H_2SO_4
IIIb	[a]	[c]	183	68	$C_{30}H_{25}NO_3$	80.51	80.54	5.63	5.84	3.13	3.13	Orange-red
IIIc	[a]	[d]	146	71	$C_{31}H_{27}NO_4$	77.97	78.20	5.70	5.68	2.93	2.62	Red
IIId	[a]	[d]	173	65	$C_{30}H_{24}NO_3Cl$[h]	74.76	75.02	4.98	5.10	2.90	2.73	Red
IIIe	[b]	[e]	167	73	$C_{23}H_{17}NOCl_2$[i]	70.05	70.00	4.31	4.29	3.55	3.77	Orange-red
IIIf	[b]	[c]	161	66	$C_{25}H_{23}NO_3$	77.92	77.41	5.97	5.68	3.63	3.69	Very pale yellow

[a] *Via* Grignard reagent. [b] By the action of acetic anhydride and sodium acetate. [c] Petroleum ether (b.p. 60–80°). [d] Benzene-petroleum ether (b.p. 40–60°). [e] Methyl alcohol. [f] All crystals were colored yellow. [g] Yield is calculated as pure material. [h] Calcd.: Cl, 7.37. Found: Cl, 7.01. [i] Calcd.: Cl, 18.02. Found: Cl, 18.02.

TABLE III

COMPOUNDS OF STRUCTURE IV

Compound	Solvent of Crystln.	M.P.°	Yield,[e] %	Formula[f]	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %		Color with Concd. H_2SO_4
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
IVb	[b]	209	75	$C_{28}H_{19}NOCl_2$	73.68	73.95	4.17	4.30	3.07	3.03	15.57	15.36	Red
IVc	[b]	195	55	$C_{30}H_{23}NO_4$	80.51	79.87	5.63	5.75	3.13	3.51			Orange-red
IVd	[b]	199	78	$C_{30}H_{25}NO$	80.51	80.30	5.63	5.71	3.13	3.22			Light-brown
IVf	[b]	202	75	$C_{23}H_{17}NOCl_2$					3.55	3.59	18.02	17.38	Orange-red
IVg	[c]	134	59	$C_{25}H_{23}NO_3$	77.90	77.54	5.97	6.15	3.63	3.94			Olive-green
IVh	[d]	196	84	$C_{24}H_{23}NO_2$	83.45	83.93	5.55	5.69	3.35	3.04			Orange-yellow
IVi	[b]	195	77	$C_{24}H_{21}NO_4Cl_2$	71.60	71.72	4.32	4.66	2.88	2.77	14.60	14.02	Orange
IVj	[a]	188	73	$C_{31}H_{27}NO_4$	77.97	78.41	5.70	5.59	2.93	2.97			Red
IVk	[c]	165	81	$C_{28}H_{20}NOCl$	79.71	79.35	4.74	4.60	3.32	3.25	8.42	8.77	Orange
IVl	[a]	218	76	$C_{28}H_{18}NOCl_3$	68.52	69.38	3.66	3.97	2.85	2.69			Yellowish-green
IVm	[a]	189	79	$C_{30}H_{24}NO_4Cl$	74.76	75.02	4.98	4.99	2.90	2.74	7.37	7.11	Orange-red

[a] Benzene-petroleum ether (b.p. 40–60°). [b] Petroleum ether (b.p. 60–80°). [c] Methyl alcohol. [d] Benzene. [e] Yield is calculated as pure material. [f] All crystals were colorless.

the total volume of solvent used in the Grignard reaction. However, we believe that the nature of the Grignard reagent itself has a more pronounced effect on the nature of the Grignard product. When phenylmagnesium bromide, *p*-chlorophenylmagnesium bromide, or *o*-anisylmagnesium bromide are allowed to react with Ia, Ib, Ic, and Id, compounds of type II are the predominant products. When *p*-anisylmagnesium bromide is used, the main product is of type III and no carbinol has been isolated even using lower concentrations. This can be attributed to the high + T effect of the *p*-anisyl group, which facilitates the liberation of the hydroxylic group of the carbinol as a hydroxide ion.

The fact that in the case of the *o*-anisyl derivative the carbinol II and not the oxazoline (III) is obtained is not incompatible, as the possible chelation of the *o*-methoxyl group with the hydrogen of the hydroxylic group definitely reduces its plus T effect in comparison with the case of the *p*-anisyl group (cf. V).

V

EXPERIMENTAL[5]

General procedure for the reaction of oxazolone (I) *with arylmagnesium halides.* To an ethereal solution of the arylmagnesium halide (3 moles) was added a fine suspension of the oxazolone (I) (1 mole) in ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) or with methyl alcohol and allowed to cool. The product was filtered and crystallized from a suitable solvent, (*cf.* Tables I and II).

Action of a hydrochloric acid–acetic acid mixture on the carbinol II *or the oxazoline* III. To a fine suspension of II or III (1.0 g.) in acetic acid (20 ml.), hydrochloric acid (10 ml.) (sp. gr. 1.18) was added. The substance went gradually into solution (yellow-brown color). The reaction mixture was warmed on a water bath and left at room temperature for 30 min. A colorless product (IV) separated; it was filtered, washed with water, and crystallized from a suitable solvent (*cf.* Table III).

Action of acetic anhydride and sodium acetate on the carbinol II. II (1.0 g.) was refluxed with acetic anhydride (50 ml.) and fused sodium acetate (0.5 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. The yellow substance thus obtained was filtered, washed with water, and crystallized from a suitable solvent (*cf.* Table II).

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(5) Microanalyses were carried out by Alfred Bernhardt, im Max-Planck Institut, Mülheim (Rühr) Germany. The melting points are not corrected.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Anodic Reductions. VII. Reduction of Nitrosobenzene, Azoxybenzene, and Azobenzene by Lower Valent Aluminum Anodically Generated

TSU TZU TSAI, WILLIAM E. McEWEN, AND JACOB KLEINBERG

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The "anodic reductions" by lower valent aluminum of nitrosobenzene, azoxybenzene, and azobenzene in lithium chloride-pyridine solution have been studied. In each case, a two-electron reduction has been observed. The results have been compared with those obtained in an analogous investigation with unipositive magnesium, anodically generated, as reducing agent.

Considerable experimental evidence for the generation of lower valent aluminum by anodic oxidation of the metal has appeared in the literature. Early experimenters[1,2] noted the evolution of hydrogen at the anode in the electrolysis of aqueous sodium chloride between aluminum electrodes; moreover, the aluminum anode dissolved with a current efficiency significantly greater than 100% on the assumption of oxidation to the tripositive state. Recently, persuasive additional support for the anodic generation of lower valent aluminum in aqueous salt solutions has been reported.[3] It was demonstrated that when a flowing anolyte consisting of sodium chloride or nitrate solution was passed over an aluminum rod serving as anode and then into a solution of an oxidizing agent, *e.g.*, permanganate or silver ion, contained in a separate vessel, reduction of the oxidant occurred, permanganate to manganese dioxide and silver ion to metallic silver. The only logical interpretation of the occurrence of reduction at a distance from the anode would appear to be in terms of the formation of lower valent aluminum as a primary anodic process.

Substantial evidence for the anodic generation of lower valent aluminum in non-aqueous solvents has also been reported.[4-8]

In this laboratory we have been concerned for some time with the "anodic reduction" of organic compounds by means of lower valent species of active metals.[9-15] Of specific significance to the current paper is the reduction of benzophenone to the conjugate bases of benzhydrol and benzopinacol by lower valent aluminum anodically generated in anhydrous pyridine.[15] We now report that nitrosobenzene, azoxybenzene, and azobenzene can also be reduced analogously. The major objective of the study herein reported is to compare the results with those obtained when the same compounds were reduced by anodically generated unipositive magnesium.[13]

In a typical electrolysis in anhydrous pyridine in which the anolyte contained nitrosobenzene and the electrolyte consisted of a saturated solution of lithium chloride, the aluminum anode entered solution with an initial mean valence number (V_i) of 1.26. After hydrolysis of the anolyte following electrolysis, azoxybenzene was isolated in an amount which exceeded slightly the theoretical based on oxidation by nitrosobenzene of aluminum from its initial mean valence state to the familiar tripositive state.

Since no evidence was found that any substantial amount of the reduction product arose by the action of some reducing species which had migrated from the catholyte, reduction in the anolyte presumably occurs through the agency of lower valent aluminum generated anodically. In view of the electronic configuration of the aluminum atom and the results of previous investigations[3,16-18] of the anodic oxidation of aluminum and other metals, it seems reasonable to suggest that unipositive aluminum is formed as the primary anodic

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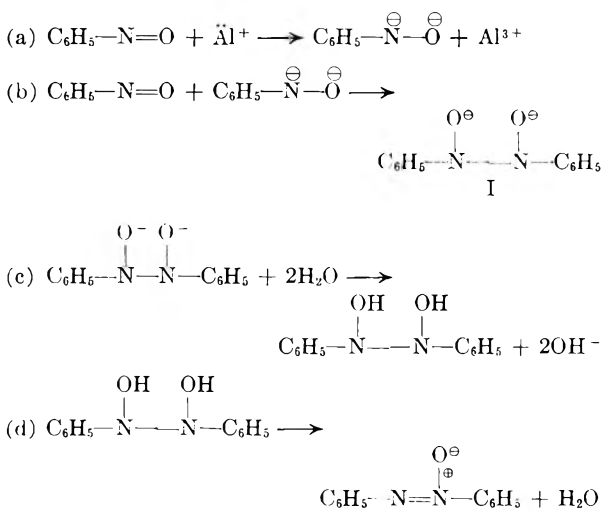
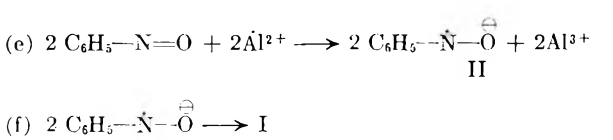
process. The observed V_i value arises as a result of the relative rates of a number of competing reactions: (1) oxidation of the unipositive aluminum by loss of electrons in a stepwise manner to the anode, and (2) oxidation of lower valent aluminum (Al^+, Al^{2+}) by nitrosobenzene.

The isolation of azoxybenzene as the sole reduction product from the anolyte hydrolyzate[19] may be reasonably explained. Azoxybenzene is believed to be formed as shown below when unipositive aluminum is the reducing agent:



When bipositive aluminum functions as the reducing agent, intermediate I is thought to arise by the reactions



Evidence for the formation of intermediate I comes from the fact that *during the course of electrolysis no inorganic oxide is formed in the anolyte.* In one experiment, the anolyte immediately following electrolysis was passed through a sintered glass filter funnel. No residue was left behind on the disk. Since metal oxides which might have been formed (lithium oxide and aluminum oxide) are insoluble in pyridine, the absence of precipitate in the anolyte definitely shows that no metal oxide was produced during electrolysis. Thus, the departure of oxygen occurred during hydrolysis.

It is of interest that "anodic reduction" of nitrosobenzene by unipositive magnesium gives (after hydrolysis) both azoxybenzene and azobenzene and that *metal oxide is formed in the anolyte during electrolysis.* The latter observation explains why azobenzene, a reduction product of azoxybenzene, is formed when unipositive magnesium acts as the reducing agent toward nitrosobenzene. The fact that intermediate I does not lose oxide ion during electrolysis when aluminum is the anode and lithium chloride the electrolyte precludes the production of azobenzene in this experiment.

A control experiment showed that nitrosobenzene dissolved in a saturated solution of lithium chloride in pyridine did not corrode an aluminum rod. However, after electrolysis the anolyte attacked aluminum very slowly; in one experiment, it was observed that four milligrams of aluminum were dissolved in a period of twenty-four hours. This is to be contrasted with the behavior of a similar anolyte remaining after anodic oxidation of magnesium.[13] In this case, a magnesium rod was corroded at a rapid rate. Furthermore, the original electrolytic solution containing nitrosobenzene attacked massive magnesium slowly. These results may reasonably be explained by the fact that aluminum is inherently less reactive than magnesium and the assumption that the concentration of the radical-ion II, the only species formed during electrolysis that is capable of attacking aluminum, is always small in electrolyses where aluminum functions as anode; that is, it is thought that reactions (a) and (b) above account for the formation of a much larger fraction of I than do reactions (e) and (f).

With azoxybenzene present in the anolyte, aluminum entered solution with V_i values in the range 2.61–2.68 and the reduction product isolated from the anolyte hydrolyzate was azobenzene in amounts corresponding to the oxidation by azoxybenzene of the metal from the observed V_i to the +3 state. Prior to hydrolysis, the anolyte solution was clear, an excellent indication that no metal oxide was formed during electrolysis. Control and corrosion experiments showed that neither before nor after electrolysis did the anolyte corrode massive aluminum. It is interesting to note that "anodic reduction" of azoxybenzene by unipositive magnesium also yielded azobenzene as the sole reduction product.[13]

Electrolyses between aluminum electrodes carried out in saturated lithium chloride–pyridine solutions containing azobenzene gave inconsistent V_i values, some normal, *i.e.*, 3, and others below 3. In an experiment in which the V_i value was 2.67, hydrazobenzene was isolated from the anolyte hydrolyzate in 68% yield. A small amount of 4,4′-dipyridyl was also obtained. Evidence is presented in the Experimental section that the dipyridyl arises at least in part from the conjugate base of tetrahydro-4,4′-dipyridyl which migrates from the catholyte compartment of the cell. This conjugate base is frequently formed in the catholyte during electrolyses in pyridine.[9,10] Hydrazobenzene, as would be expected, was also the sole product of the "anodic reduction" of azobenzene by unipositive magnesium.[13]

(19) In one experiment a trace of azobenzene was obtained in addition to the major reduction product azoxybenzene.

Although detailed mechanisms for the formation of azobenzene from azoxybenzene and of hydrazobenzene from azobenzene have not been presented, it is visualized that these two-electron reductions, like that of nitrosobenzene pictured in equations (a) through (f), occur through the agency of lower valent aluminum.

EXPERIMENTAL

Materials. The 10 mm. aluminum rod from which all electrodes were cut was of 99.98% purity and was furnished by the Aluminum Company of America. The lithium chloride employed as electrolyte was Baker and Adamson reagent grade. Pyridine, Fisher analytical reagent, was fractionally distilled from sodium and stored over barium oxide. Nitrosobenzene, azoxybenzene, and azobenzene were prepared and purified as described in a previous communication.[13]

Apparatus and procedure. The apparatus for carrying out electrolyses has been described previously.[16] All electrolyses were carried out at a constant temperature of 39.5 ± 0.5°.

The aluminum electrodes were cleaned in 10% sodium hydroxide solution, then washed with distilled water and dried in an oven at 110°. A saturated solution of lithium chloride in pyridine was made up and 50 ml. added to each compartment of the electrolytic cell. A weighed quantity of organic additive was then dissolved in the anolyte and the system was swept out with pure, dry nitrogen. Electrolysis was effected under an atmosphere of this gas. The conditions of electrolysis (current density, cell voltage, and duration) are specified in the appropriate places for the individual experiments. After electrolysis, the electrodes were cleaned with ethanol and distilled water and then dried at 110°.

From the loss in weight of the anode during electrolysis and the quantity of current passed through the cell the *initial mean valence number*, V_i, with which the aluminum entered solution was calculated.

$$V_i = \frac{\text{wt. of Ag deposited in coulometer} \times 26.97}{107.88 \times \text{wt. of Al lost from anode}}$$

Electrolyses with nitrosobenzene as additive. Two electrolyses in each of which the anolyte contained 4.000 g. of nitrosobenzene were carried out at an initial anodic current density of 0.002 amp. per cm.^{2} and a cell voltage of 150 V. The V_i values obtained were 1.09 (25 hr.) and 1.26 (10 hr.).

After the electrolysis in which the V_i value was 1.26, the dark anolyte was hydrolyzed with ice water and acidified with hydrochloric acid. The hydrolyzate was extracted continuously with petroleum ether for 24 hr. and then with ethyl ether for an additional 24 hr. Distillation of the organic solvents gave, respectively, 0.6662 g. and 0.4127 g. of black residue. The aqueous phase left after extraction was made basic by addition of sodium hydroxide, and extraction with ether gave a small quantity of brown oil. The three extracts noted above were combined and subjected to chromatographic separation on alumina. The mixture was placed on the column in petroleum ether solution and the column was developed by means of the same solvent. Elution, first with petroleum ether, then with ethyl ether–petroleum ether (1:9), gave 0.4426 g. of pure azoxybenzene, m.p. 35–36°, and 0.1008 g. of slightly impure compound, m.p. 33–34°. The infrared spectrum of the first fraction taken in 10% chloroform solution was identical with that of an analogous solution of authentic azoxybenzene, and the spectrum of the second fraction was nearly identical with that of the known.

Since the reduction of nitrosobenzene to azoxybenzene represents a two-electron process, the following equation was employed to calculate the theoretical yield of the reduction product.

$$\text{Theoretical yield of azoxybenzene} = (3 - V_i) \times \frac{\text{g. of Al dissolved}}{26.97} \times \frac{\text{mol. wt. of azoxybenzene}}{2}$$

The theoretical yield of azoxybenzene was 0.4752 g.

In addition to the reduction product, appreciable tarry material was found in the anolyte. This undoubtedly arose from decomposition of nitrosobenzene.

Electrolyses with azoxybenzene as additive. Two electrolyses in each of which the anolyte contained 3.000 g. of azoxybenzene were carried out at an initial current of 0.014 amp. and a cell voltage of 150 V. The V_i values obtained after electrolysis for 25 hr. were 2.61 and 2.68.

After the electrolysis in which the V_i value was 2.61, the anolyte was hydrolyzed with 250 ml. of 6*M* hydrochloric acid. The hydrolyzate was then extracted continuously with petroleum ether for 24 hr. Distillation of the petroleum ether left a red solid which weighed 3.0735 g. The solid was dissolved in a measured volume of petroleum ether and an aliquot containing 1.1870 g. was placed on an alumina column. Elution with chloroform–petroleum ether (1:19) gave 0.0540 g. of a red solid, m.p. 64–65°. The infrared spectrum taken in 10% chloroform solution was identical with that of a corresponding solution of authentic azobenzene.

A quantitative analysis was made of the remaining original red solid by an infrared spectrophotometric method. The spectrum of the unknown in 10% chloroform solution was compared with the spectra of known mixtures of azoxybenzene and azobenzene. It was found that the spectrum of the original red solid was identical with that of a synthetic mixture containing 5.65% azobenzene. Calculation showed that azobenzene was formed in 94.6% yield based on the oxidation of aluminum from its initial mean valence state to the tripositive state by azoxybenzene.

Electrolyses with azobenzene as additive. A number of electrolyses in each of which the anolyte contained 3.000 g. of azobenzene were carried out at an initial current of 0.012 amp. and a cell voltage of 150 V. The V_i values obtained after electrolysis for 22 hr. were 3.00, 2.67, and 2.78.

After the electrolysis in which the V_i value was 2.67, the anolyte was hydrolyzed with ice water and permitted to stand for 2 hr. The mixture was filtered (filter-aid) and the precipitate was washed with petroleum ether to remove unchanged azobenzene and then extracted with methanol. Evaporation of the methanol left 0.2737 g. of solid, m.p. 80–104°. The solid was recrystallized from methanol and there was obtained 0.1186 g. of a colorless solid, m.p. 118–119°. The infrared spectrum was taken in 10% chloroform solution and found to be identical with that of a corresponding solution of authentic hydrazobenzene. The quantity of hydrazobenzene isolated corresponds to a 68% yield based on conversion of aluminum from its initial mean valence state to the +3 state by azobenzene.

The original aqueous filtrate was extracted with ether. Evaporation of the ether left 0.1583 g. of solid. The aqueous phase was made distinctly basic with sodium hydroxide solution and again extracted with ether. Evaporation of the ether gave a small amount of brown solid which was combined with the 0.1583 g. of solid obtained above. The combined solid was washed with petroleum ether to remove any azobenzene present. To the remaining solid was added 18% hydrochloric acid solution and the mixture was filtered. After neutralization of the filtrate, 0.0586 g. of colorless solid which had precipitated was collected by filtration. Recrystallization from water gave a colorless solid, m.p. 69–72°. The infrared spectrum (in chloroform solution) corresponded to that of 4,4′-dipyridyl dihydrate.

The dipyridyl dihydrate is believed to arise at least in part by migration of the conjugate base of tetrahydro-4,4′-dipyridyl from the catholyte to the anolyte and subsequent

oxidation of the base during hydrolysis. That this is plausible was shown by the following experiment. An electrolysis of a saturated lithium chloride–pyridine solution between aluminum electrodes for 20 hr. at an initial current of 0.010 amp. and a cell voltage of 130 V. was carried out. The V_f of the aluminum entering solution was 2.94. If it is assumed that some of the conjugate base of tetrahydro-4,4′-dipyridyl is formed by reduction of the solvent by lower valent aluminum anodically generated, calculation shows that only 18 mg. of dipyridyl should have been formed; actually 58 mg. was isolated.

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LAWRENCE, KAN.

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

Metalation of 12H-Benzo[a]phenothiazine with *n*-Butyllithium

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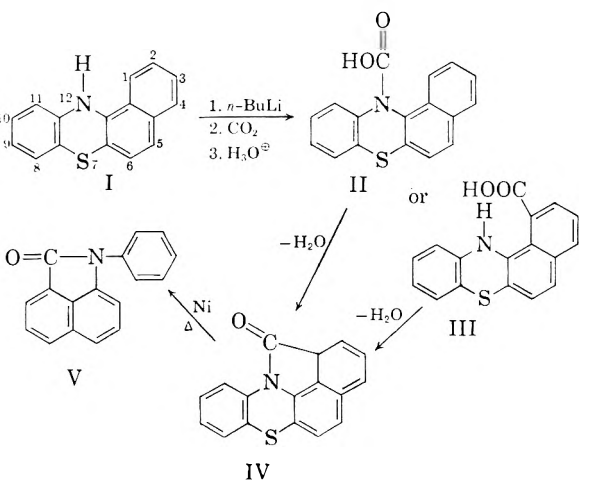
The metalation of 12H-benzo[a]phenothiazine with *n*-butyllithium followed by treatment with carbon dioxide produces 12H-benzo[a]phenothiazine-1-carboxylic acid in 94% yield. The structure of this acid is proved by its dehydration to a lactam and desulfurization to the known *N*-phenylnaphthastyril.

The metalation of a variety of heterocyclic molecules with organolithium reagents has demonstrated that this reaction is often characterized by 1) introduction of the lithium atom at positions adjacent to heteroatoms, 2) good yields, and 3) rapid reaction under mild conditions. As the positions adjacent to heteroatoms are often not the positions involved in other common substitution reactions, the metalation reaction offers a useful and convenient synthetic technique.

As a part of recent investigations[1] of the chemistry of 12H-benzo[a]phenothiazine and derivatives thereof, we have examined the metalation of this polynuclear heterocyclic type with *n*-butyllithium. Relatively few heterocyclic molecules containing >N—H bonds metalate well. The active hydrogen is rapidly replaced by metal and the resulting heterocyclic anion >N:⁻ resists metalation. Examples of this from our work are the failures of C-metalation with pyrrole,[2] indole,[3] and imidazole,[4] although the *N*-alkyl and *N*-aryl types metalate smoothly. Carbazole[5] and pyrazole[6] metalate only in poor yield. Phenothiazine is an exception, however, as it metalates readily in 52% yield in the 1-position.[7]

Treatment of 12H-benzo[a]phenothiazine (I) with a three-fold excess of *n*-butyllithium in ether produced subsequent to carbonation a 94% yield of a deep red monocarboxylic acid derivative of I. The carboxylic acid was rather unstable and could not be purified by crystallization although it had a correct analysis and melted sharply at 136–137° with loss of water vapor. Heating the carboxylic acid above its melting point caused its conversion, by loss of a molecule of water, to a bright orange-red neutral compound. These results suggested either structure II or III for the monocarboxylic and the lactam IV for the dehydration product.



Structure II was eliminated as a possibility, as no carboxylic acid was isolated from an experiment comparable to the first metalation in which equimolar amounts of organolithium and benzophenothiazine were used.

The structure of IV was proved by its desulfurization with Raney nickel to *N*-phenylnaphthastyril (V). The latter compound was identical with a synthetic sample prepared *via* the route indicated.

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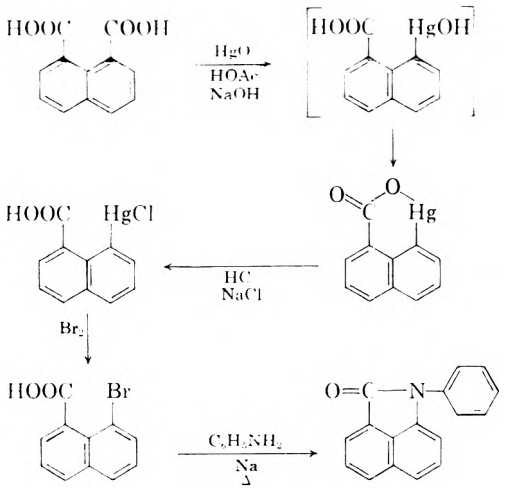

The metalation of 12H-benzo[a]phenothiazine in high yield and with remarkable selectivity of position is a further example of the effectiveness of organolithium reagents in substitution of heterocyclic systems. Polynuclear systems are generally difficult to substitute in good yield at single positions. Metalation of 12H-benzo[a]phenothiazine at the 1-position was not anticipated, as the 11-position should be quite susceptible to metalation on the basis of the results with phenothiazine.[7]

EXPERIMENTAL[8]

Metalation of 12H-benzo[a]phenothiazine (I). A solution of 5.0 g. (0.020 mole) of 12H-benzo[a]phenothiazine[1] in 75 ml. of ether was stirred under a dry nitrogen atmosphere while 78 ml. of a 0.77 molar solution of *n*-butyllithium in ether (0.060 mole of *n*-butyllithium) was added (5 min.). The now bright red solution was stirred for 90 min. after which an excess of solid carbon dioxide was added slowly. Hydrolysis with excess water, separation of the aqueous layer, washing the ether layer with water, and acidification of the combined aqueous layers yielded a red-brown crystalline solid. This was removed by filtration, washed with water, and dried. The product weighed 5.5 g. (94% yield) and melted at 136–137° with loss of water vapor but no apparent further decomposition. The product could not be recrystallized from common solvents, as it seemed to undergo decomposition. The acid could be reprecipitated from 5% aqueous sodium bicarbonate solution, but loss of acidic property seemed to occur on long standing of the solid at room temperature or more rapidly upon treatment with acid. An infrared spectrum of the product showed a carbonyl stretching band at 6.01 μ in accord with a carbonyl group conjugated to a naphthalene ring. On the basis of this data and the analyses below the product is assigned the structure of a monocarboxylic acid derivative of 12H-benzo[a]phenothiazine.

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.6; H, 3.75; N, 4.78. Found: C, 69.5, 69.7; H, 3.73, 3.71; N, 3.32, 4.60.

(8) All elemental analyses were performed by Drs. Weiler and Strauss of Oxford, England. Infrared absorption bands were observed by the potassium bromide disc technique with a Perkin-Elmer Model 21 infrared spectrophotometer.

Ring closure of the monocarboxy-12H-benzo[a]phenothiazine to lactam IV. A 0.5-g. sample of the carboxylic acid isolated above was placed in a small test tube and heated at a bath temperature of 165° for several minutes. During this time the compound gave off water vapor but no carbon dioxide. The red-brown crystalline residue was recrystallized twice from ethanol to produce in good yield a bright orange-red neutral compound, m.p. 167–168°. Further crystallization from ligroin (b.p. 90–120°) raised the melting point to 169–170°. The product is insoluble in aqueous acid and base but becomes water soluble after several minutes heating with alcoholic potassium hydroxide solution. A similar solubility behavior has been reported for phenanthridone.[9] Acidification of the aqueous solution after the latter treatment precipitated black, crude carboxylic acid. The lactam IV showed a carbonyl stretching band at 5.90 μ representing an expected[10] shift to lower wave length upon closure of the 5-membered lactam ring from the starting carboxylic acid (III).

Anal. Calcd. for $C_{17}H_9NOS$: C, 74.1; H, 3.28; N, 5.10. Found: C, 74.1, 74.6; H, 3.54, 3.33; N, 4.84, 5.15.

Desulfurization of lactam IV. About 3 to 4 g. of Raney nickel in 40–50 ml. of absolute ethanol was added to a solution of 0.25 g. of the lactam IV in 40 ml. of 95% ethanol. The mixture was heated under reflux for 30 min., filtered and the filtrate added to an ice water slurry. The precipitated light yellow needles weighed 0.20 g. and melted at 90–95°. Two recrystallizations from petroleum ether (b.p. 60–90°) raised the melting point to 102–103°.

Desulfurization of monocarboxy-12H-benzo[a]phenothiazine (III). A sample of the monocarboxylic acid from the metalation experiment was treated generally as in the preceeding experiment except that the gummy solid formed on pouring the reaction mixture into excess ice, and water was extracted with warm aqueous 5% sodium bicarbonate solution and the remaining solid recrystallized from petroleum ether (b.p. 60–90°). The product melted at 103–104° and was identical in infrared spectrum with the sample above from desulfurization of the lactam.

Both of the above samples from desulfurization experiments were identical (infrared spectra) with a synthetic sample of *N*-phenylnaphthastyril[11] (V), m.p. 103–104° (lit., 104–105°). The synthesis of *N*-phenylnaphthastyril was accomplished by the sequence (see earlier formulas) naphthalic acid ⟶ anhydro-8-hydroxymercuric-1-naphthoic acid[12] ⟶ 8-chloromercuri-1-naphthoic acid[13] ⟶ 8-bromo-1-naphthoic acid[14] ⟶ N-phenylnaphthastyril.[11]

Acknowledgment. We should like to acknowledge the help of the National Institute of Mental Health for financial aid in this research. The work was performed as a part of a larger program in benzophenothiazine chemistry under grant number M-1239.

KNOXVILLE, TENN.

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[CONTRIBUTION FROM THE MELLON INSTITUTE[1]]

Synthesis and Hydrolytic Stability of Some Organosilicon Phosphonate Esters

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A series of organosilicon phosphonates has been synthesized by the peroxide-initiated addition of dialkyl phosphonates to substituted vinyl-, allyl-, and cyclohexenylethylsilanes. Hydrolysis with concentrated hydrochloric acid gave the corresponding phosphonic acids. No cleavage of silicon-carbon bonds was observed under either acid or alkaline conditions.

A series of diethyl esters of substituted silylmethylphosphonic acids was prepared by Gilbert and Precopio[2] through the use of the Michaelis-Arbuzov reaction. These esters containing one carbon between silicon and phosphorus were stated to undergo cleavage of the silicon-carbon bonds under both acidic and alkaline conditions when oxygen was present on silicon. When all of the remaining groups attached to silicon were alkyl, hydrolysis of the ester groups was the principal reaction and silicon-substituted phosphonic acids were apparently isolated. Keeber and Post[3] prepared dibutyl trimethylsilylmethylphosphonate as well as the corresponding acid, trimethylsilylmethylphosphonic acid. This paper also contains a summary of the literature on organosilicon-phosphorus compounds which will not be repeated here. Chernyshev[4] has since reported the compounds: $Cl_3Si(CH_2)_3P(O)Cl_2$, $CH_3Cl_2Si(CH_2)_3P(O)Cl_2$, and $(C_2H_5)SiCHClCH_2P(O)Cl_2$ resulting from reactions of phosphorus trichloride and oxygen with various propyl-, vinyl-, α-chloroethyl-, and β-chloroethylsilanes.

The preparation of the present series of organosilicon phosphonates followed procedures worked out by Stiles *et al.*[5] in preparing dialkyl alkylphosphonates through the addition of dialkyl phosphonates to various olefins using either peroxide or light as initiators. After the present work was completed, Linville[6] described in a patent a similar series of organosilicon phosphonates prepared by the same type of addition. Catalysts claimed were free-radical producing compounds such as the azonitriles and peroxides, as well as various potassium complexes, metallic potassium, and other potassium compounds. Only one of the resulting organosilicon phosphonates was duplicated in this work. Six new organosilicon phosphonates and six new organosilicon phosphonic acids are now reported.

DISCUSSION

The organosilicon phosphonates were of the general formula, $CH_{3n}(RO)_{3-n}Si(CH_2)_mP(O)(OR)_2$ where n was 0, 1, 2, or 3; m was 2 or 3; and R was ethyl or n-butyl. The following is a typical example of the reaction.

$$(CH_3)_2(C_2H_5O)SiCH{=}CH_2 + HP(O)(OC_2H_5)_2 \xrightarrow[(t\text{-}C_4H_9O)_2]{\Delta} (CH_3)_2(OC_2H_5O)SiCH_2CH_2P(O)(OC_2H_5)_2 \quad (1)$$

One example of a cyclohexenylethylsilane was also included in the group of olefins used. Table I lists the resultant adducts.

The reaction conditions used followed recommendations of Stiles.[5] A two to one molar ratio of dialkyl phosphonate to alkenylsilane was employed. The initiator was di-*t*-butylperoxide at a concentration of 5 mole % based on the dialkyl phosphonate. The reactions were carried out at 120°–150° for sixteen hours under a dry nitrogen atmosphere at atmospheric pressure whenever possible. Those with low-boiling components were run in sealed glass ampoules. The yields (with one exception) were 48–62%. Increasing the ratio of dialkyl phosphonate to alkenylsilane to three to one in one trial failed to improve the yield.

In order to prevent any possible interchange of unlike radicals, the alkoxy groups on silicon and the alkoxy groups on the phosphorus were the same in each reaction.

Substitution of an alkenylchlorosilane for an alkenylalkoxysilane in one experiment led to an undesirable side-reaction which eliminated chlorosilanes as suitable reactants. The products appeared to be as shown in Equation 2:

$$(CH_3)_2ClSi(CH_2)_4CH{=}CH_2 + HP(O)(OC_4H_{9}\text{-}n)_2 \longrightarrow n\text{-}C_4H_9Cl + CH_2{=}CH(CH_2)_4(CH_3)_2SiOPH(O)(OC_4H_{9}\text{-}n) \quad (2)$$

Siloxanes also proved to be undesirable for the isolation of pure esters. The reaction investigated was that of pentamethylvinylidisiloxane and di-*n*-butyl phosphonate. Addition to the olefinic double bond appeared to have taken place, but no constant-boiling material was isolated on distillation. Apparently, this was due to the siloxane linkage which appeared to be reactive under these conditions yielding a mixture of products.

(1) Multiple Fellowship on Silicones sustained by Dow Corning Corporation and Corning Glass Works.

(2) A. R. Gilbert and F. M. Precopio, Abstracts of Papers Presented at the 125th Meeting, *Am. Chem. Soc.*, 16N (1954).

(3) W. H. Keeber and H. W. Post, *J. Org. Chem.* **21**, 509 (1956).

(4) E. A. Chernyshev, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1958**, (1) 96.

(5) A. R. Stiles, W. E. Vaughn, and F. F. Rust, *J. Am. Chem. Soc.* **80**, 714 (1958).

(6) R. G. Linville, U. S. Patent **2,843,615**, July 15, 1958.

TABLE I

ADDITION OF DIALKYL PHOSPHONATES TO ALKENYLSILANES

Organosilicon Phosphonate	Yield,[a] %	B.P.°	Mm	n_D^{25}	d_4^{25}	R_D		Silicon, %		Phosphorus, %	
						Obs.	Calcd.	Found	Calcd.	Found	Calcd.
$(CH_3)_3SiCH_2CH_2P(O)(OBu\text{-}n)_2$	55	128	1	1.4353	0.936	0.2780	0.2800	8.11[b]	9.54	10.4[b]	10.52
$(CH_3)_2(n\text{-}BuO)SiCH_2CH_2P(O)(OBu\text{-}n)_2$	59	157	1	1.4388	.954	.2756	.2758	8.9[b]	7.96	8.2[b]	8.79
								8.07[c]		8.52[c]	
$(CH_3)_2(C_2H_5O)SiCH_2CH_2P(O)(OC_2H_5)_2$	55	115	1	1.4209	.999	.2585	.2583	10.1[b]	10.46	11.65[b]	11.54
								10.87[c]		11.2[c]	
$(CH_3)_2(C_2H_5O)SiCH_2CH_2P(O)(OC_2H_5)_2$	62	120	1	1.4320	.986	.2630	.2620	9.80[c]	9.94	10.93[c]	10.90
$CH_3(C_2H_5O)_2SiCH_2CH_2P(O)(OC_2H_5)_2$[d]	48	124	2	1.4270	1.019	.2520	.2504	9.39[c]	9.41	10.43[c]	10.38
$(C_2H_5O)_3SiCH_2CH_2P(O)(OC_2H_5)_2$	33	141	2	1.4216	1.031	.2463	.2442	8.95[c]	8.55	8.83[c]	9.43
$CH_3C_6H_9O_2SiCH_2CH_2$—P(O)(OC$_2$H$_5$)$_2$	52	198	2	1.4515	1.071	.2650	.2639	7.60[c]	7.38	7.85[c]	8.14

[a] Based on alkenylsilane. [b] By Analytical Department, Dow Corning Corporation. [c] By Galbraith Laboratories, Knoxville, Tennessee. [d] Ref. 6, b.p. 170–176° at 3–4 mm., n_D 1.4365 Phosphorus, found, 8.62%.

As phosphonates containing one carbon between silicon and phosphorus were cleaved under both acidic and alkaline conditions when oxygen was present on silicon, it was of interest to determine the behavior of analogous esters having two or more carbon atoms in the chain between silicon and phosphorus.

The organosilicon phosphonates were hydrolyzed to the phosphonic acids shown in Table II in essentially quantitative yields by refluxing with concentrated hydrochloric acid. No evidence for silicon-carbon cleavage was found in any of the hydrolyses.

$$2(CH_3)_2(OC_2H_5)SiCH_2CH_2P(O)(OC_2H_5)_2 + 5H_2O \xrightarrow{H^+} [(HO)_2(O)PCH_2CH_2(CH_3)_2Si]_2O \quad (3)$$

The neutral equivalents were determined by electrometric titration and were based on the first hydrogen only. From the titration curves, the pK_1 and pK_2 values were found, although the values must be considered only approximate. The low solubility of many of the acids in water required more dilute solutions than are usually used for such measurements, and in some cases considerable amounts of ethanol were employed to obtain solution. Comparison of these values with values reported for trimethylsilylmethylphosphonic acid and ethylphosphonic acid in the literature suggests that introduction of silicon into an alkyl chain attached to phosphorus decreases the acidity when the alkyl chain contains one or two carbons, but has little effect with three carbons present. Furthermore, when the silicon is bonded to two or three oxygen atoms, an increase in the acidity is observed. This effect is not observed, however, when the silicon is bonded to only one oxygen atom.

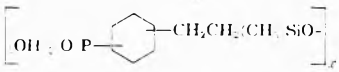
The phosphonic acids varied in appearance from viscous liquids to brittle resins as the number of silicon-oxygen bonds increased from one to three. One exception was (2-trimethylsilyl)ethylphosphonic acid which was a white, crystalline solid containing one molecule of water of hydration based on the neutral equivalent.

The organosilicon phosphonates were also hydrolysed by refluxing with 0.9*N* aqueous sodium hydroxide solutions for twenty-four hours. It was expected that the phosphorus grouping would be converted to the monosodium salts by such treatment, but it was found that the hydrolysis was not that specific. Electrometric titrations of the hydrolysis mixtures indicated that some of the phosphorus was always present as the unchanged diester and some also as the totally-changed disodium salt. No pure compounds were isolated from the alkaline hydrolyses even in the simplest example—di-*n*-butyl (2-trimethylsilyl)ethylphosphonate—with no functionality on silicon.

It was, however, possible to show that little if any silicon-carbon cleavage took place under alkaline conditions by further investigation of the mixtures. The mixtures were acidified, extracted

TABLE II

PHOSPHONIC ACIDS DERIVED FROM ACID HYDROLYSIS

Acid	Neut. Equiv. Found	Neut. Equiv. Calcd.	pK_1	pK_2	Remarks
$(CH_3)_3SiCH_2CH_2P(O)(OH)_2$	200[c]	182	3.4	8.4	White cryst. solid, m.p. 147°
$[(HO)_2(O)PCH_2CH_2(CH_3)_2Si]_2O$	176	177	3.4	8.5	Viscous liquid
$[(HO)_2(O)PCH_2CH_2CH_2(CH_3)_2Si]_2O$	182	189	2.5	8.3	Viscous liquid
$[(HO)_2(O)PCH_2CH_2(CH_3)SiO-]_x$	163	168	2.4	7.7	Stiff, tacky resin
$[(HO)_2(O)PCH_2CH_2SiO_{3/2}]_x$	169	161	2.5	7.6	Dry, brittle resin
	255	250	3.1	8.4	Dry, foam-type resin
$(CH_3)_3SiCH_2P(O)(OH)_2$[a]			3.2	8.7	
$C_2H_5(O)(OH)_2$[b]			2.45	7.85	

[a] Ref.[3]. [b] P. Rumpf and V. Chavane, *Compt. Rend.*, 224, 919 (1947). [c] A molecule of water of hydration is indicated. Repeated efforts to eliminate it by heating above the melting point failed.

with benzene, and the acidic products isolated by evaporation of the benzene. The experimental evidence considered on such products was: the weight balance, electrometric titration data, and the nuclear magnetic resonance spectra. The argument presented in the Experimental shows this evidence to be in good agreement only with a structural formula based on an assumption of no silicon-carbon cleavage. It was also observed during the initial reflux period with the alkali that there was no weight loss, thus eliminating any possibility of cleavage to yield a gas such as ethylene.

The organosilicon phosphonates containing two and three carbons between silicon and carbon and the one example containing the cyclohexylethyl-grouping all proved to be stable to cleavage of the silicon-carbon bond under both acidic and alkaline conditions regardless of the number of oxygens bonded to silicon. Linville[6] has stated a similar conclusion: "The presence of at least two carbon atoms between the phosphorus atom and the silicon atom, . . . unexpectedly lends marked stability in the presence of strong alkali or acids." However, he gave no experimental support for this statement.

EXPERIMENTAL

Materials. Diethyl phosphonate and *di-n-butyl phosphonate* were obtained from Virginia-Carolina Chemical Corp., and *di-t-butylperoxide* from Shell Corp., *vinyltriethoxysilane* and *vinylmethyldiethoxysilane* were obtained from Peninsular Chemresearch, and *vinyltrimethylsilane* from Metal and Thermit Corp. These reagents were used without further purification.

Vinyldimethyl-n-butoxysilane was prepared by the direct reaction of the corresponding chlorosilane (Dow Corning Corp.) with *n*-butanol. *Dimethylethoxyvinylsilane* and *(2-cyclohex-3-enylethyl)methyldiethoxysilane* were prepared from the reaction of the corresponding chlorosilanes with ethyl orthoformate.[7] The chlorosilane for the latter reaction was prepared by the addition of methyldichlorosilane to 4-vinylcyclohexene with a chloroplatinic acid catalyst.[8] Allyldimethylethoxysilane[9] was prepared in a two-step procedure in poor yield. The addition of dimethylchlorosilane to allylmagnesium chloride yielded the intermediate, allyldimethylsilane, which was then converted to the desired product with sodium ethoxide in ethanol. *Hex-5-enyldimethylchlorosilane* was isolated from the addition of one mole of dimethylchlorosilane to 1,5-hexadiene using a chloroplatinic acid catalyst. *Pentamethylvinyldisiloxane* was prepared by cohydrolysis of *vinyldimethylchlorosilane* and trimethylchlorosilane.

General procedure for the additions. The alkenylsilane, phosphonate, and catalyst were thoroughly mixed in a three necked flask equipped with a nitrogen inlet tube, thermometer, and condenser, and placed in an oil bath thermostatically controlled at 120°. Trimethylvinylsilane (b.p. 55°) was treated in a sealed glass ampoule. Two olefins required temperatures higher than 120° to react: vinyltriethoxysilane (130°) and (2-cyclohex-3-enylethyl)methyldiethoxysilane (150°). In most cases, the reaction was quite exothermic during the first hour, the temperature rising above that of the bath, and it was necessary to remove the flask temporarily and cool with an air stream. In no case was the reaction vigorous after the first hour, although reaction continued to take place during the 16-hr. period allowed. The progress of the reaction could be determined at any time by titration,[5] or qualitatively by refractive index rise.

The reaction mixtures were distilled through a small Podbielniak column at 1–2 mm. in order to minimize thermal decomposition. Resultant data are compiled in Table I.

Hex-5-enyldimethylchlorosilane and di-n-butyl phosphonate. This mixture was sealed in a glass ampoule for reaction. Upon distillation, a low-boiling fraction collected in the Dry Ice trap appeared to be *n*-butyl chloride, 2.7 g. (theory: 2.7 g.), n_D^{25} 1.3983 (lit. n_D^{20} 1.4015). A fraction obtained in the range expected for adduct (123°/1 mm.) in approximately 30% yield (if desired product) was examined by NMR spectra. The H^1 spectrum revealed, however, that both H—P and C=C were present in large amounts and in approximately a 1 to 1 molar ratio.

Pentamethylvinyldisiloxane and di-n-butyl phosphonate. The general procedure was used in this reaction. Conversion, based on titration, was 73%, but no constant-boiling material was obtained on distillation.

Hydrolysis with hydrochloric acid. Mixtures of the organosilicon phosphonate and a ten-fold excess, by volume, of concd. hydrochloric acid were refluxed for 24 hr., after which time all of the mixtures were homogeneous; some were so initially. The volume of the mixture was then reduced 50% by distillation. No organic layer was observed in any of the aqueous distillates. The concentrated solutions were evaporated to dryness several times on a steam bath to re-

(7) L. M. Shorr, *J. Am. Chem. Soc.*, **76**, 1390 (1954).

(8) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, **79**, 974 (1957).

(9) J. Swiss and C. E. Arntzen, U. S. Patent 2,595,729, May 6, 1952.

move residual hydrogen chloride. The resulting phosphonic acids were dried to constant weight at 100°, under vacuum when necessary. The one crystalline solid acid was recrystallized three times from cyclohexane and appeared to contain one molecule of water of hydration.

Hydrolysis with alkali. A typical example of an alkaline hydrolysis follows: (n-C_4H_9O)$(CH_3)_2SiCH_2CH_2P(O)(OC_4H_9$-$n)_2$, 10.56 g., 0.03 mole, was refluxed for 24 hr. with a 0.9N NaOH solution. The acidified hydrolysis mixture was extracted with benzene from which the product was isolated on evaporation of the benzene. The product weighed 5.0 g. and an electrometric titration gave neutral equivalents of 279 and 211 for one hydrogen and both hydrogens, respectively. Assuming no cleavage, the titration values would be satisfied by an overall structural formula of:

$$[(n\text{-}C_4H_9O)_{0.93}(HO)_{1.07}P(O)CH_2CH_2(CH_3)_2Si]_2O \quad (A)$$

with 24 mole % of the phosphorus present with 2(—OH), 59 mole % with 1(—OC_4H_9-n) and 1(—OH), and 17 mole % with 2(—OC_4H_9-n). The 5.0 g. of product isolated represents a 73% yield based on formula A. A second structural formula in agreement with the titration data, but in which cleavage to yield dimethylsiloxy-units is assumed, would be:

$$[(n\text{-}C_4H_9O)_{0.70}(HO)_{1.30}P(O)CH_2CH_2(CH_3)_2SiO_{1/2}]_{1.00}\cdot (CH_3)_2SiO_{0.80} \quad (B)$$

with 30 mole % of the phosphorus present with 2(—OH), 70 mole % with 1(—OC_4H_9-n), and 1(—OH), and none with 2(—OC_4H_9-n). The 5.0 g. of product would then represent a 120% yield; this was the first evidence against formula B. The H^1 NMR spectra were obtained on the product diluted to 50% in carbon tetrachloride and on the product diluted to 25% by addition of benzene to the carbon tetrachloride solution. Only one methyl-silicon peak was found in each spectrum. The benzene solvent was chosen because a single peak is often split into two peaks by benzene if two different groups are present but give superimposed resonances. Only one methyl-silicone peak is consistent with formula A, but two peaks would be expected for formula B. Also, from these spectra, the ratio of —CH_2O— to —OH groups estimated from the area under the respective peaks to be 0.85. The ratio calculated for formula A is 0.87 and for formula B 0.54. Thus, all of the evidence available is in agreement with the product having structural formula A rather than B.

Analyses. The phosphorus bond refraction values used in this work were calculated from organophosphorus compounds found in the literature, and agreed favorably with values recently reported by Gillis *et al.*[10] Their data included only one value for the P=O bond refraction in either phosphate or phosphonate structures, whereas our data indicated that two different values were necessary as listed in Table III.

TABLE III

BOND REFRACTION (CC.$^{-1}$)

Bond	Gillis	Our Values
P—O	3.18	3.14
P=O in phosphates	−1.22	−1.07
P=O in phosphonates		−1.42
P—C	3.60	3.66

Both silicon and phosphorus were determined gravimetrically following a sodium peroxide fusion in a Parr peroxide bomb. Considerable difficulty was encountered in this procedure by both analytical laboratories.

A Beckman pH meter, model H 2, was used for the electrometric titrations.

Acknowledgment. The NMR spectra and interpretations thereof were performed by Mr. P. C. Lauterbur of this laboratory.

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(10) R. G. Gillis, J. T. Horwood, and G. L. White, *J. Am. Chem. Soc.*, **80**, 2999 (1958).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY]

Some Derivatives of Tribenzylsilane

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A series of compounds containing the tribenzylsilyl group has been prepared from tribenzylsilane and the appropriate organolithium reagent. One of these compounds, tetrakis(p-tribenzylsilylphenyl)silane, is apparently the highest molecular weight compound containing only carbon, hydrogen, and silicon. Compounds containing the tribenzylsilyl group are characteristically low-melting solids or liquids and are thermally stable.

The unusual stability of tetrabenzylsilane[1] and tribenzylsilane[2] prompted the preparation of a series of tetrasubstituted silanes containing the tribenzylsilyl group.

The tribenzylsilyl derivatives were prepared by treatment of tribenzylsilane with the appropriate aryllithium reagent, a method which has been used for the synthesis of tetrasubstituted silanes.[3]

$$(C_6H_5CH_2)_3SiH + ArLi \longrightarrow (C_6H_5CH_2)_3SiAr + LiH$$

The aryllithium reagents were obtained by reaction of the organic halide with lithium metal, by halogen-metal interconversion reactions, and by metalation reactions. The new tribenzylsilyl derivatives and their physical properties are listed in Table I.

In the preparation of p-bromophenyltribenzylsilane from p-bromophenyllithium[4] and tribenzyl-

(1) A. Polis, *Ber.*, **19**, 1012 (1886).

(2) H. Gilman, R. A. Tomasi, and D. Wittenberg, *J. Org. Chem.*, **24**, 821 (1959).

(3) H. Gilman and S. P. Massie, Jr., *J. Am. Chem. Soc.*, **68**, 1128 (1946); R. N. Meals, *J. Am. Chem. Soc.*, **68**, 1880 (1946); H. Gilman and H. W. Melvin, *J. Am. Chem. Soc.*, **71**, 4050 (1949); H. Gilman and E. A. Zuech, *J. Am. Chem. Soc.*, **81**, 5925 (1959).

TABLE I

$(C_6H_5CH_2)_3SiR$ COMPOUNDS

R	Product	S[a]	M.P.°	Yield, %	Silicon, % Calcd.	Silicon, % Found	Volatilization Temperature[b]
o-Tolyl	$C_{28}H_{28}Si$	A	70–72	48	7.15	7.19, 7.15	465
m-Tolyl	$C_{28}H_{28}Si$		[d]	30.8	7.15	7.27, 7.16	440
p-Tolyl	$C_{28}H_{28}Si$[c]		41–43	68	7.15	7.13, 7.22	460
o-Biphenylyl	$C_{33}H_{30}Si$	A	124–125	15.8	6.18	6.17, 6.18	480
m-Biphenylyl[e]	$C_{33}H_{30}Si$	A	133–134	8.1	6.18	6.10, 6.22	
p-Biphenylyl	$C_{33}H_{30}Si$	A	121–123	51.6	6.18	6.14, 6.25	490
o-Phenoxyphenyl	$C_{33}H_{30}OSi$	A	81–82.5	13.6	5.97	5.85, 5.84	450
m-Phenoxyphenyl	$C_{33}H_{30}OSi$		[f]	68.6	5.97	6.06, 5.79	490
p-Phenoxyphenyl	$C_{33}H_{30}OSi$	A	105–107	56.8	5.97	6.00	490
p-Trimethylsilylphenyl[g]	$C_{30}H_{34}Si_2$		[g]	28.3			440
p-Bromophenyl[h]	$C_{27}H_{25}BrSi$	A	72–74	32.8	6.14	6.19, 6.23	465[i]
p-Bromobiphenylyl	$C_{33}H_{29}BrSi$	B	114.5–115.8	25.9	5.26	5.23, 5.20	
p-Terphenyl-4-yl[j]	$C_{39}H_{34}Si$	C	125–127	24.6	5.29	5.28, 5.20	510

[a] Solvent for recrystallization. A = petroleum ether (b.p. 60–70°), B = pentane-benzene mixture, and C = petroleum ether (b.p. 60–70°)–toluene mixture. [b] See Ref. 6. [c] B.p. 198–200°/0.007 mm. [d] B.p. 187–191°/0.005 mm., n_D^{20} 1.6163, d_{20}^{20} 1.0692, MR_D 128.36 (Calcd. MR_D 128.0). [e] Prepared by W. J. Trepka of these laboratories. [f] B.p. 240–243°/0.003 mm. [g] Prepared by E. A. Zuech of these laboratories, b.p. 200–202°/0.005 mm., n_D^{20} 1.5952, d_{20}^{20} 1.0362, *Anal.* Calcd. for $C_{30}H_{34}Si_2$: C, 79.93; H, 7.60; MR_D 149.09. Found: C, 79.91, 79.90; H, 7.41, 7.30; MR_D 146.85. [h] *p*-Phenylenebis(tribenzylsilane) was also isolated. See Table II. [i] Turns amber color at this temperature. [j] Prepared by E. A. Zuech of these laboratories.

TABLE II

COMPOUNDS PREPARED FROM *p*-TRIBENZYLSILYLPHENYLLITHIUM

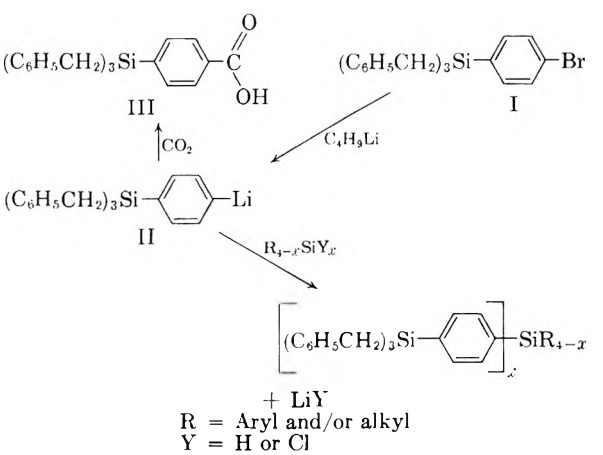
Reagent	Product	Formula	S[a]	M.P.°	Yield, %	Silicon, % Calcd.	Silicon, % Found	Volatilization Temperature[b]
Carbon Dioxide	*p*-Tribenzylsilylbenzoic Acid	$C_{28}H_{26}O_2Si$	A	150–152	36.5	6.65	6.57, 6.58	440[c]
Tribenzylsilane	*p*-Phenylenebis(tribenzylsilane)	$C_{48}H_{46}Si_2$	B	155–157	15	8.27	8.28, 8.28	520[d]
Diphenyldichlorosilane	Bis(*p*-tribenzylsilylphenyl)diphenylsilane	$C_{66}H_{60}Si_3$	B	142–143.5	43.4	8.99	8.82, 8.90	540[e]
Methylphenyl-*p*-tolylsilane	Methylphenyl-*p*-tolyl(*p*-tribenzylsilylphenyl)silane	$C_{41}H_{40}Si_2$	[f]	[f]	56.1	9.54	9.34, 9.43	475
Silicon tetrachloride	Tetrakis(*p*-tribenzylsilylphenyl)silane	$C_{108}H_{100}Si_5$	A	159–161	51	9.13	9.07, 9.22	510

[a] Solvent for recrystallization. A = petroleum ether (b.p. 60–70°) and B = benzene–petroleum ether (b.p. 60–70°) mixture. [b] See Ref. 6. [c] Turns an amber color at 425°. [d] Condensate was light amber. [e] Turns yellow to amber 525–535°. [f] Viscous oil, b.p. 290–291°/0.003 mm., which slowly forms a soft waxy product.

silane, *p*-phenylenebis(tribenzylsilane)[5] was isolated as a side-product. The compound was identical with that formed by the interaction of *p*-tribenzylsilylphenyllithium and tribenzylsilane. Evidently some 1,4-dilithiobenzene was formed in the halogen-metal interconversion reaction for the preparation of *p*-bromophenyllithium.

The compounds of Table II were obtained by the reaction of *p*-tribenzylsilylphenyllithium (II) with the appropriate reagent. The organolithium compound II, formed also *via* a halogen-metal interconversion reaction, was partially characterized by carbonation to the benzoic acid derivative III.

The monomeric tribenzylsilanes (Table I) were



all crystalline low melting solids with the exception of *m*-tolyl- and *p*-trimethylsilylphenyltribenzyl-

(4) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, 62, 2327 (1940).

(5) The names used herein are those preferred by *Chemical Abstracts*.

silane which were liquids. The tribenzylsilyl derivatives of both Tables I and II are also noteworthy for their good thermal stability properties, volatilizing above 440°.[6]

Tribenzylsilyl compounds previously prepared are also low-melting solids or liquids and, in those cases studied, possess rather high volatilization temperatures. These compounds with their physical properties are shown in Table III.

TABLE III

PHYSICAL PROPERTIES OF TRIBENZYLSILYL COMPOUNDS

	M.P.°	B.P.°/mm.	Volatilization Temperature	Reference
Tribenzylsilane	91			[a]
Tribenzyldodecylsilane		216/0.06	430	
Tribenzylcyclohexylsilane		198/0.25	420	[b]
Tribenzylphenylsilane	59		450	[b]
Tribenzyl-*p*-anisylsilane	83			[c]
Tribenzyl-1-naphthylsilane		314/26		[d]
Tribenzylvinylsilane	76.5			[e]
Tetrabenzylsilane	127.5	550		[f]
Tetra(*m*-fluorobenzyl)silane	62			[g]
(Oxydi-*p*-phenylene)bis(tribenzylsilane)		320/0.001	540	[h]

[a] W. E. Evison and F. S. Kipping, *J. Chem. Soc.*, 2830 (1931). See also Ref. 2. [b] H. Gilman and D. Miles, *J. Org. Chem.*, **21**, 254 (1956). [c] H. Gilman and F. G. Marshall, *J. Am. Chem. Soc.*, **71**, 2066 (1949). [d] V. S. Chugunov and A. D. Petrov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 713 (1953), [*Chem. Abstr.*, **48**, 12716 (1954)]. [e] R. Nagel and H. W. Post, *J. Org. Chem.*, **17**, 1379 (1952). [f] See Ref. 1. [g] H. Gilman and R. K. Ingham, *J. Am. Chem. Soc.*, **77**, 1680 (1955). [h] H. Gilman and D. Miles, *J. Org. Chem.*, **23**, 1363 (1958).

The compounds of Table II were also rather low-melting solids, except for methylphenyl-*p*-tolyl(*p*-tribenzylsilylphenyl)silane, which was a very viscous oil slowly solidifying to a waxy solid. The low melting points of these compounds can be contrasted with the high melting points of the perphenylated analogs (Table IV).

The most interesting compound of Table II is tetrakis(*p*-tribenzylsilylphenyl)silane obtained from the reaction of the organolithium compound II with silicon tetrachloride. This low-melting solid has a molecular weight of 1537 and can be crystallized from petroleum ether (b.p. 60–70°). Only a few compounds containing only carbon, hydrogen, and silicon and having a molecular weight of this order, are known: 1,2-ethylenebis(tri-*n*-hexadecylsilane) ($C_{98}H_{202}Si_2$)[7a]; *m*-phenylenebis(tri-*n*-hexadecylsilane) ($C_{102}H_{202}Si_2$),[7b] and *p*-biphenylenebis(tri-*n*-hexadecylsilane) ($C_{102}H_{206}Si_2$, isolated as a slightly impure liquid).[8] Apparently, tetrakis(*p*-tribenzylsilylphenyl)silane is the first known example of a pure nonpolymeric organosilicon compound containing only carbon, hydrogen, and silicon with a molecular weight greater than 1500. However, compounds containing other elements in addition to the above with known molecular weights equal to or greater than 1500 have been reported.[9]

(6) Volatilization points were determined by heating the compounds in an unsealed capillary tube mounted in a flame-heated copper block. All the compounds produced clear or pale yellow condensates unless otherwise noted.

EXPERIMENTAL[10]

Starting materials. Except for *m*-bromophenyl phenyl ether and *p*-bromophenyltrimethylsilane, the aryl halides were commercially available. *m*-Bromophenyl phenyl ether was prepared, in a manner similar to the preparation of *p*-bromophenyl phenyl ether,[11] by heating *m*-dibromobenzene and potassium phenoxide in the presence of copper catalyst at 205° for 20 hr.: 39.4%, b.p. 168–171°/15 mm., n_D^{20} 1.6075, d_{20}^{20} 1.3944.

Anal. Calcd. for $C_{12}H_9BrO$: C, 57.82; H, 3.64; Br, 32.08. Found: C, 58.50, 58.75; H, 3.74, 3.80; Br, 31.18, 31.40.

p-Bromophenyltrimethylsilane was prepared as described previously from *p*-bromophenyllithium[4] and trimethylchlorosilane.[12]

o-Tolyltribenzylsilane. *o*-Tolyllithium (0.047 mole) in 40 ml. of dry ether was added to 9.07 g. (0.03 mole) of tribenzylsilane dissolved in 50 ml. of ether. After refluxing 68 hr., Color Test I[13] was negative. The reaction mixture was hydrolyzed with dilute acid and the layers separated. The organic layer was washed free of acid, dried, and distilled. The residual oil was distilled under reduced pressure to give 5.85 g. of material boiling over the range 172–192° at 0.018 mm. After standing, the distillate crystallized, and upon recrystallization from petroleum ether (b.p. 60–70°), there was obtained 5.65 g. (48%) of pure product melting at 70–72°.

Anal.[14] Calcd. for $C_{28}H_{28}Si$: Si, 7.15. Found: 7.19, 7.15.

The same general procedure was used to prepare *m*- and *p*-tolyl-, *o*-, *m*-, and *p*-biphenylyl-, and *p*-trimethylsilylphenyltribenzylsilane (Table I).

(7) (a) R. D. Gorsich, Ph.D. thesis, Iowa State University, 1957; (b) R. D. Gorsich, unpublished studies.

(8) D. Miles, Ph.D. thesis, Iowa State University, 1957.

(9) See, for example, Pharmazeutische Industrie G.m.b.H. and R. Hauschka, Austrian Patent 86,131, *Chem. Abstr.*, **17**, 1865 (1923); G. Klein and H. Nienberg, *Ber.*, **69B**, 2066 (1936); V. Morrill, Jr., U.S. Patent 2,416,531, *Chem. Abstr.*, **41**, 3819 (1947); H. Staudinger and W. Hahn, *Makromol. Chem.*, **11**, 24 (1953); V. A. Zeitler and C. A. Brown, *J. Am. Chem. Soc.*, **79**, 4616 (1957).

(10) All reactions were carried out under a dry, nitrogen atmosphere using oven-dried glass ware. All melting points are uncorrected. The infrared spectrum of each of the compounds was compatible with the assigned structure.

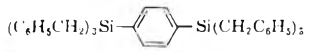
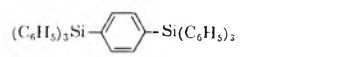
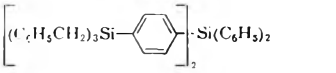
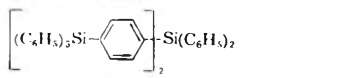
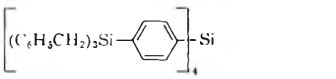
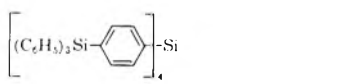
(11) E. Krause and K. Weinberg, *Ber.*, **62**, 2235 (1929).

(12) C. A. Burkhard, *J. Am. Chem. Soc.*, **68**, 2103 (1946); H. Gilman, H. W. Melvin, and J. J. Goodman, *J. Am. Chem. Soc.*, **76**, 3219 (1954).

(13) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(14) The silicon content was determined by the method of H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

TABLE IV

Tribenzylsilyl	M.P.°	Perphenylated	M.P.°
	155		360[a]
	142		419[b]
	159		385[b]

[a] K. Oita, Ph.D. thesis, Iowa State University, 1955, and J. J. Goodman, Ph.D. thesis, Iowa State University, 1955. [b] L. Spialter and C. W. Harris, Aeronautical Research Laboratory, Wright Air Development Center Technical Report 58-276 Wright-Patterson Air Force Base, Ohio, January 1959.

o-Phenoxyphenyltribenzylsilane. *o*-Phenoxyphenyllithium[15] was added to 8.57 g. (0.028 mole) of tribenzylsilane in 100 ml. of ether. After refluxing 14 hr., Color Test I was negative. The reaction mixture was cooled and hydrolyzed with dilute sulfuric acid. The organic layer was separated, dried, and distilled to remove the solvent. The oily residue was distilled under reduced pressure to give a viscous fraction which crystallized on standing. The material was recrystallized from petroleum ether (b.p. 60–70°) to yield 1.79 g. (13.6%) of pure *o*-phenoxyphenyltribenzylsilane, m.p. 81–82.5°.

Anal. Calcd. for $C_{33}H_{30}OSi$: Si, 5.97. Found: Si, 5.85, 5.84.

From lower boiling fractions collected during the distillation, tribenzylsilane, amounting to 5.75 g. (67.9%), was recovered.

m-Phenoxyphenyltribenzylsilane. *m*-Phenoxyphenyllithium was prepared by adding 0.02 mole of an ethereal solution of *n*-butyllithium[16] to 4.98 g. (0.02 mole) of *m*-bromophenyl phenyl ether at −15°. When the addition was complete, Color Test II[17] was negative. Tribenzylsilane (5.44 g., 0.018 mole) dissolved in 60 ml. of ether was added to the *m*-phenoxyphenyllithium while maintaining the temperature near −15°. The reaction mixture was warmed to room temperature and then refluxed 20 hr. at which time Color Test I was negative. Careful hydrolysis with a saturated solution of ammonium chloride, followed by the usual separation, drying, and distillation procedures gave an oily product which was distilled to give 5.81 g. (68.6%) of *m*-phenoxyphenyltribenzylsilane, b.p. 240–243°/0.003 mm.

Anal. Calcd. for $C_{33}H_{30}OSi$: Si, 5.97. Found: Si, 6.06, 5.79.

Similarly, *p*-phenoxyphenyl-,[18] *p*-bromobiphenylyl-,[4] and *p*-terphenyl-4-yllithium[19] were prepared as described and reacted with tribenzylsilane (Table I).

p-Bromophenyltribenzylsilane. *p*-Bromophenyllithium[4] was prepared as previously described from 81.6 g. (0.35 mole) of *p*-dibromobenzene and 0.35 mole of *n*-butyllithium in 250 ml. of ether. The temperature was maintained between −15° and −20°, and after 5 hr. of stirring at this temperature, Color Test II was negative. Tribenzylsilane (107 g., 0.35 mole), dissolved in 950 ml. of ether, was added to the organolithium reagent. The solution was allowed to warm to room temperature and then refluxed for 34 hr. Although Color Test I was positive at the end of this period, the reaction mixture was hydrolyzed with dilute hydrochloric acid and filtered to remove the white solid which had formed at the interface. The aqueous layer was separated, extracted with ether, and discarded. The organic layer was washed with water and dried over anhydrous calcium sulfate. The insoluble solid was crystallized from a benzene–petroleum ether (b.p. 60–70°) mixture to give 16.96 g. (14.3%, based on tribenzylsilane) of a crystalline solid melting at 155–157°, and identified as *p*-phenylenebis(tribenzylsilane) by its silicon analysis, synthesis from *p*-tribenzylsilylphenyllithium and tribenzylsilane, and by comparison of the infrared spectra.

Anal. Calcd. for $C_{48}H_{46}Si_2$: Si, 8.27. Found: Si, 8.28, 8.09, 8.28.

The dried organic layer was concentrated, and ethanol added to the residue. The solid that formed was removed by filtration and recrystallized twice from petroleum ether (b.p. 60–70°) to give 52.5 g. (32.8%) of pure *p*-bromophenyltribenzylsilane melting at 72–74°.

Anal. Calcd. for $C_{27}H_{25}BrSi$: Si, 6.14. Found: Si, 6.19, 6.23.

p-Tribenzylsilylbenzoic acid. *p*-Tribenzylsilylphenyllithium was prepared by adding 0.005 mole of *n*-butyllithium to 2.33 g. (0.005 mole) of *p*-bromophenyltribenzylsilane dissolved in 50 ml. of ether. After stirring 2 hr. at room temperature, Color Test I was positive and Color Test II was negative. The mixture was poured onto a slurry of Dry Ice and ether and warmed to room temperature. Subsequent to hydrolysis, the organic layer was separated from the basic aqueous layer. The aqueous layer was acidified and the crude acid removed by filtration. Recrystallization of the acid from petroleum ether (b.p. 60–70°) gave 0.77 g. (36.5%) of pure product, m.p. 150–152°.

Anal. Calcd. for $C_{28}H_{26}O_2Si$, 6.65. Found: Si, 6.57, 6.58.

Methylphenyl-p-tolyl(p-tribenzylsilylphenyl)silane. *p*-Tribenzylsilylphenyllithium was prepared as described above from 10.06 g. (0.022 mole) of *p*-bromophenyltribenzylsilane and 0.022 mole of *n*-butyllithium in 75 ml. of ether. To this solution there was added 4.67 g. (0.022 mole) of methylphenyl-*p*-tolylsilane[20] in 25 ml. of ether. After stirring 3 hr. at room temperature, hydrolysis was effected with dilute acid and the reaction worked up in the usual manner. Distillation of the residue gave 6.71 g. (56.1%) of a viscous oil, b.p. 290–291°/0.003 mm.

Anal. Calcd. for $C_{41}H_{40}Si_2$: Si, 9.54. Found: Si, 9.34, 9.43.

Tetrakis(p-tribenzylsilylphenyl)silane. Silicon tetrachloride (1.19 g., 0.007 mole) in 15 ml. of ether was added dropwise to 0.028 mole of *p*-tribenzylsilylphenyllithium prepared as described above. The solution was allowed to stir for 18 hr.

(15) K. Oita and H. Gilman, *J. Org. Chem.*, 21, 1009 (1956).

(16) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, 71, 1499 (1949).

(17) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, 62, 1847 (1940).

(18) H. Gilman and J. J. Goodman, *J. Org. Chem.*, 22, 25 (1957).

(19) H. Gilman and E. A. Weipert, *J. Org. Chem.*, 22, 446 (1957).

(20) H. G. Brooks, Jr., unpublished studies.

after which Color Test I was negative. The reaction mixture was hydrolyzed with dilute acid and treated as previously described. There was obtained from the organic layer, a white solid which was recrystallized from petroleum ether (b.p. 60–70°) to give 5.1 g. (51%) of crystalline product melting at 159–161°.

Anal. Calcd. for $C_{108}H_{100}Si_5$: C, 84.31; H, 6.55; Si, 9.13. Found: C, 84.41, 84.43; H, 6.53, 6.43; Si, 9.07, 9.22.

The reactions of *p*-tribenzylsilylphenyllithium with tribenzylsilane and diphenyldichlorosilane were carried out in an analogous manner (Table II).

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AMES, IOWA

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

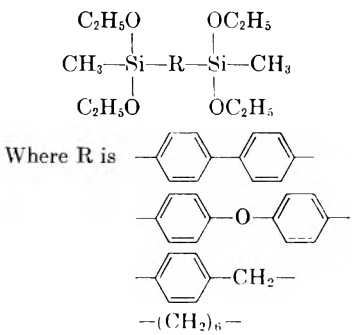
Synthesis of Bis(diethoxymethylsilyl) Derivatives of 4,4′-Dibromobiphenyl, 4-Bromophenyl Ether, α,*p*-Dibromotoluene, and 1,6-Dibromohexane[1]

L. W. BREED

Received January 15, 1960

The syntheses of bis-*p*-(diethoxymethylsilyl)phenyl ether, 4,4′-bis(diethoxymethylsilyl)biphenyl, 1,6-bis(diethoxymethylsilyl)hexane, and α,*p*-bis(diethoxymethylsilyl)toluene are described.

As a part of our continued interest in novel silane monomers for use in the preparation of cross-linked siloxane polymers, we have prepared a series of compounds with the following structure:



Although the synthesis of *p*-phenylenedisilanes was investigated earlier,[2] procedures for their preparation could not be extended to this series. For each of the new compounds it was necessary to find a method that would give pure materials in satisfactory quantities for evaluation studies.

Derivatives of 4,4′-dibromobiphenyl and p-bromophenyl ether. According to the literature, lithium and sodium reactions give 4,4′-disilyl derivatives of 4,4′-dibromobiphenyl and *p*-bromophenyl ether, but only the lithium derivatives have been used to prepare silane derivatives with hydrolyzable functionality. With dilithium intermediates Baum obtained 4,4′-bis(chlorodimethylsilyl)biphenyl and bis-*p*-(chlorodimethylsilyl)phenyl ether[3]; however, others have reported difficulty in repeating his procedure.[4] Various totally alkylated and arylated derivatives, also prepared *via* the dilithium intermediates, have been reported by Gilman.

By means of condensations in the presence of sodium, Clark prepared 4,4′-bis(trimethylsilyl)biphenyl, 4,4′-bis(dimethylphenylsilyl)biphenyl, and bis-*p*-(dimethylphenylsilyl)phenyl ether from the dibromides and the appropriate chlorosilanes, but reported no yields.[5]

Polymeric materials were the chief products when dilithium reagents were treated with polyfunctional silanes in our laboratory. Polyfunctionality of both reactants required inverse addition, but the dilithium derivative could not be transferred and added satisfactorily to the silane because it was a solid.

Although the bis-*p*-(diethoxymethylsilyl)phenyl ether was conveniently prepared by a condensation in ethyl ether in the presence of sodium, the corresponding derivative of 4,4′-dibromobiphenyl could not be prepared by the same method. The limiting factor was apparently the solubility of the dibromide whose concentration in solution was too low to permit the reaction to proceed at a satisfactory rate. Arylsodium intermediates were apparently formed in tetrahydrofuran, but were destroyed by the solvent. Only *p*-bromophenyl ether in ethyl ether provided adequate dibromide concentration to promote an exothermic reaction; the same reactants in toluene did not produce the con-

(1) This research was supported in whole or in part by the United States Air Force under Contract AF 33(616)-3675, monitored by the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

(2) L. W. Breed, W. J. Haggerty, Jr., and F. Baiocchi, *J. Org. Chem.*, in press.

(3) G. Baum, *J. Org. Chem.*, **23**, 480 (1958).

(4) R. L. Schaaf, P. T. Kan, and K. L. Rinehart, Jr., WADC Technical Report 58-187, Part II (1959); ASTIA Document No. 216451.

(5) H. A. Clark, U. S. Patent 2,628,242 (1953); Brit. Patent 671,553 (1952).

densation product. For these syntheses a rapid condensation was necessary because the reaction of coupling to form polysilanes could be expected to predominate if the initial reaction of sodium with the dibromide were slow.

No disilane derivates of biphenyl or phenyl ether, prepared from intermediate di-Grignard reagents, are reported in the literature, although several citations record the synthesis of the di-Grignard reagents.[6-8] Where experimental details are available, the di-Grignard reagent derivatives were prepared in yields of about 40% by entrainment of the dibromide in ethyl ether with either iodine or ethyl bromide.

In our laboratory, disilane derivatives were not obtained when the Grignard reagents, prepared by either entrainment procedure, were added to methyltriethoxysilane or to methylchlorodiethoxysilane, except in one case. When the Grignard reagent of *p*-bromophenyl ether, obtained by entrainment with ethyl bromide, was added to methyltriethoxysilane a mixture of the mono- and disilane derivatives was produced in low yield. As in the case of dilithium intermediate, the solid nature of the di-Grignard reagents offered difficulties in manipulation.

Both dibromides failed to form a Grignard reagent in ether under conventional conditions, in the presence or absence of the silane. In tetrahydrofuran, however, Grignardization of the dibromides appeared to proceed normally. After only two hours reflux of the reactants, titration of the mixtures produced by both dibromides indicated that 40% of the bromine atoms were present as Grignard reagents.

Through the di-Grignard intermediate of 4,4′-dibromobiphenyl in tetrahydrofuran, 4,4′-bis(diethoxymethylsilyl)biphenyl was obtained in a 23% yield. *p*-Biphenyldiethoxymethylsilane was also obtained in a 14% yield suggesting an interaction with the solvent, but substitution of dibutyl ether for toluene in this synthesis failed to change the proportion of the products. Although the Grignard reagent formed readily, forcing conditions were required to effect condensation with the silane. To obtain a product it was necessary to add the dibromide and silane to the magnesium concomitantly, replace the largest part of the solvent with toluene, and reflux the mixture overnight. If the product was filtered and distilled after a five-hour reflux period in tetrahydrofuran, the product was decomposed by uncondensed Grignard reagent during the distillation. Pouring such a mixture into water, however, gave the expected product, but in a lower yield. The yield of the disilylbiphenyl was not uniformly reproduced in replicate runs.

The necessity of using longer reaction times and higher reaction temperatures for the condensation of the di-Grignard reagent of 4,4′-dibromobiphenyl in tetrahydrofuran with chlorosilanes indicates that the product might also have been obtained by the various entrainment procedures had more vigorous conditions been used.

Derivatives of α-p-dichlorotoluene and 1,6-dibromohexane. 1,6-Bis(diethoxymethylsilyl)hexane was readily prepared by adding the intermediate di-Grignard reagent, prepared according to the method of Kreuchunas,[9] to a stirred solution of methyltriethoxysilane. Yields as high as 43% were obtained. Substitution of chlorodiethoxymethylsilane for methyltriethoxysilane in the synthesis gave a product whose empirical formula and neutralization equivalent corresponded to the product plus one equivalent of chlorine ($C_{16}H_{38}O_4Si_2Cl$). No structure was assigned to this compound.

The preparation of a silicon-functional 1,6-disilylhexane has been previously reported by Sveda.[10] He treated a mixture of magnesium and dichlorodimethylsilane in ether with 1,6-dichlorohexane to obtain 1,6-bis(chlorodimethylsilyl)hexane, but reported no yield.

The synthesis of α,*p*-bis(diethoxymethylsilyl)-toluene required a 2-step procedure. An attempt to prepare the diGrignard reagent of α,*p*-dichlorotoluene in tetrahydrofuran gave 4,4′-dichlorobibenzyl in a 46% yield.

p-Chlorobenzyldiethoxymethylsilane was obtained in a 70% yield when α,*p*-dichlorotoluene and chlorodiethoxymethylsilane were added concomitantly to magnesium in ether. The yield was substantially lowered when methyltriethoxysilane was substituted for chlorodiethoxymethylsilane. *p*-Chlorobenzyldiethoxymethylsilane was conveniently converted to α,*p*-bis(diethoxymethylsilyl)toluene by condensation with chlorodiethoxymethylsilane in the presence of sodium in refluxing toluene. The yield was about 70%.

EXPERIMENTAL

Unsuccessful attempts to couple dilithium reagents with various silanes. The dilithium derivative of 4,4′-dibromobiphenyl, prepared by the method of Gilman, *et al.*,[11] was a gummy solid adhering to the walls of the flask and the stirrer, and could not be transferred to a dropping funnel for addition to a silane.

The dilithium derivative *p*-bromophenyl ether, prepared according to the same procedure, was a grayish solid. Addition of the latter reagent to a stirred solution of methyltrichlorosilane or methyltriethoxysilane in benzene failed to yield any identifiable products. Distillation residues contained large quantities of resinous, nondistillable materials.

Unsuccessful attempts to condense 4,4′-dibromobiphenyl and p-bromophenyl ether with chlorodiethoxymethylsilane in the presence of sodium. When a stirred mixture of 13.0 g. of fused

(6) M. S. Malinovskii and V. M. Pokrovskii, *Trudy Gor'kov. Gosundarst. Pedogog. Inst.*, **1940**, No. 5, 51, *Khim. Referat. Zhur.* **4**, No. 2, 45 (1941); *Chem. Abstr.*, **37**, 3077 (1943).

(7) H. R. Snyder, C. Weaver, and C. D. Marshall, *J. Am. Chem. Soc.*, **71**, 289 (1949).

(8) R. Gibert, *Compt. rend.*, **205**, 443 (1939).

(9) A. Kreuchunas, *J. Am. Chem. Soc.*, **75**, 3340 (1953).

(10) M. Sveda, U. S. Patent 2,561,429 (1946).

(11) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).

sodium and 50 ml. of refluxing toluene was treated with 20% of a solution containing 39.0 g. (0.125 mole) of 4,4′-dibromobiphenyl, 42.3 g. (0.25 mole) of chlorodiethoxymethylsilane and sufficient toluene to dissolve the dibromide, no exothermic reaction could be initiated even though the characteristic purple color developed. Neither could a reaction be initiated when *p*-bromophenyl ether was treated under similar conditions.

With ether as the solvent, 31.2 g. (0.10 mole) of 4,4′-dibromobiphenyl, 39.1 g. (0.20 mole) of chlorodiethoxymethylsilane, 11.5 g. (0.5 mole g.-atom) of sodium as 1 mm. diam. wire and 350 ml. ether were stirred at reflux for 24 hr. The mixture became pale purple, but none of the desired product was isolated when the product was filtered, stripped, and the residue distilled.

In the absence of solvent, a mixture of 6.0 g. (0.26 mole) of sodium and 25 ml. of chlorodiethoxymethylsilane, heated at 120° and stirred, was treated with about 5 ml. of a solution containing 16.4 g. *p*-bromophenyl ether in 25 g. chlorodiethoxymethylsilane. A brown coating formed on the sodium and no reaction could be initiated.

When a mixture of 120 ml. of tetrahydrofuran, 16.5 g. (0.05 mole) of 4,4′-dibromobiphenyl, 5.5 g. (0.2 g.-atom) of sodium as 1 mm. diam. wire, and 20 g. (0.1 mole) of chlorodiethoxymethylsilane was stirred, the customary deep blue-purple color developed and external cooling was required to maintain the temperature between 35–40°. The color gradually became gray, then red-purple when the reaction was no longer exothermic. The product was filtered with difficulty and the color dissipated on exposure to air. None of the desired disilane was recovered when the filtrate was distilled, but inspection of the filtration residue showed that all the sodium had been used.

Bis-p-(diethoxymethylsilyl)phenyl ether. In a 5-l. flask equipped with stirrer and condenser were placed 164 g. (0.5 mole) of *p*-bromophenyl ether, 195 g. (2.2 moles) of chlorodiethoxymethylsilane, 50.6 g. (2.2 g.-atoms) of 1 mm. diam. sodium wire, and 1375 ml. of anhydrous ether. Although a reaction began immediately and spontaneously, it was not so vigorous as to require external cooling. After 3 hr. it was necessary to heat and occasionally stir the mixture to maintain a gentle reflux. Reflux was continued an additional 20 hr., and then the product was stirred rapidly for 2 hr. When the product was filtered and fractionally distilled, bis-*p*-(diethoxymethylsilyl)phenyl ether was collected at 195°, 0.1 mm., n_D^{25} 1.5013, d_4^{25} 1.054. In six similar runs the average yield was 29.3%.

Anal. Calcd. for $C_{22}H_{34}O_5Si_2$: C, 60.78; H, 7.88; Si, 12.92; MR_D 121.4. Found: C, 60.57; H, 7.70; Si, 12.56; MR_D 121.5.

In smaller batches, for example with 0.1 mole of *p*-bromophenyl ether, 0.44 g.-atom of sodium wire, 0.22 mole of chlorodiethoxymethylsilane, and 550 ml. of ether, the reaction did not begin spontaneously. If this mixture was stirred rapidly and refluxed for 24 hr., however, the product was obtained in about the same yield. Larger pieces of sodium failed to give a product.

Attempted preparation of bis-p-(diethoxyphenylsilyl)phenyl ether. When 11.6 g. (0.5 g.-atom) of 1 mm. diam. sodium wire, 32.8 g. (0.1 mole) of *p*-bromophenyl ether, 46.2 g. (0.2 mole) of chlorodiethoxyphenylsilane, and 650 ml. of anhydrous ether were stirred at reflux for 14 hr., and the product was filtered and distilled at atmospheric pressure to remove the solvents, a residue was obtained that could not be crystallized. Distillation at 10^{-4} mm. in a Hickman still heated to 325° gave 6 g. of a product, n_D^{25} 1.5555, d_4^{25} 1.2398, which was apparently impure 4-bromophenyl 4′-(diethoxyphenylsilyl)phenyl ether.

Anal. Calcd. for $C_{22}H_{23}BrO_3Si$: C, 59.58; H, 5.24; Si, 6.33; MR_D 114.54. Found: C, 60.90, 60.74; H, 5.87, 5.89; Si, 7.64, 7.61; MR_D 114.90.

DiGrignard reagents of 4,4′-dibromobiphenyl and p-bromophenyl ether in ethyl ether. A reaction could not be initiated when a solution of the dibromide, methyltriethoxysilane, and diethyl ether was added to magnesium turnings.

In an entrainment procedure, 15.6 g. (0.05 mole) of 4,4′-dibromobiphenyl, 4.3 g. (0.175 g.-atom) of magnesium shavings, and 30 ml. of anhydrous ether were treated with a solution of 3.8 ml. (0.05 mole) of ethyl bromide at a rate that maintained gentle boiling. After the product was refluxed 20 hr., all the 4,4′-dibromobiphenyl had dissolved and two liquid phases remained in the reaction flask. This Grignard reagent was transferred under nitrogen to a dropping funnel and added dropwise to a rapidly stirred solution of 32 g. (0.19 mole) of chlorodiethoxymethylsilane in 100 ml. of toluene. A voluminous white precipitate formed almost at once. When the product was filtered and distilled at 1.0 mm., 2.9 g. of material was obtained boiling at 170–205°. There was evidence of decomposition during the distillation and the product darkened and solidified on several days' storage. Addition of a similar Grignard reagent to 30 g. (0.17 mole) of triethoxymethylsilane in 100 ml. toluene gave two liquid phases. A heavy white precipitate formed when the mixture was refluxed 2 hr., but no material was obtained in the expected boiling range when the product was filtered and distilled at reduced pressure.

A Grignard reagent was prepared from 0.1 mole of *p*-bromophenyl ether by the addition of a solution of the dibromide and ethyl bromide in ether to magnesium. Addition of this intermediate to chlorodiethoxymethylsilane gave 13.5 g. of a product that distilled between 180–205° at 1.5 mm. The product however, fumed on exposure to moist air and formed dark tarry materials on standing. Redistillation produced further decomposition. When a similarly prepared Grignard reagent was added to methyltriethoxysilane, and the product was filtered and distilled, 5.2 g. (12.5% as the disilane) of a product which boiled at 180–220° at 0.5 mm. was obtained. Analyses correspond to a mixture of 30% of the disilane and 70% of the monosilane.

Anal. Calcd. for 70% $C_{17}H_{21}BrO_3Si$ and 30% $C_{22}H_{34}O_5Si_2$: C, 55.5; H, 6.4; Si, 8.9. Found: C, 55.85, 56.04; H, 6.12, 6.10; Si, 8.72, 8.43.

In another entrainment procedure 7.5 g. (0.3 g.-atom) of magnesium turnings, 50 ml. of anhydrous ether, and 50 ml. of anhydrous benzene were treated with 25.4 g. (0.2 g.-atom) of iodine in small portions. When the reaction subsided, 31.2 g. (0.1 mole) of 4,4′-dibromobiphenyl and 53.4 g. (0.3 mole) of methyltriethoxysilane were added in one portion. The mixture, heated 48 hr. at reflux and hydrolyzed in an ice water–toluene mixture, did not yield any products boiling over 110° at 0.1 mm.

DiGrignard reagents of 4,4′-dibromobiphenyl and p-bromophenyl ether in tetrahydrofuran. The Grignard reagents, prepared by the usual procedure, formed without the application of external heat in tetrahydrofuran. Both gave a weakly positive Gilman Color Test I, and titration[12] of a hydrolyzed aliquot of each indicated that about 40% of the bromine atoms were converted to Grignard reagent in both reactions. When the Grignard reagent of *p*-bromophenyl ether was carbonated, the resulting acids, purified by solution in 10% sodium carbonate, filtration, and reprecipitation with dilute sulfuric acid, had a neutralization equivalent of 200. Calcd. for *p*-bromophenoxybenzoic acid, 293; for 4,4′-oxydibenzoic acid, 129.

Both Grignard reagents, cooled to 20° and treated with chlorodiethoxymethylsilane, failed to yield the corresponding disilanes, regardless of whether the reaction mixtures were purified by hydrolysis and distillation or by filtration and distillation.

4,4′-Bis(diethoxymethylsilyl)biphenyl. A previously activated mixture of 42 g. of 4,4′-dibromobiphenyl (recrystallized from toluene), 24.5 g. of (1.06 g.-atoms) magnesium turnings, and 160 ml. of tetrahydrofuran was treated with a solution of 83 g. (total 0.4 mole) of 4,4′-dibromobiphenyl,

(12) H. Gilman, H. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, 51, 1576 (1929).

135 g. (0.8 mole) of chlorodiethoxymethylsilane, and 800 ml. of tetrahydrofuran by dropwise addition over a period of 3 hr. The product was heated with slow stirring for 3 hr. and then refluxed overnight. After 1 l. of dry toluene was added, 1800 ml. of solvents were distilled from the mixture and heating was continued for 16 hr. Filtration, followed by removal of the solvents by distillation and filtration of precipitated solids, yielded a residue which gave 163 g. of crude product boiling 42–163° at 0.1 mm. on distillation. Fractional distillation of the crude product yielded 18.8 g. (14%) of *p*-biphenylyldiethoxymethylsilane boiling 131–132°, 0.3 mm., n_D^{26} 1.5470, d_4^{25} 1.076, and 37.5 g. (23%) of 4,4′-bis(diethoxymethylsilyl)biphenyl boiling 185–187°, 0.4 mm., n_D^{25} 1.5253, d_4^{24} 1.084.

Anal. Calcd. for $C_{17}H_{22}O_2Si$: C, 71.30; H, 7.74; Si, 9.81; MR_D 84.02. Found: C, 71.11; H, 7.65; Si, 9.71; MR_D 84.40.

Anal. Calcd. for $C_{22}H_{34}O_4Si_2$: C, 63.11; H, 8.19; Si, 13.42; MR_D 118.38. Found: C, 63.02; H, 8.12; Si, 13.32, 13.19; MR_D 119.63.

When the procedure was modified and the product was refluxed 5 hr. without the addition of toluene, purification by decanting the product into water gave only 6.3% of the disilane and 7.9% of the monosilane along with biphenyl, bromobiphenyl, and unchanged 4,4′-dibromobiphenyl. Purification of a similar run by simple filtration and distillation gave two immiscible phases in the distillation flask. The lower phase, which solidified on cooling, decomposed during an attempted distillation. The upper phase yielded only unchanged 4,4′-dibromobiphenyl.

The yields of the two products were lower when larger quantities were treated. Substitution of *n*-butyl ether for toluene in the procedure failed to decrease the proportion of *p*-biphenylyldiethoxymethylsilane in the product.

1,6-Bis(diethoxymethylsilyl)hexane. The Grignard reagent, prepared by the method of Kreuchunas,[9] from 7.3 g. (0.3 g.-atom) of magnesium turnings and 23 g. (0.1 mole) of 1,6-dibromohexane in 100 ml. of anhydrous ether, was transferred to a dropping funnel under an atmosphere of nitrogen, then added dropwise to a stirred mixture containing 33.8 g. (0.24 mole) of chlorodiethoxymethylsilane and 100 ml. of anhydrous ether that had been cooled to −30° in a Dry Ice–methanol bath. After the addition was complete, the mixture was refluxed 2 hr. When the product was filtered and fractionally distilled, a product weighing 8.1 g. was obtained at 105–106°, 0.1 mm. This material hydrolyzed to form an acid on contact with water and gave a positive Beilstein test.

Anal. Calcd. for $C_{16}H_{38}O_4Si_2Cl$: C, 49.75; H, 9.94; Si, 14.54; Cl, 9.18; neut. equiv., 386. Found: C, 49.71, 49.82; H, 9.94, 10.03; Si, 14.94, 14.68; Cl, 9.17, 9.11; neut. equiv., 385.

In a second experiment, the Grignard reagent was prepared and added to a solution containing 42.7 g. (0.24 mole) of methyltriethoxysilane and 100 ml. of anhydrous ether which was cooled to −10°. When the addition was complete 100 ml. of benzene was added, the ether was distilled, and the mixture was refluxed at 80° for 3 hr. The product, worked up in a similar manner, gave 10.6 g. (29.4%) of 1,6-bis(diethoxymethylsilyl)hexane boiling at 130° at 0.1 mm. n_D^{25} 1.4252, d_4^{25} 0.910. This product was unaffected by water and gave a negative Beilstein test.

Anal. Calcd. for $C_{16}H_{38}O_4Si_2$: C, 54.80; H, 10.92; Si, 16.02; MR_D 98.51. Found: C, 54.47, 54.63; H, 10.57, 10.77; Si, 15.89, 15.80; MR_D 95.58.

Repetition of this experiment using 244 g. (1 mole) of 1,6-dibromohexane gave 123 g. (42.5%) of the same product.

p-Chlorobenzyldiethoxymethylsilane. In a 5-l. flask were placed 24.3 g. (1.86 g.-atoms) of magnesium turnings and 25 ml. of a mixture containing 240 g. (1.49 moles) of α,*p*-dichlorotoluene, 262 g. (1.55 moles) of chlorodiethoxymethylsilane, and 850 g. of anhydrous diethyl ether. The reaction was initiated and the remainder of the reactants were added dropwise over a 3-hr. period. When addition was complete, 1300 ml. of toluene were added and the mixture was stirred at 35° for a total of 2 hr. The product was filtered and the filtrate stripped to remove solvents. During the concentration, more salts separated, and an additional filtration was required. The residue was fractionally distilled at 5 mm. and yielded 268 g. (70%) of *p*-chlorobenzyldiethoxymethylsilane boiling at 118–119°, n_D^{25} 1.4854, d_4^{25} 1.066.

Anal. Calcd. for $C_{12}H_{19}O_2SiCl$: C, 55.68; H, 7.40; Si, 10.85; MR_D 70.29. Found: C, 55.59; H, 7.59; Si, 10.85, 10.92; MR_D 69.66.

Repetition of the same procedure with 0.1 mole of α,*p*-dichlorotoluene and 0.12 mole of methyltriethoxysilane gave 4.8 g. (18.5%) of *p*-chlorobenzyldiethoxymethylsilane.

p-Chlorobenzyldiethoxymethylsilane was satisfactorily prepared in a yield of 63% in an experiment in which 0.1 mole of α,*p*-dichlorotoluene and 0.1 mole of chlorodiethoxymethylsilane were used and the crude reaction mixture poured over a water–toluene–sodium bicarbonate–ice mixture. All attempts, however, to effect purification by hydrolysis of a run based on 0.8 mole of α,*p*-dichlorotoluene yielded no product.

p-Bromobenzyldiethoxymethylsilane. In a similar procedure, 50 g. (0.24 mole) of *p*-bromobenzylchloride was treated with 7.1 g. (0.3 g.-atom) of magnesium turnings and 49 g. (0.3 mole) of chlorodiethoxymethylsilane to yield 31.1 g. (42.4%) of *p*-bromobenzyldiethoxymethylsilane boiling 124–128° at 3 mm., n_D^{25} 1.5027, d_4^{25} 1.216.

Anal. Calcd. for $C_{12}H_{19}BrO_2Si$: C, 47.51; H, 6.31; Si, 9.25; MR_D 73.13. Found: C, 48.35; H, 5.86; Si, 9.49; MR_D 73.59.

α,p-Bis(diethoxymethylsilyl)toluene. Thirty-six grams (1.57 g.-atoms) of sodium was placed in a 3-l. flask equipped with a dropping funnel, stirrer, reflux condenser, and thermometer and covered with 85 ml. of toluene and 22 g. of chlorodiethoxymethylsilane. The mixture was heated to reflux, then stirred at 600 r.p.m. with a 12 mm. diam. blade to disperse the sodium. Addition of 10 ml. of a solution containing 168 g. (0.65 mole) of *p*-chlorobenzyldiethoxymethylsilane, 110 g. (total, 0.78 mole) chlorodiethoxymethylsilane, and 320 ml. toluene, caused a dark blue color to develop at once, and the remainder of the reactants were added dropwise at a rate which maintained reflux (liquid temperature, 110–114°). When the addition was complete, the mixture was stirred under reflux an additional hour, cooled, and filtered. Solvents were stripped from the filtrate by downward distillation and the residue was combined with a similar product prepared from 100 g. (0.39 mole) of *p*-chlorobenzyldiethoxymethylsilane. When the combined residues were fractionally distilled at 0.1 mm., 256 g. (69.5%) of α,*p*-bis(diethoxymethylsilyl) toluene was collected between 122–124°, n_D^{24} 1.4665, d_4^{25} 0.996.

Anal. Calcd. for $C_{17}H_{32}O_4Si_2$: C, 57.26; H, 9.05; Si, 15.76, MR_D 99.81. Found: C, 57.25; H, 8.84; Si, 15.76, 15.66; MR_D 99.33.

Unsuccessful Grignard reaction of α,p-dichlorotoluene in tetrahydrofuran. In a 500-ml. flask were placed 5.5 g. (0.22 g.-atom) of magnesium turnings and a sufficient portion of a mixture containing 16.1 g. (0.1 mole) of α,*p*-dichlorotoluene, 33.8 g. (0.2 mole) of chlorodiethoxymethylsilane, and 50 g. of tetrahydrofuran to cover the magnesium was added. The reaction was initiated and the remainder of the mixture was added at a rate to maintain the reaction. When the addition was complete, stirring was commenced and the mixture was heated at the reflux temperature for 3 additional hr. The product, filtered and poured over a mixture containing 100 g. of water, 100 g. of toluene, 15 g. of sodium bicarbonate, and ice, was separated and washed four times with 100-ml. portions of water, and dried over Drierite. On distillation, 5.8 g. of *p,p′*-dichlorobibenzyl (46.4%) was obtained boiling at 160° at 0.1 mm., and melting at 97–99° (from alcohol).

Anal. Calcd. for $C_{14}H_{12}Cl_2$: C, 66.94; H, 4.82. Found: C, 67.08; H, 4.89.

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[CONTRIBUTION FROM THE AERONAUTICAL RESEARCH LABORATORY, WRIGHT AIR DEVELOPMENT DIVISION, AIR RESEARCH AND DEVELOPMENT COMMAND]

Urea Complexes of Partially Fluorinated Esters[1]

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The effect of fluorine on the ability of a partially fluorinated unbranched ester to form a urea channel complex was found to be predominantly steric and not polar. Complex formation depended upon the number of unfluorinated chain atoms referred to as anchor length and upon the location of the anchor in either the alkyl or acyl moieties of the ester. Knowing the anchor length of the shortest homologue forming a complex, the conformational analysis of an immobilized ester trapped in the prism of urea was determined. The x-ray powder diffraction data were used to determine the presence of urea complexes by indicating the presence of tetragonal urea, hexagonal complex, or a mixture of both. The most stable complexes showed no interplanar spacings for tetragonal urea. The less stable complexes partially dissociated giving characteristic spacings for urea and complex.

Because 2,2-difluorooctane forms a urea complex, the presence of two fluorine atoms upon a single carbon atom in a linear chain does not prevent complex formation.[2] Whether two or more fluorinated carbon atoms linked together in the chain would likewise permit complexing is not known.

EXPERIMENTAL

All complexes were prepared[3] by adding 30 drops of the sample[4] to 4.5 ml. of urea-methanol solution (0.15 g. urea/ml. of methanol) in a test tube. The tube was stoppered and shaken for 30 seconds and allowed to stand at 4° for 24 hr. The crystals that formed were filtered with suction and washed with 10 ml. of absolute ethanol at 4°. The product was vacuum-dried at 4° (1 mm.) over anhydrous calcium chloride for 24 hr. No crystals formed when the urea-methanol solution was used as a blank. In some cases tetragonal urea crystallized from the urea-methanol solution after a noncomplex forming compound had been added.

The dried urea complexes were finely ground with a mortar and pestle and applied to the surface of a roughened glass slide. The interplanar spacings and relative intensities were obtained using the Norelco X-ray diffractometer with a Geiger tube detector at 35,000 volts and 15 milliamps with a scanning rate of 1° per min. A General Electric recorder was used to obtain the data.

The following normal fluorinated acids and alcohols failed to form a complex: CF_3COOH, C_2F_5COOH, C_3F_7COOH, $C_5F_{11}COOH$, $C_7F_{15}COOH$, $C_9F_{19}COOH$, CF_3CH_2OH, $C_3F_7CH_2OH$, $H(CF_2)_2CH_2OH$, $H(CF_2)_4CH_2OH$, $H(CF_2)_6CH_2OH$, $H(CF_2)_8CH_2OH$ and $H(CF_2)_{10}CH_2OH$. From this and the knowledge of which partially fluorinated esters will form complexes, one may conclude that esters of perfluoro acids with either α,α-dihydroperfluoro alcohols or α,α,ω-trihydroperfluoro alcohols will not form a complex; no members of either aforementioned class of hydroperfluoro alcohols, or perfluoro acid formed a complex.

From Table II it can be determined which compounds formed a pure complex, which caused the crystallization of pure urea, and which complexes partially dissociated giving the characteristic patterns of both. The compounds present in Table I and missing from Table II produced no crystalline material under complexing conditions.

In each series of esters where two homologues caused urea only to crystallize, the anchor lengths for the two esters were one and two less, respectively, than the minimum anchor length required for complex formation in that series. The shorter of the two caused the deposition of less urea. In all cases complexes of the higher homologues showed no evidence for dissociated urea which has a characteristic interplanar spacing line in the interval 4.00 to 4.04 Å. This line is most useful because it is relatively strong and does not occur in the x-ray powder diffraction patterns of any of the complexes. The most characteristic line for the urea complexes occurs between 4.11 and 4.17 Å. Other interplanar spacings useful for characterizing a urea complex appear at 3.55–3.64 Å and 7.13–7.19 Å. These spacings show a greater variation in intensity than does the 4.11–4.17 Å spacing. In a homologous series forming urea complexes the relative intensity of the 3.55–3.64 Å and 7.13–7.19 Å shows, in general, a gradual increase as the anchor length of the complexed molecule increases. This same trend[3] is observed for the urea complexes of alkylsilanes.

All measured cross-sectional diameters are maximum values of the planar zigzag conformation obtained from Stuart-Briegleb molecular models. This maximum is less than the maximum obtained from any other configuration.

DISCUSSION

The cross-sectional diameter of the fluorinated monoesters (Series II–VI, Table I) is 5.6 Å compared to 4.8 Å for the corresponding unfluorinated esters, because the effective radius of fluorine (1.3 Å) is 1.3 times greater than hydrogen (1.0 Å). The correspondingly bulkier fluorinated ester would be expected to form a less stable urea com-

(1) Presented before the International Symposium on Fluorine Chemistry in Birmingham, England, July 14–17, 1959.

(2) W. J. Zimmershied, R. A. Dinerstein, A. W. Weitkamp, and R. F. Marschner, *Ind. Eng. Chem.*, **42**, 1300 (1950).

(3) J. Radell and P. D. Hunt, *J. Am. Chem. Soc.*, **80**, 2683 (1958).

(4) The preparation of these compounds will be described in a separate publication.

TABLE I

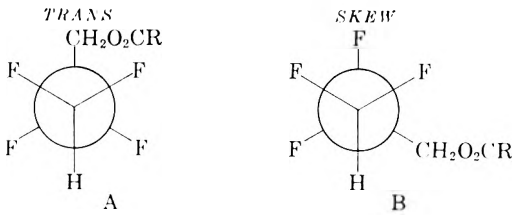
SUMMARY OF UREA FORMING ABILITY OF PARTIALLY FLUORINATED ESTERS

Series	Unbranched Esters	n		Anchor Length[a] of Shortest Complex Former	Cross-Sectional Diameter A[b]	Number of Fluorine Atoms
		Noncomplex Formers	Complex Former			
I	$CH_3(CH_2)_nCO_2CH_2CF_3$	2	3–6	7	5.1	3
II	$CH_3(CH_2)_nCO_2CH_2(CF_2)_3H$	2, 3	4	8	5.6	4
III	$CH_3(CH_2)_nCO_2CH_2(CF_2)_3F$	2, 3	4–6	8	5.6	7
IV	$CH_3(CH_2)_nCO_2CH_2(CF_2)_4H$	2, 3	4–6	8	5.6	8
V	$C_7F_7CO_2(CH_2)_nCH_3$	4, 5	6, 7, 9	9	5.6	7
VI	$C_5H_{11}CO_2(CH_2)_nCH_3$	5, 6	7, 8	10	5.6	11
VII	$CF_3CO_2(CH_2)_nO_2CCF_3$	5				
VIII	$C_7F_7CO_2(CH_2)_nO_2CC_3F_7$	4–6				
IX	$C_3F_7CH_2O_2C(CH_2)_nCO_2CH_2C_3F_7$	4, 5	7, 8			
X	$C_3F_7CH_2O_2C(CF_2)_3CO_2(CH_2)_nO_2C(CF_2)_3CO_2CH_2C_3F_7$	3, 5				

[a] Number of chain atoms not bearing fluorine. [b] Maximum cross-sectional diameter of the planar zigzag conformation measured on Stuart-Briegleb models.

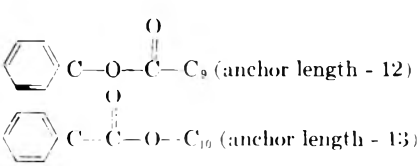
plex based upon the behavior of other bulky molecules.[3,5] In addition to the steric effect, information was sought as to whether the electronegativity of fluorine would have any effect on the complexing ability of partially fluorinated esters. To determine the relative influence of the steric and inductive effects of fluorine in the formation of urea complexes, the shortest homologues of series I–IV in Table I which formed a complex were examined. Each of these esters with fluorine exclusively in the alkyl part showed that an increase in the number of fluorine atoms from 3 (series I, $n = 3$) to 4 (series II, $n = 4$) is associated with an increase of 7 to 8 of the anchor length. When the number of fluorine atoms was increased from 4 to 7 (series III, $n = 4$) and 7 to 8 (series IV, $n = 4$) the anchor length remained unchanged. A comparison of the cross-sectional diameters of the shortest complex formers in Series I–IV, Table I, shows that anchor length varies as does the cross-sectional diameter of the molecule. Series II–IV had the same cross-section and the same anchor length for the respective shortest homologues complexing. In series I the anchor length and the cross-sectional diameter of the shortest complexing homologue was less. The importance of the steric effect of fluorine is far greater than the inductive effect of fluorine as the variation in the complexing ability of the smallest homologue of each series bears a direct relationship to the maximum cross-sectional diameter of the planar zigzag conformation of the ester and not to the number of fluorine atoms present in the alkyl part.

Two conformers of the series II ester in Table I are shown in the planar zigzag form using the Newman projection formula.



Form A had a measured cross-sectional diameter of 5.6 Å; form B had a measured cross-sectional diameter of 5.2 Å. The actual immobilized conformer present in the urea complex was determined in the following way. All esters with fluorine in the alkyl part of the molecule and with a measured cross-sectional diameter of 5.6 Å (Series III and IV, Table I) had an experimentally determined minimum anchor length of 8 for urea complex formation. Where fluorine was in the alkyl part of the molecule and the measured cross-sectional diameter was 5.1 Å (Series I, Table I), the minimum anchor length for urea complex formation was 7. Of the two possible Series II planar zigzag conformers, A was chosen as the conformation in the complex because the shortest homologue forming a urea complex had a minimum anchor length of 8. Conformer A would be preferred for polar and steric reasons as well.

The effect of fluorine varies depending on whether it appears in the alkyl or acyl portion of the ester. A minimum anchor length of 8 is required for urea complex formation in Series III (Table I). In contrast, the minimum anchor length required for complex formation in Series V (Table I) is 9, although the maximum cross-sectional diameter of both esters is 5.6 Å. A similar difference is noted when a bulky group appears in an unfluorinated ester on the acyl or alkyl side. The following two esters with a bulky phenyl group are the shortest homologues of each which form a urea complex:[5]



(5) E. V. Truter, *J. Chem. Soc.*, 2116 (1951).

TABLE II

INTENSITIES[a] OF INTERPLANAR SPACINGS OF UREA INCLUSION COMPOUNDS, Å

n-R	Anchor Length[b]	7.13–7.19[c]	4.37–4.44	4.11–4.17	4.00–4.04	3.80–3.90	3.55–3.64	3.40–3.41	3.28–3.29	Urea Inclusion Compounds
				MONOESTERS $RCOOCH_2CF_3$						
C_3H_7	6				1.00		0.05			−
C_4H_9	7	0.30	0.20	1.00	0.70	0.15	0.75	0.40		+
C_5H_{11}	8	0.50		1.00	0.40		0.80	0.10	0.15	+
C_6H_{13}	9	0.10		1.00			0.20	0.05	0.05	+
C_7H_{15}	10	0.35	0.10	1.00		0.15	0.85	0.30	0.15	+
				$RCOOCH_2CF_2CF_2H$						
C_3H_7	6				1.00		0.05			−
C_4H_9	7				1.00		0.05			−
C_5H_{11}	8	0.20	0.05	1.00	0.40	0.05	0.60	0.15	0.10	+
				$RCOOCH_2CF_2CF_2CF_3$						
C_3H_7	6				1.00		0.05			−
C_4H_9	7				1.00		0.05			−
C_5H_{11}	8	0.35		1.00	0.70		0.40	0.30	0.20	+
C_6H_{13}	9	0.20	0.10	1.00	0.10		0.30	0.10	0.10	+
C_7H_{15}	10	0.25	0.05	0.40			1.00	0.10	0.05	+
				$RCOOCH_2CF_2CF_2CF_2CF_2H$						
C_3H_7	6				1.00					−
C_4H_9	7				1.00					−
C_5H_{11}	8	0.10		0.45	1.00	0.10	0.20	0.10	0.05	+
C_6H_{13}	9	0.10	0.10	1.00	0.20	0.30	0.40	0.30	0.20	+
C_7H_{15}	10	0.30		1.00			0.60	0.25	0.10	+
				$CF_3CF_2CF_2COOR$						
C_7H_{15}	9	0.05		1.00	0.30		0.40	0.10		+
C_8H_{17}	10	0.20	0.10	0.90	1.00	0.20	0.80	0.25	0.15	+
$C_{10}H_{21}$	12	0.80		0.95			1.00	0.25		+
				$CF_3CF_2CF_2CF_2CF_2COOR$						
C_6H_{13}	8				1.00		0.05			−
C_7H_{15}	9				1.00		0.05			−
C_9H_{17}	10	0.40		1.00	0.05		0.60	0.10		+
C_9H_{19}	11	0.30	0.05	1.00	0.05		0.60	0.45	0.05	+
				DIESTERS						
$C_3F_7CH_2O_2C(CH_2)_7CO_2CH_2C_3F_7$	13	0.15	0.15	0.40 (4.21Å)	1.00	0.20	0.30 (3.69)	0.25	0.25	+
$C_3F_7CH_2O_2C(CH_2)_8CO_2CH_2C_3F_7$	14	0.10	0.10	1.00 (4.21Å)	0.60	0.10	0.40	0.30	0.15	+
$C_3H_7CO_2(CH_2)_5O_2CC_3H_7$	15	0.20		1.00		0.25	0.50	0.60	0.30	+

TABLE II (*Continued*)

n-R	Anchor Length[b]	7.13–7.19[c]	4.37–4.44	4.11–4.17	4.00–4.04	3.80–3.90	3.55–3.64	3.40–3.41	3.28–3.29	Urea Inclusion Compounds
				Monoesters[d] (nonfluoro)						
$C_3H_7CO_2C_2H_5$	7	0.64 (7.05Å)		1.00 (4.08Å)	0.69 (3.97Å)	0.14 (3.77Å)	0.18 (3.64Å)	0.13		+
							0.90 (3.52Å)	0.45 (3.37Å)		
$C_4H_9CO_2C_2H_5$	8	0.85 (7.05Å)	0.07 (4.33Å)	1.00 (4.10Å)	0.15 (3.97Å)	0.23	0.85	0.23 (3.37Å)		+
$C_5H_{11}CO_2C_2H_5$	9	0.75 (7.08Å)	0.05 (4.33Å)	0.86 (4.09Å)	0.05 (3.97Å)	0.07 (3.93Å)	1.00 (3.54Å)	0.38 (3.37Å)	0.08 (3.25Å)	+
						0.22				
$C_6H_{13}CO_2C_2H_5$	10	0.68 (7.08Å)	0.12 (4.33Å)	0.95 (4.09Å)		0.32	1.00	0.48 (3.37Å)	0.16 (3.25Å)	+
$C_7H_{15}CO_2C_2H_5$	11	0.58 (7.02Å)	0.07 (4.34Å)	1.00 (4.09Å)		0.22	0.87 (3.54Å)	0.42 (3.36Å)	0.06 (3.25Å)	+
$C_8H_{17}CO_2C_2H_5$	12	0.50 (7.08Å)	0.07 (4.34Å)	1.00 (4.10Å)		0.19	0.87	0.67 (3.38Å)	0.07 (3.26Å)	+

[a] Relative intensity; 1.0 the strongest. [b] See *a* Table I. [c] CuKα radiation. [d] Commercially obtained.

In the case of the diesters the information is more obscure. The anchor length of the smallest molecule forming a complex is greater for diesters than for monoesters. This is shown in Table I for Series VIII and IX. The picture is further complicated by the fact that the anchor length varies depending on whether the unfluorinated part of the molecule is a dihydric alcohol or a dibasic acid.

The shortest unfluorinated diester reported to form a complex is diethyl malonate[6] with an anchor length of 9. On the other hand, the shortest unfluorinated amyl monoester forming a complex is the acetate[5] with an anchor length of 8. These results parallel our observations (Table I) made on the partially fluorinated mono- and diesters.

The data indicate that the relative effectiveness of the methylene groups in their contribution toward the minimum anchor length requirements of esters to form urea complexes depends upon whether the methylene group occurs in the alkyl or acyl part of the monoesters. In order to determine this relative contribution free of steric effects a series of ethyl esters of unfluorinated *n*-aliphatic alcohols was compared with the amyl esters for urea complex forming ability. Ethyl butyrate with an anchor length of 7 was the shortest of the ethyl esters which formed a complex. Amyl acetate[5] with an anchor length of 8 was the shortest amyl ester forming a complex. Although both had the same cross section, we observed that methylene groups more effectively enhance urea complex formation when they occur in the acyl rather than the alkyl moiety of the molecule. This same generalization may also be applied to esters containing a bulky constituent. In Table I the cross-sectional diameter of Series III and IV are the same, but larger than the cross-sectional diameter of the corresponding unfluorinated esters. When the fluorine occurred in the alkyl part of the molecule, the minimum anchor length in the acyl part necessary for complex formation was 8. Here all but one of the methylene groups occurred in the acyl part. When the fluorine occurred in the acyl part and the methylene groups in the alkyl moiety of the ester (Series V and VI, Table I), an anchor length of at least 9 was necessary for complex formation. In no case has a molecule with a maximum cross-sectional diameter in the planar zigzag conformation of over 6 Å been reported to form a urea complex. As the maximum cross-sectional diameter of the molecule in the planar zigzag conformation increases over that of an unbranched hydrocarbon (4.6 Å), a compensatory increase in anchor length is required to permit complex formation. This was also demonstrated by the work on urea complexes of alkylsilanes.[3]

Although the steric effect of fluorine predominates, this does not mean that the polar effect is

(6) R. P. Linstead and M. Whalley, *J. Chem. Soc.*, 80, 2683 (1958).

unimportant. For example, although series V and series VI (Table I) both have the same cross-sectional diameters in the planar zigzag conformation, the minimum anchor length is 10 for the latter and 9 for the former. This may be due to a change in the I effect resulting from an increase in the number of fluorine atoms in the molecule from 7 to 11.

Several methods have been previously employed to determine the relative stabilities of the urea inclusion compounds of a homologous series: the dissociation constant at a fixed temperature,[7] the measured heats of formation[2,8] for the inclusion compound, and the use of the dissociation temperatures of the inclusion compounds.[9] A fourth method which was used in our laboratory involves the use of x-ray powder diffraction data. In this and earlier[3] research it was noted (Table II) that the shortest and next to the shortest homologue which showed the characteristic interplanar spacings for complexes also showed spacings for dissociated tetragonal urea. Urea spacings were relatively stronger for the complex of the shorter homologue. Complexes of still higher homologues than these two give characteristic spacings for complex only.

Fluorinated esters containing a sufficiently long unbranched unfluorinated segment can form a urea complex. This generalization can be safely extended to molecules other than esters, *e.g.*, alcohols, acids, amines, etc., so long as the functional group does not increase the maximum cross-sectional diameter of the planar zigzag conformation beyond 6 Å.

The properties of the urea complexes of the fluorinated esters are similar to those of the unfluorinated complexes. The former have transition points[9] and x-ray powder diffraction patterns characteristic of the urea complexes of unfluorinated compounds. Both are made and decomposed in the same manner. No fluorinated ester with an anchor length of less than 7 (see Table I) formed a complex.

The applications which may be made of this technique are essentially the same as for the urea complexes of unfluorinated molecules. These applications (separation, purification, characterization, and storage) have been listed in detail elsewhere.[10]

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[CONTRIBUTION FROM THE NAVAL STORES RESEARCH STATION][1]

Preparation and Some Reactions of the Vinyl Ester of Maleopimaric Acid

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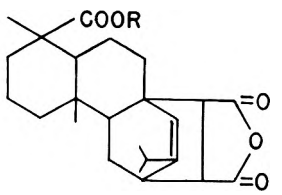
Maleopimaric acid has been vinylated. The vinyl ester has been characterized, its reactions with alcohols and cyclohexylamine have been delineated and it has been copolymerized with vinyl acetate and vinyl chloride.

Levopimaric acid, a constituent of gum oleoresin, condenses at room temperature with maleic anhydride to form the Diels-Alder addition compound[2] maleopimaric acid, 6,14-dihydrolevopimaric acid-6,14-*endo*-α,β-succinic anhydride (I). Most of the resin acids in conventional rosin react with maleic anhydride under vigorous conditions to form I.[3] There are no recorded preparations of the vinyl ester of this acid.

I R = H
II R = Vinyl
III R = Ethyl



Vinyl esters of the resin acids in rosin have been reported by Reppe.[4] Robinson[5] has prepared the vinyl esters of disproportioned and catalytically reduced rosin. Schildknecht,[6] however, states

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) R. G. R. Bacon and L. Ruzicka, *Chem. & Ind. (London)*, 546 (1936). (b) H. Wienhaus and W. Sandermann, *Ber.*, **69**, 2202 (1936).

(3) V. M. Loeblich, D. E. Baldwin, and R. V. Lawrence, *J. Am. Chem. Soc.*, **77**, 2823 (1955).

(4) Walter Reppe (to I. G. Farbenindustrie, AKF.), U. S. Patent **2,066,075**, Dec. 29, 1936.

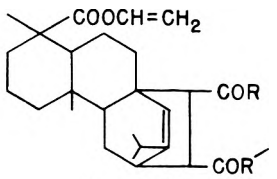
(5) J. C. Robinson, Jr. (to Hercules Powder Co.), U. S. Patent **2,615,012**, Oct. 21, 1952.

(6) C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley & Son, Inc., New York, N. Y., 1952, Chap. 5, p. 385

that high polymers have not been prepared from vinyl esters of this type. Since I is one of the few pure and cheap compounds derivable from rosin, it was of interest to determine whether the carboxyl group could be vinylated without affecting the anhydride group and further to determine whether the vinyl ester would polymerize upon initiation with a free radical catalyst.

Maleopimaric acid (I) was vinylated by the vinyl interchange reaction of Adelman[7] using vinyl acetate and a mercuric sulfate catalyst in 88% yield without affecting the anhydride group. The product, vinyl maleopimarate (II), was characterized by conversion to ethyl maleopimarate (III), a known compound,[8] by catalytic reduction.

The vinyl ester (II) was characterized further by opening the anhydride ring either with ethyl alcohol to yield a mixed ester (IV) or with cyclohexylamine to yield the cyclohexylamine salt of a cyclohexylamide (V). In both cases the vinyl group was unaffected and it was not possible to determine the direction in which the anhydride ring was opened. The ester (IV) lost ethanol and reverted to II at about 100°. Attempts to prepare dibutyl esters of II were unsuccessful using either acidic or basic catalysts. After one mole of butyl alcohol had been added to the anhydride linkage, transesterification of the vinyl group proved to be more facile than esterification of the free carboxylic acid group.



IV R = OH R = OC_2H_5
or
R′ = OC_2H_5 R′ = OH

V R = $C_6H_{11}NH$— R = $[C_6H_{11}NH_3]^+{}^-O$—
or
R′ = $[C_6H_{11}NH_3]^+{}^-O$— R′ = $C_6H_{11}NH$—

The homopolymerization of II with benzoyl peroxide in benzene or ethyl acetate solution gave a high-melting, brittle powder which was not a high polymer. Copolymerization with vinyl acetate (Table I) in ethyl acetate using benzoyl peroxide initiator gave polymers which were soluble and colorless, with film-forming properties. The melting points and brittlenesses of the copolymers increased and the intrinsic viscosities decreased as the amount of II in the copolymers increased. The vinyl maleopimarate (II) content of each copolymer was calculated from its carbon analysis and is given in Table II with the elemental analysis and vinyl maleopimarate content of the monomer charge. In all cases the copolymer contained a higher percentage of II than the monomer mixture.

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(8) M. M. Graff, *J. Am. Chem. Soc.*, **68**, 1937 (1946).

TABLE I

COPOLYMERIZATION OF VINYL MALEOPIMARATE AND VINYL ACETATE AT APPROXIMATELY 80°

	Charge[a]					
Number	Ethyl acetate, ml.	Vinyl maleopimarate, g.	Vinyl acetate, g.	Softening point, °C	Conversion, %	Intrinsic Viscosity
1	40	0	20	65	40	.577
2	40	2	20	70	70	.281
3	40	10	20	100	39	.178
4	20	10	10	110	38	.120
5	20	10	0	250	12	...

[a] Reaction time 16 hr.; initiator, 0.1 g. benzoyl peroxide per charge.

TABLE II

VINYL MALEOPIMARATE CONTENT OF VINYL MALEOPIMARATE–VINYL ACETATE COPOLYMERS AND MONOMER MIXTURES

Polymer No.	Elemental Analysis		Wt. % of Vinyl Maleopimarate	
	% C	% H	Monomer	Polymer
2	57.88	7.29	9.1	11.9
3	62.93	7.56	33.3	40.9
4	66.51	7.78	50.0	67.3

The copolymers of II with vinyl chloride (Table III) were slightly discolored, brittle and soluble powders. The melting points increased and the conversions decreased with increasing concentrations of II. The vinyl maleopimarate (II) content of each copolymer was calculated from its chlorine analysis and is given in Table IV with the chlorine analysis and vinyl maleopimarate content of the monomer charge. The copolymer compositions approximated those of the monomer mixtures.

TABLE III

COPOLYMERIZATION OF VINYL MALEOPIMARATE AND VINYL CHLORIDE AT 60°

	Charge[a]			
Polymer No.	Vinyl maleopimarate, g.	Vinyl chloride, g.	Conversion, %	Softening Point, °C.
6	0	20	61	85–90
7	3	17	35	100–110
8	10	10	13	110–120

[a] Reaction time, 24 hr.; solvent, 20 ml., tetrahydrofuran per charge; initiator, 0.2 g. benzoyl peroxide per charge.

TABLE IV

VINYL MALEOPIMARATE CONTENT OF VINYL MALEOPIMARATE–VINYL CHLORIDE COPOLYMERS AND MONOMER MIXTURES

Polymer No.	Chlorine Analysis, % Cl	Wt. % of Vinyl Maleopimarate	
		Monomer	Polymer
7	49.07	15	15.6
8	29.89	50	47.3

EXPERIMENTAL

Vinyl maleopimarate (II). The ester (II) was prepared by the method of Adelman[7] using vinyl acetate and mercuric acetate–sulfuric acid catalyst. Deviations from this procedure were in the amount of vinyl acetate used and in isolation method. Maleopimaric acid (I), $[\alpha]_D^{22}$ −24.1 (10% in acetone) m.p. 225–228° (200 g., 0.5 mole), was allowed to react with 880 ml. (9.5 moles) of vinyl acetate. After addition of the catalyst and 4 or 5 hr. agitation at 20°, I went into solution and colorless II started to crystallize. After standing 2 or more days, sodium acetate was added. Yields of 60% were obtainable by filtering at this point. The vinyl acetate was removed by stripping *in vacuo* and the pot residue treated with Norite in hot acetone (600 ml.). After the solution was filtered to remove the charcoal and cooled, the product crystallized in colorless plates. The solid was isolated by filtration and a second crop of crystals was obtained by allowing some of the acetone to evaporate. Recrystallization of the combined solids from acetone gave 187.5 g. (88%) of II, m.p. 164–165.5°, $[\alpha]_D^{24}$ −37.6 (5% in chloroform).

Anal. Calcd. for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04; hydrogenation equiv., 426.5; neut. equiv., 213.3 (in acetone), 426.5 (in ethanol). Found: C, 73.19; H, 8.19; hydrogenation equiv. (5% palladium on carbon in acetic acid), 431; neut. equiv., 213.2 (in acetone), 426.0 (in ethanol). Mercury less than 1 part per million.[9]

The reduced vinyl ester (5% palladium on carbon in glacial acetic acid) was identical with the ethyl maleopimarate of Graff.[8]

Reactions of vinyl maleopimarate (II). An ethanolic solution of II was refluxed for 1 hr. in the presence of an equimolar amount of anhydrous sodium carbonate; after filtration to remove sodium bicarbonate and concentration, a sodium salt was obtained. Titration with standard acid to a phenol red end-point and extraction with ether gave a quantitative yield of IV. The product started to melt at 60° and finally melted at 98.5°, resolidified and melted again at 164–165.5°.

Anal. Calcd. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53; hydrogenation equiv., 472.6; neut. equiv., 472.6. Found: C, 71.86; H, 8.36; hydrogenation equiv. (5% palladium on carbon in acetic acid) 472; neut. equiv. 472.0.

A sample of IV heated overnight at 56° under vacuum did not change. However at 110°, II was obtained, m.p. 164–165.5°, neut. equiv. 426.6 (in ethanol).

Refluxing ethyl alcohol was saturated with II, filtered and cooled; IV crystallized in 70% yield.

A toluene solution of II was refluxed with 2 equivalents of *n*-butyl alcohol in a flask equipped with a Dean-Stark decanter; the top of the condenser was vented through a trap containing Tollens reagent. After several hours of refluxing, no water had collected in the trap. The evolution of a minor amount of acetaldehyde was apparent from the precipitation of silver in the Tollens reagent. The mixture was allowed to cool, 2 g. of *p*-toluenesulfonic acid was added and heating was resumed. Under these conditions acetaldehyde was eliminated rapidly. No water was liberated. Identical results were obtained when chloroform was the solvent (64°). In a similar reaction using octadecanol and xylene (pot temperature 150°) with a little metallic sodium as a catalyst, no water formed. However, acetaldehyde was again liberated.

A solution of II (12.78 g., 0.03 mole) in 200 ml. of diethyl ether was treated with cyclohexylamine (8.94 g., 0.09 mole). A solid separated, which was washed with hexane to remove excess amine. Analytical data indicated that this was the cyclohexylamine salt of a cyclohexylamide (V), m.p. 139–140°.

Anal. Calcd. for $C_{38}H_{60}N_2O_5$: N, 4.48; hydrogenation equiv., 624.9; neut. equiv., 624.9. Found: N (Kjeldahl), 4.48 hydrogenation equiv. (5% palladium on carbon in acetic acid), 631; neut. equiv. (in acetone with cresol red indicator), 624.0.

Polymerization. These polymerizations were conducted in 16 oz. snap-cap bottles sealed with neoprene gaskets. The charges are given in Tables I and III. The vinyl acetate copolymers were heated without shaking on the steam bath and the vinyl chloride copolymers were prepared in a constant temperature bath. The vinyl acetate and vinyl chloride copolymers were isolated by pouring into a large volume of ether and reprecipitated, respectively, from benzene or tetrahydrofuran with pentane.

Acknowledgment. The authors wish to express their appreciation to Mr. L. E. Brown and Mrs. A. F. Cuculla, Southern Utilization Research and Development Division, New Orleans, La., for carbon and hydrogen analyses; to Mr. L. E. Brown for mercury determinations, and to Mr. M. Stark, Jr., for intrinsic viscosity determinations.

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(9) Fritz Feigl, *Qualitative Analysis by Spot Tests*, 3rd Ed., Elsevier Publishing Co., New York, N. Y., 1946, p. 49.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, QUEEN'S UNIVERSITY]

Preparation and Certain Physical Properties of Some Plant Steryl Esters[1,2]

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The even numbered C_2-C_{22} saturated and some C_{18} unsaturated fatty acid esters of β- and γ-sitosterol, stigmasterol, their saturated analogs, and ergosterol were prepared by treating the corresponding acid chloride or anhydride with the sterol in the presence of pyridine in an inert solvent. Adsorption chromatographic purification of the steryl esters was essential if contamination with free sterols was to be avoided. In all cases the melting points of the esters were relatively sharp and decreased with increasing molecular weight of the fatty acid till a minimum was reached in the myristate-palmitate region, after which they increased. The introduction of a double bond into the fatty acid residue produced a 37 to 45° drop in the melting point when compared with the corresponding saturated ester. Additional double bonds brought about a further decrease but of lower magnitude. During melting the anisotropic solids were observed to change cleanly into isotropic liquids, and the temperature range required for this transformation broadened with increasing chain length of the fatty acid. Only the temperatures at which the samples became completely liquid and the polarized light field dark were reproducible. Little evidence was obtained for the formation of any other well defined and discrete transition states. A number of possibilities that might account for the hitherto reported mesomorphic behavior of steryl esters of long chain fatty acids are discussed. The specific rotations of the esters decreased with lengthening of the fatty acid chain; the molecular rotations remained essentially constant; and unsaturation of the fatty acid moiety had little or no effect. With the exception of the steryl esters of the lower fatty acids, these physical constants could not be used for a reliable identification of these compounds. The construction of a special heating stage for use in conjunction with a polarizing microscope is described in detail.

The isolation[3] of relatively large quantities of mixed plant steryl esters from the molecular distillates of corn oil appeared to offer an excellent opportunity for the study of this little known lipid class. Previous studies on the unsaponifiable matter of corn oil had revealed the presence of a complex mixture of plant sterols from which stigmasterol, β- and γ-sitosterol and their saturated analogs had been isolated.[4] The presence of ergosterol had been implied on the basis of the ultraviolet absorption spectrum of corn oil.[5] Though it could be readily demonstrated[3] that the ester mixture was made up of different fatty acid esters of several of these sterols, the absence of suitable means for their fractionation prevented the isolation and identification of any individual compounds. To facilitate the development of such means for the separation and possible identification of these esters, it was necessary that a number of reference compounds of unquestionable purity be prepared and their physical and chemical characteristics determined.

Although the acetates, benzoates, and dinitrobenzoates of these sterols are readily prepared and purified, and their physical properties well known, only rarely have the longer chain fatty acid esters of the plant sterols been prepared synthetically[6] or isolated from natural sources[7] and their properties studied. An examination of the esterification methods, such as fusion,[6b,8] heating in a closed vessel,[6d] strong acid catalysis,[9] and acid chloride alcoholysis in pyridine solution,[8c,9b,10] used for the syntheses of the few known plant steryl and the more frequently studied cholesteryl long chain fatty acid esters, indicated that significant modifications in the existing techniques would have to be made if maximum yields of high purity products were to be obtained.

From this survey it also became obvious that much of the present uncertainty[9b,11] in the physical properties of the steryl esters in general was due either to the use of unsuitable methods for their

(1) Presented in part before the Canadian Federation of Biological Societies, Second Annual Meeting, Toronto, Ontario, June, 1959. For an abstract, see A. Kuksis, *Proc. Can. Fed. Biol. Soc.*, **2**, 37 (1959).

(2) Supported in part by a research grant from the Nutrition Foundation, Inc.

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(9) (a) E. L. Cataline, L. Worrell, S. F. Jeffries, and S. A. Aronson, *J. Am. Pharm. Assoc.*, **33**, 107 (1944); (b) D. Kritchevsky and M. E. Anderson, *J. Am. Chem. Soc.*, **74**, 1857 (1952).

(10) L. Swell and C. R. Treadwell, *J. Biol. Chem.*, **212**, 141 (1955).

(11) (a) C. E. Bills, *The Vitamins*, W. H. Sebrell, Jr., R. S. Harris, eds., Academic Press, Inc., New York, N. Y., 1954, Vol. 2, p. 183 ff.; (b) G. W. Gray, *J. Chem. Soc.*, 3733 (1956).

preparation or to incomplete subsequent purification or to both. Thus, in addition to the large discrepancies noted in some of the physical constants, it has been reported that the melting points of the long chain saturated cholesteryl esters decrease[10,11b,12] or increase[15] with increasing chain length of the fatty acid, and that some[8c,14] or all[11b,15] show mesomorphic transition states. Extended turbidity phases have also been observed[6c,8a] for some saturated fatty acid esters of plant sterols. In the case of the unsaturated fatty acid esters the situation has been equally confusing. Thus, Labarrere *et al.*[13] reported that the melting point of cholesteryl oleate was about 33° below that of the stearate, and that additional unsaturation decreased it still further. Page and Rudy[8c] and Bladon,[12] however, listed for cholesteryl linolenate a melting point higher than either that for oleate or linoleate, with an isotropic transition point approaching that for the stearate. The unsuitability of thionyl chloride for the preparation of unsaturated fatty acid chlorides now appears to be generally recognized[10,15] yet oxalyl chloride as commonly employed may also cause difficulties. For instance, Klein and Janssen[16] noted that the arachidonate ester of cholesterol prepared using the oxalyl chloride method of Wood *et al.*[17] gave low recoveries on adsorption chromatography, while the recoveries of natural arachidonate esters were considerably higher under the same chromatographic conditions. It is difficult to evaluate the significance of these reports, since the purity of the starting materials employed has seldom been defined.

In order to contribute to a more satisfactory knowledge of the physical and chemical properties of this class of compounds the original study was extended beyond the limited needs of our particular problem to include all the even numbered C_2-C_{22} saturated and the C_{18} unsaturated fatty acid esters of the corn oil sterols mentioned above. In developing improved techniques for the syntheses and purification of these compounds, recent observations on the preparation of acid chlorides in solution,[18] the beneficial effect of inert solvents on the esterification with acid chlorides and pyridine,[19] and the adsorption chromatographic behavior of steryl esters[20] have been extensively utilized.

RESULTS AND DISCUSSION

Starting materials. The difficulty of obtaining high quality starting material for the preparation of pure steryl esters can be readily appreciated. Both sterols and long-chain fatty acids are notoriously difficult to purify because of the similar physical and chemical characteristics of isomers and near homologs. Melting point depressions are often small and optical rotation differences slight. These criteria of purity, often unreliable, have been supplemented in this work by chromatography and spectrophotometry.

Using such means all the fatty acids, with the exception of linolenic acid, which contained minor amounts of *trans* and conjugated isomers and some linoleic acid, were demonstrably of high purity. The purity of ergosterol was verified by ultraviolet absorption measurements. The preparation of the acetate tetrabromide served to ensure the uniformity of stigmasterol. The β-sitosterol isolated from cottonseed oil, shown by Wallis and Chakravorty[21] to be almost free from other sterols, was considered sufficiently reliable.

No methods of a similar nature were available for double checking the purity of the γ-sitosterol preparations. Even the physical constants attributed to this sterol have been questioned by several workers. Thus, a comparison[22] of the molecular rotation differences of the γ-sitosterol derivatives with those obtained for the corresponding derivatives of cholesterol and stigmasterol shows considerable discrepancies. As a result it has been suggested that either γ-sitosterol is not the C_{24} epimer of 22,23-dihydrostigmasterol, or, more likely, that the preparations thus far obtained have been contaminated with a more levorotatory component such as 22,23-dehydro-γ-sitosterol. A compound giving molecular rotations corresponding approximately to those expected for a C_{24} epimer of β-sitosterol has been recognized[22] in the clionasterol isolated from sponges, and a recent review[12] on the chemistry of sterols lists for γ-sitosterol the constants of clionasterol. Further complicating the problem is the question of the correct molecular weight. On the basis of the recently observed[23] slightly greater polarity of γ-sitosterol in reversed phase partition systems, where there supposedly should not be any significant

(12) P. Bladon, *Cholesterol*, R. P. Cook, ed., Academic Press, Inc., New York, N. Y., 1958, p. 15 ff.

(13) J. A. Labarrere, J. R. Chipault, and W. O. Lundberg, *Anal. Chem.*, **30**, 1466 (1958).

(14) G. Friedel, *Ann. phys.*, **17**, 273 (1922).

(15) O. Lehmann, *Z. phys. Chem.*, **56**, 750 (1906).

(16) P. D. Klein and E. T. Janssen, *J. Biol. Chem.*, **234**, 1417 (1959).

(17) T. R. Wood, F. L. Jackson, A. R. Baldwin, and H. E. Longenecker, *J. Am. Chem. Soc.*, **66**, 287 (1944). Since the halogenation proceeds *via* the anhydride, 2.5 moles of oxalyl chloride are required per mole of acid.

(18) C. G. Youngs, A. Epp, B. M. Craig, and H. R. Sallans, *J. Am. Oil Chemists' Soc.*, **34**, 107 (1957).

(19) J. A. Mills, *J. Chem. Soc.*, 2332 (1951).

(20) (a) D. L. Fillerup and J. F. Mead, *Proc. Soc. Exptl. Biol. Med.*, **83**, 574 (1953); (b) E. J. Barron and D. J. Hanahan, *J. Biol. Chem.*, **231**, 493 (1958).

(21) E. S. Wallis and P. N. Chakravorty, *J. Org. Chem.*, **2**, 335 (1937).

(22) W. Bergmann and E. M. Low, *J. Org. Chem.*, **12**, 67 (1947).

(23) (a) H. Sulser and O. Hoegl, *Mitt. Gebiete Lebensm. u. Hyg.*, **48**, 245 (1957); (b) J. C. Riemersma and W. Stoutjesdijk, *Mitt. Gebiete Lebensm. u. Hyg.*, **49**, 115 (1958).

differences between truly epimeric pairs, it has been suggested[23b] that γ-sitosterol might not be the C_{29} system as presently believed,[24] but possibly a C_{28} compound as implied earlier.[25] This difference in the molecular weight, though accounting for the greater mobility and explaining a number of other observations,[26] would still not bring the molecular rotation differences for γ-sitosterol and derivatives into line with those for other sterols.

The possibility that γ-sitosterol isolations might have resulted in a product contaminated with some higher melting and more levorotatory component, such as 22,23-dehydro-γ-sitosterol, as suggested by Bergmann and Low,[22] or even stigmasterol, is quite probable in view of the relatively recent recognition[27] of the failure of the Windaus-Hauth process,[28] as commonly conducted, to remove all the 22,23-dehydrosterol. The use of exhaustive acetate tetrabromide precipitations or the insolubilization of stigmasterol[29] and possibly any other 22,23-dehydrosterols as their α-naphthyl carbamates, should then produce γ-sitosterol preparations with lower melting points and less negative optical rotations. In the preparations described in the present experiments conducted with the above considerations in mind, lower melting and less levorotatory samples were in fact obtained. These γ-sitosterol preparations, however, though almost identical with clionasterol in specific rotations, differed significantly from it in the melting points, and agreed fairly closely in such constants with certain descriptions of γ-sitosterol.[4,30]

In the procedures used for the isolation of γ-sitosterol, which were based on the work of Bonstedt[31] and Dirscherl and Nahm,[32] and were carried out on material freed from stigmasterol by exhaustive precipitation of the acetate tetrabromides, the α-naphthyl carbamates, or both, additional improvements were introduced. Among these the most important was believed to be the preliminary removal of the difficultly soluble campesterol by the method of Fernholz and MacPhillamy.[33] Paper partition[23a] and adsorption chromatographic techniques[30,34] capable of some degree of segregation of sterol mixtures served as a further check on the uniformity of the final sample.

As a result of a careful application of the above methods and a failure to demonstrate any residual 22,23-*trans* unsaturation in the γ-sitosterol preparations by an infrared assay,[27b] it was concluded that the physical constants obtained would not necessarily represent material contaminated with the 22,23-dehydrosterols, but might be those of the pure compound. This belief is strengthened by the observation that numerous isolations of γ-sitosterol from a wide variety of plant and marine invertebrate sources[35] performed since the contamination was first suggested have resulted in preparations with closely similar physical constants, which, however, differed greatly from clionasterol in melting points. It would be difficult to imagine that all of these preparations could have been contaminated with the same 22,23-dehydrosterols and in about the same proportions.

Preparation of steryl esters. The preparation of low molecular weight fatty acid esters of sterols proceeds readily and the high reactivity of the fatty acids and their derivatives commonly employed in esterifications ensures an almost quantitative yield under most conditions. Esterifications with the relatively inert longer chain fatty acids and their derivatives, however, require the presence of catalysts and elevated temperatures and even then only moderate yields are obtained.[6b,6d,8a,8c,9a] The undesirable side effects (isomerization, dehydration, polymerization, etc.) exercised upon the starting materials and the final products by such catalysts and high temperatures, prohibit the utilization of these techniques in the preparation of high purity compounds.

The use of more reactive fatty acid derivatives such as the acid chlorides has permitted the application of lower temperatures[36,9b,10] resulting in higher yields of better quality products. While this method gives excellent results with stable

(24) C. W. Shoppe, *Chemistry of the Steroids*, Butterworths Scientific Publications, Ltd., London, 1958, p. 63.

(25) H. Sandqvist and E. Bengtsson, *Ber.*, **64**, 2169 (1931).

(26) For a discussion and repudiation of this possibility, see K. Bonstedt, *Z. physiol. Chem. Hoppe-Seyler's*, **205**, 137 (1932).

(27) (a) R. Neu and P. Ehrbacher, *Arch. Pharm.*, **283**, 227 (1950); (b) J. L. Johnson, M. F. Grostic, and A. O. Jensen, *Anal. Chem.*, **29**, 468 (1957).

(28) A. Windaus and A. Hauth, *Ber.*, **39**, 4378 (1906).

(29) J. A. Campbell, O. H. Shepherd, B. A. Johnson, and A. C. Ott, *J. Am. Chem. Soc.*, **79**, 1127 (1957).

(30) Hung-Shuin Ting, Yu Wang, Wei-Yi Ting, and Yao-Tseng Huang, *Hua Hsüeh Hsüeh Pao*, **22**, 288 (1956); *Chem. Abstr.*, **52**, 6463f.

(31) K. Bonstedt, *Z. physiol. Chem. Hoppe-Seyler's*, **176**, 269 (1928).

(32) W. Dirscherl and H. Nahm, *Ann.*, **555**, 57 (1944); **558**, 231 (1947).

(33) E. Fernholz and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **63**, 1155 (1941).

(34) (a) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953); (b) A. Weizmann, A. Meisels, and Y. Mazur, *J. Org. Chem.*, **20**, 1173 (1955).

(35) (a) C. Djerassi, M. Gorman, A. L. Nussbaum, and J. Reynoso, *J. Am. Chem. Soc.*, **76**, 4463 (1954); (b) T. Matsumoto and T. Tamura, *Nippon Kagaku Zasshi*, **76**, 951 (1955); *Chem. Abstr.*, **51**, 18356*h*; (c) R. N. Chakravarty, D. Chakravarty, M. N. Mitra, B. Dasgupta, and P. C. Maiti, *J. Sci. Ind. Research (India)*, **15C**, 86 (1956); (d) M. Dymicky and R. L. Stedman, *Tobacco*, **148**, 48 (1959); (e) T. Tsukamoto, I. Nishioka, K. Mihashi, and H. Miyara, *Yakugaku Zasshi*, **78**, 1099 (1958); *Chem. Abstr.*, **53**, 5337*g*; (f) S. R. Bhattacharjee and D. K. Mullick, *Sci. and Culture (Calcutta)*, **24**, 293 (1958).

(36) E. Abderhalden and K. Kautsch, *Z. physiol. Chem. Hoppe-Seyler's*, **65**, 69 (1910).

materials, the preliminary treatment with the acid chloride, and the excess pyridine, usually used as solvent, present difficulties when working with acid sensitive compounds. The fatty acid anhydrides are also more reactive than the free acids themselves, but hitherto only those of the lower fatty acids have been widely employed.[6a,6c,8c,10,11b]

Since the anhydrides are known[37] to be the mildest esterifying agents, they appeared to be particularly suited for the esterification of such acid sensitive sterols as ergosterol.[11a,38] Experimentation with these under a variety of conditions[39] indicated that their reactivity decreased progressively with increasing molecular weight. Thus, while the acetic to caproic acid anhydrides gave yields varying from quantitative to 70% when refluxed for one hour in a benzene solution with a trace of pyridine, caprylic to lauric acid anhydrides under similar conditions gave only 30 to 40% yields. Palmitic, stearic, arachidic, and behenic acid anhydrides appeared almost completely inert at the boiling point of benzene. At higher temperatures (boiling toluene or xylene) they were observed to produce the steryl esters in about the same yields as with the free fatty acids. This latter observation suggests that the esterification of the sterols by the free acids probably proceeds through the anhydrides which are continuously formed under the dehydrating conditions prevailing at elevated temperatures. These observations on the behavior of the long chain fatty acid anhydrides in sterol esterification are in line with certain accounts[40] of the behavior of these compounds towards water and aqueous alkali, which decompose them only with difficulty.

The lack of success with the long chain acid anhydrides led us to use the acid chlorides. For the elimination or at least reduction of the acid effect during esterification with acid chlorides, it was found profitable to perform the reaction in an inert solvent, such as benzene or toluene. These solvents precipitate most of the pyridine hydrochloride as soon as it is formed, and suppress the ionization of the rest. Mills[19] suggested this modification as an essential prerequisite for a successful esterification of a number of labile alcohols. Utilization of inert solvents is advantageous also when acid sensitivity is not a problem. In such cases the use of polar chlorocarbon solvents (*e.g.*, chloroform, ethylene chloride) which promote the reaction by immediately dissolving the reactants may result in improved yields and purer products. The use of such solvents may be advantageously combined with the preparation of acid chlorides in solution,[18] utilizing either phosphorus pentachloride for saturated acid chlorides or oxalyl chloride for unsaturated acid chlorides.

The ergosteryl esters were the most difficult to prepare. While the acetate and butyrate could be prepared in reasonable yields in the cold or at room temperature by treating the free sterol with the corresponding anhydride in the presence of pyridine, the higher esters had to be made by going through the acid chlorides. When the caproic, caprylic, and capric acid chlorides were allowed to react overnight with ergosterol at room temperature in the presence of the calculated amount of pyridine, yields of 70, 40, and 30%, respectively, were obtained. These yields could be further improved by extending the time of reaction to about three days. The ergosteryl esters of the longer chain fatty acids could not be made in satisfactory yields under these conditions. Heating was necessary, and it was accompanied by some destruction and isomerization of the sterol as indicated by the discoloration of the reaction products. The highest yields (50–70%) with the least destruction were obtained by performing the reaction in boiling benzene for up to thirty minutes under nitrogen. The preparation of the saturated fatty acid esters of the other sterols under similar conditions presented little difficulty, yields of 70 to 95% being obtained. The use of the higher boiling solvents such as toluene and xylene appeared to give somewhat higher yields with the saturated C_{16}, C_{18}, C_{20}, and C_{22} acid chlorides. The preparation of the unsaturated fatty acid esters in all cases required special care, and it was necessary to choose between a fair yield of a partially degraded product and a poor yield of a somewhat better product. The use of benzene to ensure the continuous removal of the pyridine hydrochloride formed and a short period of heating appeared to provide an acceptable compromise. Esterifications performed at temperatures lower than that of boiling benzene gave impractical yields.

The purification of the esters by recrystallization from the common organic solvents generally employed to free them from unchanged starting materials and by-products of the reaction was found to be unsatisfactory. The removal of the free sterols was particularly difficult, as they possess solubilities closely similar to those of their long chain fatty acid esters in these solvents. Recrystallization from glacial acetic acid has been described[11b] with apparently successful results. Since the sterols are very readily[34a] esterified by this reagent the final product is liable to be contaminated with the acetic acid ester. Samples giving no immediate precipitation with digitonin,[41] as commonly tested, could be demonstrated to contain residual free sterol when subjected to chromatography. The addition of aluminum chloride[42] to such test

(37) K. Kulka, *Am. Perfumer*, **51**, 141, 251, 253, 255, 342 (1948).

(38) (a) C. E. Bills and W. M. Cox, *J. Biol. Chem.*, **84**, 455 (1929); (b) C. E. Bills and F. G. McDonald, *J. Biol. Chem.*, **88**, 337 (1930).

(39) A. Kuksis and J. M. R. Beveridge, unpublished results.

(40) (a) D. Holde and R. Gentner, *Ber.*, **58B**, 1424 (1925); (b) N. O. V. Sonntag, J. R. Trowbridge, and I. J. Krems, *J. Am. Oil Chemists' Soc.*, **31**, 151 (1954).

TABLE I

CERTAIN PHYSICAL PROPERTIES OF SOME β-SITOSTERYL ESTERS

Ester	Method of Preparation[a]	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$[b] Obsd.	Specific Rotations, $(\alpha)_D$[b] Lit.	Specific Rotations, $(\alpha)_D$[b] Calcd.	Molecular Weights[c] Obsd.	Molecular Weights[c] Calcd.
Acetate	1A	98	125	127 [44][d]	−41	−42 [44]	−42 [44]	450	457
Butyrate	1A	95	111	93 [6][e]	−40		−39.6		485
Caproate	2B	95	105.5		−38		−37.5	520	513
Caprylate	2B	95	99		−36		−35.5	535	541
Caprate	2B	80	92		−33		−33.8	580	569
Laurate	2B	82	84		−31		−32.2		597
Myristate	2C	85	86.5		−30		−30.8	630	625
Palmitate	2C	80	85.5	83.5 [7][e]	−28	−7.3 [7][e]	−29.4		653
Stearate	2C	80	89	89 [7][e]	−28		−28.2	685	681
Oleate	2B	70	52	39 [6][e]	−28		−28.3		679
Linoleate	2B	60	43		−28		−28.4	670	677
Linolenate	2B	60	36		−28		−28.5	670	675
Arachidate	2D	65	92		−27		−27.2		709
Behenate	2D	65	95		−27		−26.1	745	737

[a] Methods 1 and 2 as described in the text: A refers to benzene used as solvent, room temperature, and an overnight reaction time. B refers to boiling benzene and 60- and 30-min. reaction times for the anhydrides and chlorides, respectively. C refers to boiling toluene and a 30-min. reaction time. D refers to boiling xylene and a 30-min. reaction time. [b] Specific rotations calculated from acetates by Tschugaeff's method. [c] Molecular weights of the esters synthesized were calculated from their saponification equivalents determined by standard methods. [d] Numbers in brackets indicate references.

TABLE II

CERTAIN PHYSICAL PROPERTIES OF SOME γ-SITOSTERYL ESTERS[a]

Ester	Method of Preparation	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$ Obsd.	Specific Rotations, $(\alpha)_D$ Lit.	Specific Rotations, $(\alpha)_D$ Calcd.	Molecular Weights Obsd.	Molecular Weights Calcd.
Acetate	1A	90	140	144[44]	−43	−45[44]	−45[44]	449	457
Butyrate	1A	90	121.5				−42.4		485
Caproate	2B	90	114.5				−40.0	520	513
Caprylate	2B	92	108		−39		−38.0		541
Caprate	2B	85	101				−36.2		569
Laurate	2B	75	95				−34.4		597
Myristate	2B	75	91				−32.9		625
Palmitate	2B	77	95		−30		−31.5	641	653
Stearate	2C	79	98				−30.2		681
Oleate	2B	63	55				−30.3		679
Linoleate	2B	55	51		−30		−30.4		677
Linolenate	2B	51	39				−30.5		675
Arachidate	2D	63	101		−28		−29.0	701	709
Behenate	2D	61	104				−27.9		737

[a] See notes at the foot of Table I.

solutions improved the sensitivity, but when sufficient ester was present, the water in the aqueous reagents caused its partial precipitation. Purification of the esters on silica or alumina columns was found to be essential. This permitted the removal of any nonpolar by-products, free sterols, and any peroxidized material formed during the esterification.

Performance of the esterification in the less polar solvents such as benzene or toluene or their mixtures with petroleum ether had also certain advantages for subsequent purification. When excessive amounts of pyridine were avoided, and the cooled reaction mixture poured on to the adsorbent column, all the pyridine was immobilized as its difficultly soluble hydrochloride or the unchanged acylpyridinium chloride at the top. The use of appropriate dilutions of benzene or ethyl ether in petroleum (b.p. 60–80°) removed selectively the desired reaction mixture component. Such an esterification in an inert solvent combined with the preparation of the acid chloride in solution, and followed by a direct adsorption chromatographic fractionation of the total reaction mixture, avoids unnecessary handling and time-consuming processing of the materials through distillations, washings, dryings, and numerous recrystallizations. Adsorption chromatographic methods for the purification of

(41) The steryl ester preparations were tested for the presence of free sterol by treating up to 10 mg. of the material dissolved in 5 cc. of acetone-ethanol (1:1) with a few drops (1 cc. max.) of 1% digitonin in ethanol-water (1:1). If no turbidity developed within a few hours 1 drop of a 30% aqueous solution of aluminum chloride hexahydrate[42] was added.

(42) H. H. Brown, A. Zlatkis, B. Zak, and A. J. Boyle, *Anal. Chem.*, 26, 397 (1954).

TABLE III

CERTAIN PHYSICAL PROPERTIES OF SOME STIGMASTERYL ESTERS[a]

Ester	Method of Preparation	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$ Obsd.	Specific Rotations, $(\alpha)_D$ Lit.	Specific Rotations, $(\alpha)_D$ Calcd.	Molecular Weights Obsd.	Molecular Weights Calcd.
Acetate	1A	95	142	144[44]	−54	−56[44]	−56[44]	462	455
Propionate[b]				122[28]					
Butyrate	1A	90	123	113[6c]	−53		−52.8		483
Caproate	2B	95	115		−51		−49.9	497	511
Caprylate	2B	93	112		−48		−47.3		539
Caprate	2B	91	106		−46		−44.9		567
Laurate	2B	73	102.5		−44		−42.8	600	595
Myristate	2B	71	101.5		−41		−40.9		623
Palmitate	2B	74	99.5	99[6b]	−41		−39.2	638	651
Stearate	2B	70	102	101[6b]	−39		−37.6		679
Oleate	2B	57	57	44[6b]	−39		−37.7		677
Linoleate	2B	54	50.5				−37.8		675
Linolenate	2B	49	38				−37.9		673
Arachidate	2D	63	104		−37		−36.1	693	707
Behenate	2D	67	106		−35		−34.7		735

[a] See notes at the foot of Table I. [b] Included for comparison.

TABLE IV

CERTAIN PHYSICAL PROPERTIES OF SOME STIGMASTANYL ESTERS[a]

Ester	Method of Preparation	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$ Obsd.	Specific Rotations, $(\alpha)_D$ Lit.	Specific Rotations, $(\alpha)_D$ Calcd.	Molecular Weights Obsd.	Molecular Weights Calcd.
Acetate	2B	99	136	138[44]	+13.3	+14[44]	+14[44]		459
Butyrate	2B	87	117				+13.2	500	487
Caproate	2B	84	109		+12.7		+12.5		515
Caprylate	2B	86	102		+12		+11.8		543
Caprate	2B	83	96				+11.2	557	571
Laurate	2C	80	91		+10		+10.7		599
Myristate	2C	77	89.5		+10		+10.2	613	627
Palmitate	2C	74	90.5				+9.8		655
Stearate	2D	76	92				+9.4		683
Oleate	2B	67	53		+9.5		+9.45	667	681
Linoleate	2B	59	48				+9.5		679
Linolenate	2B	47	42				+9.53		677
Arachidate	2D	62	95		+8.5		+9.05	706	711
Behenate	2D	53	98		+8.5		+8.7		739

[a] See notes at the foot of Table I.

steryl ester preparations have been used occasionally[43] before, but apparently it has not been generally appreciated that some such technique is essential to ensure removal of free sterol.

The methods used and the yields obtained in the preparation of the individual steryl esters together with the molecular weights calculated from the saponification equivalents determined are listed in Tables I–VI.

Properties of steryl esters. The melting points and the specific rotations of the steryl esters prepared are recorded in Tables I–VI. For the esters described previously the reported values are given for comparison. Since on heating, the crystalline steryl esters, because of their large and flat molecules, cannot pass into the isotropic state with a suddenness characteristic of the sharp melting low molecular weight compounds, but retain a considerable degree of order during the early stages of melting, difficulty is experienced in ascertaining the temperature at which this material starts to melt. After numerous observations it was noted that the most reliable temperature to record was that at which the material became fully liquid and the field of polarized light dark. These isotropic transitions were reproducible and the corresponding temperatures represent the melting points in the above tables. The rate of heating was critical, rapid rates giving lower melting points. For all steryl esters these melting points decreased with increasing molecular weight of the saturated fatty acids, until a minimum was reached in the myristate-palmitate region, after which the melting points tended to increase. For the esters of the β- and γ-sitosterols and of their saturated analogs the minima in the melting point curves were located at the myristates, while for the

(43) (a) R. O. Clinton, H. C. Neumann, S. C. Laskowski, and R. G. Christiansen, *J. Org. Chem.*, **22**, 473 (1957); (b) D. Gould, L. Finckenor, E. B. Hershberg, J. Cassidy, and P. L. Perlman, *J. Am. Chem. Soc.*, **79**, 4472 (1957).

TABLE V

CERTAIN PHYSICAL PROPERTIES OF SOME γ-SITOSTANYL ESTERS[a]

Ester	Method of Preparation	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$ Obsd.	Specific Rotations, $(\alpha)_D$ Lit.	Specific Rotations, $(\alpha)_D$ Calcd.	Molecular Weights Obsd.	Molecular Weights Calcd.
Acetate	2B	93	139	144[44]	+12	+10[44]	+10[44]	451	459
Butyrate	2B	91	120		+10.3		+9.4	482	487
Caproate	2B	90	112.5		+9.5		+8.9		515
Caprylate	2B	89	104.5				+8.5		543
Caprate	2C	77	97		+7.5		+8.0		571
Laurate	2C	75	92		+7.5		+7.7	607	599
Myristate	2C	73	90				+7.3		627
Palmitate	2C	75	93				+7.0		655
Stearate	2C	69	96		+7.0		+6.7	693	683
Oleate	2B	70	52		+6.5		+6.75		681
Linoleate	2B	61	44				+6.8		679
Linolenate	2B	57	39				+6.83		677
Arachidate	2D	76	101		+6.0		+6.45		711
Behenate	2D	78	103				+6.2	747	739

[a] See notes at the foot of Table I.

TABLE VI

CERTAIN PHYSICAL PROPERTIES OF SOME ERGOSTERYL ESTERS[a]

Ester	Method of Preparation	Yield, %	M.P., ° Obsd.	M.P., ° Lit.	Specific Rotations, $(\alpha)_D$ Obsd.	Specific Rotations, $(\alpha)_D$ Lit.	Specific Rotations, $(\alpha)_D$ Calcd.	Molecular Weights Obsd.	Molecular Weights Calcd.
Formate[b]				161.5[6a]		−97.9[6a]			
Acetate	1A	95	177	181[11]	−88	−90[44]	−90[11]		439
Butyrate	1A	90	134	129.5[6a]	−85		−84.7	451	467
Isobutyrate[b]				162[6c]		−84[6c]			
Isovalerate[b]				160[6c]		−82[6c]			
Caproate	1B	75	125.5				−79.8		495
Caprylate	1B	65	121		−80		−75.5	505	523
Caprate	1B	50	117.5				−71.7	550	551
Laurate	2B	70	116				−68.3		579
Myristate	2B	70	115		−67		−65.2	619	607
Palmitate	2B	72	110	107[7b]		−50.0[7b]	−62.2		635
Stearate	2B	60	113	110.5[7d]	−59	−53.4[7d]	−59.3	655	663
Oleate	2B	50	68	42[6c]			−59.7	647	661
Linoleate	2B	40	58		−58		−60.0		659
Linolenate	2B	40	47				−60.3		657
Arachidate	2C	50	116		−58		−57.2	703	691
Behenate	2C	50	115				−55.0		719

[a] See notes at the foot of Table I. [b] Included for comparison.

esters of the higher melting sterols (stigmasterol and ergosterol) the minima were at the palmitates. The decrease in the melting point per ethylene unit varied within an ester series and from one series to the other, but in all cases it was found to diminish progressively as the minimum was approached, after which there was a smaller but regular increase. The oleates melted 37 to 45° lower than the corresponding stearates and the introduction of additional double bonds in the fatty acid part of the steryl ester brought about further though considerably smaller lowering in the melting point.

In the cholesteryl ester series, Labarrere *et al.*[13] observed the minimum at myristate, after which the melting points increased regularly by about 5° per each ethylene unit added. Their observations were limited to the sequence laurate, myristate, palmitate, and stearate. They also reported the oleates to melt about 33° lower than the stearates, and each additional double bond was observed to lower the melting point by another 7°. The contamination of the linolenates with the linoleates in the present preparations did not permit such an exact evaluation of the effect of unsaturation upon the melting behavior of these series of steryl esters. The isotropic transition points reported by Gray[11b] for the complete series of the lower cholesteryl esters, however, indicate considerably more variation in the melting points and include a maximum at the acetate, a minimum at the caproate, and another maximum at the caprylate after which a progressive decrease was observed with the palmitates and the stearates having the same and the lowest isotropic transition points. In addition, a variety of other well defined transition states and temperatures corresponding to the smectic and nematic or cholesteric phases have been reported for cholestryl esters.[8a,11b,14,15] In the present investigation no such

definite and discrete mesomorphic transition states were observed. Though the alcohol parts of the esters are different it is doubtful whether one would be dealing here with a new phenomenon.

It appears very likely that the cholesteryl[8a,14,15] and other steryl[8a,8g] esters in which the mesomorphic melting transformations were first noted were impure. Recently, however, Gray[11b] was able to confirm these observations to some extent, and explained any differences in terms of purity of the samples and the conditions of examination. It is unfortunate that this report does not indicate the sources and properties of the starting materials and that the final products were characterized only by carbon and hydrogen analyses. Evidently the transition temperatures varied with impurity as the author continued the recrystallizations of the esters from glacial acetic acid and ethanol until these became constant.

When the rather sharply melting esters prepared in the present study were combined in various proportions, the mixtures melted over a wider range of temperatures, often with irregularities characteristic of the mesomorphic transitions, and with or without an actual change in the isotropic transition point of the major component. Similar effects have also been observed with other long chain compounds. Small amounts of octadecane have been found to cause the formation of two crystalline forms in hexadecane.[44] It may be of interest to note that the presence of a homolog has been reported to stabilize the metastable form of higher alcohols and nitriles.[45,46] Furthermore, work on the dimorphism of long chain secondary amines has shown that the relative stabilities of the polymorphic forms are influenced by extremely small amounts of impurities.[47] This influence of traces of contaminants on the polymorphic behavior of long chain compounds[48] raises the question whether even some of the supposedly well established observations upon the meso- and polymorphic states of pure compounds may actually relate to the behavior of mixtures.[48a] In the sterol series this dramatic effect of foreign material upon the melting point is particularly exaggerated. Thus, besides the esters, there have been described several loose combinations, for example, of ergosterol with glycerol, orcinol, urea, and substituted ureas, all of which exhibit more or less extended turbid phases in their melting.[8b] The possibility has also been expressed that the phenomenon of mesomorphism might be related to the turbidity associated with moisture.[11a] This latter effect is particularly pronounced when the melting points are determined under conditions where the escape of water is hindered, *e.g.* sealed capillaries.[6c] Since many of the compounds exhibiting mesomorphism are also easily oxidized, the impurity necessary for the stabilization of these transition states may come from air oxidation of the sample during melting. Melting points taken in evacuated capillaries have been demonstrated to result in sharp transitions.[34a]

Dr. Gray very kindly examined samples of β-sitosteryl laurate and myristate provided by us and also found that they melted sharply passing directly into the isotropic phase without going through any mesomorphic transition state. On cooling (including rapid chilling), however, though sometimes the melts crystallized directly, Dr. Gray was able to detect a mesophase resembling the smectic state, which was monotropic with respect to the crystals. That is, the mesomorphic-isotropic transition occurred at a temperature below the melting point of the crystals. Jaeger[8a] also noted that equilibrium disturbances such as sudden cooling of the sample facilitated the observation of certain mesomorphic transitions. In view of the above mentioned possibility of air oxidation, particularly on repeated remelting of the sample, the transitions observed on cooling should be viewed with caution. It may be further noted that neither the instrument of Gray[49] nor that described here may have been capable of recording the true transition temperatures. Thus, the reversion of the smectic state formed on cooling, to the isotropic, on raising the temperature again, may not be said with certainty to have taken place at the corresponding block temperature, as the melt may not have been in equilibrium with it. It is well known that when supercooled melts crystallize, the temperature immediately rises to the true melting or freezing point. In these apparatuses such a rise in temperature within the sample alone could not be determined. The rising temperature bringing about the reversion may have provided little more than a disturbance of the metastable supercooled melt.

The specific rotations decreased slightly with increasing molecular weight of the fatty acid residue, and the molecular rotations remained essentially constant. The introduction of unsaturation into the fatty acid moiety had little or no effect on the rotation. Similar observations have been made before[10,13] in the cholesteryl ester series and are in agreement with theory.[50] The measurements, however, were not sufficiently accurate to distinguish between the hypothesis of Tschugaeff[50a] and of Gerson.[50b] As a result of the high purity of the start-

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(48) (a) A. W. Ralston, *Fatty Acids and Their Derivatives*, John Wiley & Sons, New York, N. Y., 1948, p. 322 ff.; (b) G. H. Brown and W. G. Shaw, *Chem. Revs.*, **57**, 1049 (1957).

(49) G. W. Gray, *Nature*, **172**, 1137 (1953).

(50) (a) L. Tschugaeff, *Ber.*, **1**, 360 (1898); (b) T. Gerson, *Nature*, **179**, 310 (1957).

ing materials, the relatively sharp melting points, and the failure to demonstrate the presence of impurities in any of the esters other than the linolenates by the chromatographic methods described, the physical constants reported are believed to be reliable. Because of the characterisic melting point curves of these homologous series, the melting temperatures of the longer chain fatty acid esters differ little, and cannot be used for a reliable identification of unknown plant steryl esters.

EXPERIMENTAL[51]

Ordinarily melting points were taken either in open capillary tubes using a modified Hershberg type melting point apparatus or the Fisher-Johns hot stage and were corrected. Sealed capillaries and overnight equilibration at −25° were used for the determination of the melting points of the lower melting fatty acids and their derivatives. For the detection of the mesomorphic transition stages of the steryl esters a specially constructed heating stage mounted on a polarizing microscope was used.[52] The rate of heating in all instruments was about 0.5° per min. in the region of melting.

The infrared measurements were made on a Perkin Elmer Infracord Spectrophotometer equipped with sodium chloride optics. Unless otherwise specified 10% solutions in carbon disulfide and 0.1-mm. cells were used. The ultraviolet measurements were made on a Beckman Model DK2 recording spectrophotometer with 1-cm. matched silica cells. Optical rotations were measured at 25° on 2% solutions in chloroform with a Hilger Model M 412 polarimeter equipped with a sodium vapor lamp. A 4-cc. top-filled cell was used.

Fatty acids. The acids, acetic to myristic (reagent grade), arachidic (synthetic, highest purity), and behenic (practical) were purchased from Fisher Scientific Co. Linolenic acid was obtained from Nutritional Biochemicals Corporation, Cleveland, Ohio. Palmitic, stearic, oleic, and linoleic acids were gifts from E. F. Drew and Co., Inc., Boonton, N. J. The acids were purified by low temperature crystallization[53] until correct[54] melting points of free acids and anilides, and satisfactory iodine (Yasuda) numbers were obtained. The recrystallized materials, with the exception of acetic, butyric, and caproic acids, were checked for purity using reversed phase paper partition chromatography.[55] The acids were stained either with iodine,[55a] the copper acetate–ferrocyanide[55b] or the mercuric acetate-s-diphenylcarbazide[55c] reagents. The only material to contain readily detectable amounts of contaminants was linolenic acid. It was estimated[55a] to contain not more than 10% linoleic acid, but in the absence of any ready means for the separation of the two acids, no attempt was made at further purification. The oleic and the linoleic acids were the natural isomers and appeared[56] to be free from *trans* isomers. The linolenic acid contained *trans* double bonds corresponding to an estimated maximum of about 15% of a *cis cis trans* isomer. In addition this acid also contained an estimated 2% of the conjugated form when assayed as described by Wood *et al.*[17]

Fatty acid chlorides. The acid chlorides, acetyl to myristyl (highest purity) were obtained from Fisher Scientific Co. and except for the lower three were demonstrated to be essentially free from homologs when chromatographed as the free acids.[55] The higher saturated fatty acid chlorides were prepared from the corresponding fatty acids by the method of Youngs *et al.*,[18] and the unsaturated acid chlorides by a modification of the procedure of Wood *et al.*[17] The unsaturated fatty acids (5 g.) were dissolved in 100 cc. of light petroleum (b.p. 30–60°) and the solution dried by distilling a small portion of the solvent. To the dried solution were added 2.5 to 3.0 molecular equivalents of oxalyl chloride and the solution refluxed for 1 hr. The reaction mixture was then cooled and the excess oxalyl chloride destroyed by extracting the solution with ice water. To elimi-

(51) All samples were dried in an Abderhalden drying pistol over phosphorus pentoxide for several hours at 60 or 80° and 2 mm. before being analyzed.

(52) The apparatus was similar in principle to that described by Gray[49] but differed in certain essential features. The heating stage consisted of an aluminum block 90 mm. in diameter and 26 mm. thick. A hole 13 mm. in diameter was bored through the center of the block and a recess 18 mm. in diameter and 7 mm. deep was provided at the top, into which an ordinary cover glass could be lowered. A small slot in the top connected with the circular recess to enable special bent forceps to be used when inserting or removing cover glasses. At the side of the block, just below the bottom of the recess, a hole was drilled to take a thermometer, the bulb of which protruded slightly into the 13 mm. diameter central hole. An aluminum tube was pressed part way into the side hole, leaving a clear space around the thermometer bulb. The tube extended far enough from the main block to provide ample support for the thermometer body (Fisher Scientific Co., Cat. No. 14-985). At the bottom of the main block a large diameter shallow recess accommodated a standard 100 watt Chromalox Ring Type heating element (Canadian Chromalox Co., Ltd., 251 Queen Street East, Toronto, Ontario), which was held in contact with the aluminum block by an aluminum plate with a 6-millimeter thick asbestos millboard in between. The plate was larger in diameter than the main block and was arranged to carry a tubular shield for protecting the block from air currents. The center of the plate was provided with a recess in which a glass disk was held by means of a split ring. Three Bakelite supporting posts were used to prevent heat dissipation through the microscope stage and frame. The posts were attached to another aluminum plate which was fastened to the microscope stage by knurled screws. The whole assembly was about 60 mm. high and could be readily accommodated on the rotating stage of a Leitz Model III M (E. Leitz, Wetzlar) polarizing microscope. Using a 30 mm. objective (12×) there is, after focusing, enough air space left between the heating stage and the lens (6 or 10×) to provide satisfactory insulation for temperatures up to 150°. A Leitz "Ultralux" illuminator served as an effective light source. The accuracy of the instrument was determined by taking melting points of purified organic substances covering a range of temperatures from 40 to 150°. The corrected values obtained with this instrument agreed within less than ±0.5° with those obtained in the Hershberg type melting point apparatus. For the determination, the sample was spread out evenly between two 18-mm. diameter cover slips and lowered into the central hole of the heating block. A microscope slide was then placed over the top of the hole and the melting behavior examined in the appropriate temperature range. Removal of the knurled screws (see above) permitted limited movement of the heating stage allowing examination of any part of the melt.

(53) J. B. Brown and D. K. Kolb, *Progress in the Chemistry of Fats and Other Lipids*, R. T. Holman, W. O. Lundberg, and T. Malkin, eds., Pergamon Press, New York, N. Y., 1955, Vol. 3, p. 57.

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(55) (a) H. Schlenk, J. L. Gellerman, J. A. Tillotson, and H. K. Mangold, *J. Am. Oil Chemists' Soc.*, **34**, 377 (1957); (b) H. P. Kaufmann and W. H. Nitsch, *Fette u. Seifen*, **56**, 154 (1954); (c) H. Wagner, L. Abisch, and K. Bernhard, *Helv. Chim. Acta.*, **38**, 1536 (1955).

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nate any significant hydrolysis of the acid chlorides excessive shaking was avoided and each time the water layer was removed as soon as it was formed. Usually such preparations of the fatty acid chlorides, as estimated by the method of Youngs *et al.*,[18] contained 2 to 6% of free acid. This contamination was not considered serious as the relatively inert fatty acids did not interfere with the esterification and the 20 to 50% excess of acid chloride used in most preparations was enough to ensure a complete esterification of the sterol. The acid chlorides gave anilides with correct melting points.[54]

Fatty acid anhydrides. The acid anhydrides, acetic, butyric, and caproic (highest purity) were purchased from Fisher Scientific Co. The other anhydrides, caprylic to behenic, were prepared as described by Wallace and Copehaver[57] from the corresponding fatty acids and acetic anhydride. These anhydrides possessed physical constants in good agreement with those reported in the literature.[40b]

Ergosterol. Purified ergosterol was prepared from a commercial product (m.p. 160°, $[\alpha]_D$ −137°) purchased from the Mann Research Laboratories, Inc., New York, by adsorption chromatography on aluminum oxide deactivated by ethyl acetate as described by Weizmann *et al.*[34b] The sterol was adsorbed from a benzene solution and the column developed by successive treatments with benzene containing increasing concentrations of ethyl ether. The major portion of the material was eluted as a continuous band with benzene:ether, 4:1 by volume. After discarding the front and the end fractions, which deviated considerably in their properties from ergosterol, the middle fractions were rechromatographed. The material (m.p. 163°; $[\alpha]_D$ −132°) consisting of the newly obtained front and middle fractions was pooled and recrystallized four times from methanol-ether, m.p. 164°; $[\alpha]_D$ −131.5°, lit.,[60] m.p. 165°; $[\alpha]_D$ −130°. The ultraviolet absorption maxima were at 271, 282, and 293 mμ with ε of 11,100, 11,700, and 6600, respectively, identical with the literature.[58]

Stigmasterol (Method 1). This method was essentially the same as that described by Windaus and Hauth.[28] The zinc dust used in the debrominations was freshly prepared.[59] In this way 5 g. of stigmasterol was isolated from 100 g. of crude soy sterols (Distillation Products Industries, Rochester, N. Y.). Repetition of this treatment two more times yielded 4 more g. of stigmasterol, m.p. 168°, $[\alpha]_D$ −48°. On aluminum oxide chromatography (*cf.* procedure for ergosterol) a small amount of more polar material was removed. The recovered stigmasterol after three recrystallizations from methanol-ether melted at 168°, $[\alpha]_D$ −48°; lit.,[60] m.p. 170°; $[\alpha]_D$ −49°.

Stigmasterol (Method 2). This method was similar to that described by Campbell *et al.*[29] and permitted a nearly quantitative[27b] removal of stigmasterol from the crude soy sterol mixture. A total of 20 g. of stigmasterol, m.p. 164°, $[\alpha]_D$ −46°, was isolated from about 100 g. of the soy sterols. Repeated adsorbtion chromatographic purification (*cf.* procedure for ergosterol) of this preparation with repeated removal of the lower melting front fractions yielded stigmasterol which after four recrystallizations from methanol-ether melted at 168.5° and $[\alpha]_D$ −48.5°. A more effective way for the final purification of this stigmasterol preparation was by the precipitation of the acetate tetrabromides.

γ-Sitosterol (Method 1). The method of Dirscherl and Nahm[32] based on an earlier description by Bonstedt[31] was followed. The mixed soy steryl acetate dibromides, freed from the stigmasteryl acetate tetrabromides by repeated (five times) application of the Windaus-Hauth process, were debrominated and saponified. The free sterols were recrystallized from absolute ethanol to remove the dihydrositosterols. After twenty recrystallizations by the diamond type of triangulation,[61] the top 5 to 10% of the material was discarded. The rest of the material was pooled, acetylated, and the acetates recrystallized from absolute ethanol. The γ-sitosteryl acetate crystallized preferentially. After thirty-five recrystallizations the top 10% of the acetate (m.p. 142°; $[\alpha]_D$ −43.5°) was pooled, saponified, and the sterol recrystallized six times from methanol-ether, m.p. 146.5; $[\alpha]_D$ −41.9°; lit.,[62] m.p. 147–148°; $[\alpha]_D$ −43°. No change in these constants was observed when the γ-sitosterol preparation was subjected to adsorption chromatographic fractionation on aluminum oxide.

γ-Sitosterol (Method 2). The sitosteryl α-naphthyl carbamates free from stigmasterol were hydrolyzed[29] and the sterols recovered. These were freed from any dihydrositosterols by recrystallization from absolute ethanol.[31] The diamond type of triangulation was performed on 100-g. batches of the mixed sitosterols and after twenty recrystallizations the top 5% of each batch, enriched in the saturated sterols, were discarded. The rest of the material was pooled and the solvent removed. The dry sterols were taken up into acetone and any campesterol removed as described by Fernholz and MacPhillamy.[33] After twenty-five recrystallizations the top 5% of the material enriched in campesterol was discarded. The remaining material was pooled, the solvent removed, and the sterols acetylated. The acetates were recrystallized from absolute ethanol by triangulation when the more difficultly soluble γ-sitosteryl acetate accumulated in the top fractions. After about twenty-five recrystallizations the top fractions melted at 143°, $[\alpha]_D$ −41°. The recrystallization was continued and the top fractions pooled. After a total of thirty-five recrystallizations about 10% of the original acetate had reached the physical constants specified above. This material was saponified and the sterols recrystallized six times from absolute ethanol. Bromination-debromination or adsorption chromatography of this γ-sitosterol preparation on deactivated aluminum oxide (*cf.* procedure for ergosterol) effected no further segregation. The recovered sterol after two recrystallizations from methanol-ether melted at 143°, $[\alpha]_D$ −41.3°. Mixed melting point with the γ-sitosterol preparation from Method 1 resulted in a value (144–145°) intermediate between the melting points of the two preparations. Bergmann and Low[52] report a melting point of 138°, $[\alpha]_D$ −42° for the γ-sitosterol or clionasterol prepared from sponges.

β-Sitosterol (Method 1). This method was identical with that used by Wallis and Chakravorty.[21] The cottonseed oil was supplied by Canada Packers Limited, Toronto, Ontario. From 2.7 kg. of the oil a total of 4.5 g. of presumably pure β-sitosterol, m.p. 139°, $[\alpha]_D$ −35.1° was obtained. The constants remained unchanged on further recrystallization or aluminum oxide chromatography. Wallis and Chakravorty report a melting point of 140° and $[\alpha]_D$ −36°.

β-Sitosterol (Method 2). The bottom 25 to 30% of the steryl acetate fractions from the γ-sitosteryl acetate recrystallizations (pooled from Methods 1 and 2) were combined and saponified. The free sterols (m.p. 135°, $[\alpha]_D$ −33°) were converted into the benzoates by standard methods. The benzoates were recrystallized from a mixture of benzene-ethanol as described by Wallis and Fernholz[63] to remove any α-sitosteryl benzoates present. The top fractions reached a constant melting point at 146°, $[\alpha]_D$ −14°, after about sixteen recrystallizations. The recrystallization was con-

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(60) M. H. Thornton, H. R. Kraybill and J. H. Mitchell, Jr., *J. Am. Chem. Soc.*, **62**, 2006 (1940).

(61) R. S. Tipson, *Technique of Organic Chemistry*, A. Weissberger, ed., Academic Press, Inc., New York, N. Y., 1956. Vol. 3, Part 1, p. 395 ff.

(62) W. Dirscherl, *Z. physiol. Chem. Hoppe-Seyler's*, **257**, 242 (1939).

(63) E. S. Wallis and E. Fernholz, *J. Am. Chem. Soc.*, **58**, 2446 (1936).

tinued and when sufficient material was collected with the above constants, it was saponified and the sterol isolated. After about four recrystallizations from methanol-ether the β-sitosterol melted at 139°, $[\alpha]_D$ −35.2°. Further crystallization of the sterol or adsorbtion chromatography failed to change these constants. A mixture with the β-sitosterol preparation from Method 1 melted at 140°.

Stigmastanol. This compound was prepared by catalytic hydrogenation[64] of the β-sitosterol isolated from cottonseed oil. It melted at 140°, $[\alpha]_D$ +25°; lit.,[65] m.p. 140°; $[\alpha]_D$ +24.9° for stigmastanol prepared from β-sitosterol by similar methods.

γ-Sitostanol was prepared from γ-sitosterol by the method described for stigmastanol. Both γ-sitosterol preparations gave the same saturated derivative, m.p. 144° and $[\alpha]_D$ +18°; lit.,[31] m.p. 144°; $[\alpha]_D$ +19°. For poriferastanol, prepared synthetically, but supposedly identical with γ-sitostanol, Lyon and Bergmann[66] report m.p. 143°; $[\alpha]_D$ +25°. The material gave a faint Liebermann-Burchard test[67] after 10 to 15 min. at room temperature.

Preparation of steryl esters (Method 1). The sterols (0.1–0.2 g.) were dissolved in benzene, toluene, or xylene (50 cc.), depending on the ester to be made, and the solution dried by distilling a small portion of the solvent. To the dried solution were added 1.2–1.5 molecular equivalents of the acid anhydride and a few drops (1 ml. max.) of dry pyridine. After refluxing for 1 hr. or standing overnight at room temperature, the solutions were suitably diluted with light petroleum (b.p. 30–60°) and chromatographed on silicic acid as previously described.[20] The steryl esters were eluted with 20% benzene in light petroleum (b.p. 30–60°), free fatty acids with 5% diethyl ether in light petroleum (b.p. 30–60°), and free sterols with 25% diethyl ether in petroleum (b.p. 30–60°). Any undecomposed fatty acid anhydrides were recovered with the free fatty acids or free sterols. Yields of chromatographically purified esters varied from quantitative for the acetates to as low as 10% for the stearates and other long chain fatty acid anhydrides. In the latter cases the yields could be improved by extending the time of heating.

Preparation of steryl esters (Method 2). The sterols (0.1–0.2 g.) were dissolved in benzene (10 cc.) and petroleum ether (b.p. 60–80°) or benzene (90 cc.) added. The solution was refluxed for a few minutes, and dried by distilling a portion (25 cc.) of the solvent. To the dried solution was added about 1.2–1.5 molecular equivalents of acid chloride dissolved in the appropriate solvent and just enough pyridine to combine with the hydrogen chloride formed. After refluxing for 30 min., the solution was cooled to room temperature, diluted with petroleum ether, if necessary, and poured on a silicic acid column. The chromatography was performed as described above. The pyridine hydrochloride formed and any undecomposed acylpyridinium chloride remained at the top of the column. Yields ranged from 60 to 95% of chromatographically purified material. For the determination of the physical constants the esters were recrystallized from methanol-ether mixtures.

Purity of products. Following the preparation of the steryl esters, reversed phase paper partition chromatographic techniques were developed for their separation and identification.[68] By this means it was demonstrated that the steryl esters synthesized and purified by the methods described above were free of readily detectable amounts of homologs and isomers and were not contaminated with unesterified sterol. Digitonide precipitation,[41] customarily employed for ascertaining the absence of free sterol from steryl ester preparations, was observed not to be sufficiently sensitive.

Acknowledgment. The authors are indebted to Mr. R. D. Bradfield, Department of Physics, for the design and construction of the heating stage, and to Dr. L. G. Berry, Department of Geology, for supplying the polarizing microscope.

Appreciation is expressed to Dr. G. W. Gray Department of Chemistry, University of Hull, England, for the examination of the melting behavior of β-sitosteryl laurate and myristate in his instruments. Thanks are due to Mr. J. D. Cook for the syntheses of a number of the steryl esters, and to Miss R. Hokanson and Mrs. M. Froats for the determination of many of the physical constants.

The constructive criticism of the manuscript by Dr. D. G. M. Diaper, Department of Chemistry, Royal Military College, is gratefully acknowledged.

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(66) A. M. Lyon and W. Bergmann, *J. Org. Chem.*, **7**, 428 (1942).

(67) This test was performed on about 1 to 5 mg. of material dissolved in 1 to 2 cc. of chloroform. Approximately 0.5 cc. of acetic anhydride and 2 to 3 drops of concd. sulfuric acid were added.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOWARD UNIVERSITY]

Dissociation Constants of Some Sweet and Tasteless Isomeric *m*-Nitroanilines[1]

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The dissociation constants of some 2- and 4-substituted 5-nitroanilines were determined spectrophotometrically. Their relative basicities were also determined by potentiometric titration in glacial acetic acid. A good linear relationship was found between the potentials at half-neutralization in acetic acid and the dissociation constants in aqueous solutions.

There is a marked resemblance of the spectra of the substituted *m*-nitroanilines in acid to the spectra of the correspondingly substituted nitrobenzenes in ethanol. This relationship indicates that the effects of electronegativity, resonance, steric requirements, etc., which control the spectra of the substituted nitrobenzenes have the same total effects on the spectra of the *m*-nitroanilines in acid solution.

No simple correlation was found or anticipated between the tastes and base strengths of these substituted *m*-nitroanilines.

It is well known that 2-substituted 5-nitroanilines are intensely sweet while the isomeric 4-substituted 5-nitroanilines are bitter or tasteless (*cf.* Table IV). It is an intriguing challenge to be able to account for this sharp difference in taste in terms of the chemical or physical properties of the isomeric pairs. In spite of the attempts of many chemists, no reliable, widely applicable correlation has been found between the tastes and molecular properties of substances. It appears that chemoreception depends upon several properties. As a part of a program to find a set of molecular properties which may be used as a parameter for predicting the tastes of substances, attention has been given to the electron distributions in these *m*-nitroanilines. This paper reports their relative base strengths.

The pK_a values for the substituted *m*-nitroanilines were determined spectrophotometrically by the method of Flexser, Hammett, and Dingwall.[3] The order of relative base strengths was also established by potentiometric perchloric acid titration in glacial acetic acid.[4] Good agreement was found for the relative basicities of the *m*-nitroanilines by the two methods.

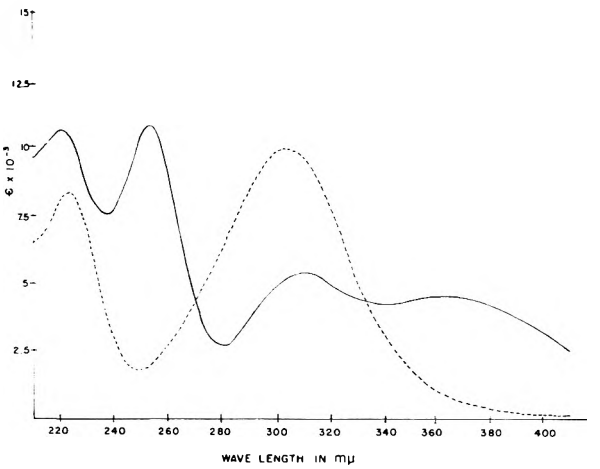


Fig. 1. Absorption spectrum of 2-methoxy-5-nitroaniline in 0.1*N* sodium hydroxide ———; and in 0.1*N* sulfuric acid .....

EXPERIMENTAL

Materials. With the exception of the 2-fluoro- and the 4-fluoro-5-nitroanilines, the preparation of all of the substituted *m*-nitroanilines has been described.[5]

Twenty-three grams of *o*-fluoroaniline, b.p. 82°/41 mm., was dissolved in 100 ml. of concd. sulfuric acid and nitrated with 9.7 ml. of fuming nitric acid dissolved in 100 ml. of concd. sulfuric acid at −10°.[6] The crude product was recrystallized from aqueous alcohol, m.p. 101–102° (lit.,[7] m.p. 101.5°); acetanilide, m.p. 179–180° (lit.,[8] m.p. 178.4°).

Spectroscopic measurements. Stock solutions for each base were prepared by dissolving a weighed amount of base (about 0.1 g. except in the case of the slightly soluble 2-bromo-5-nitroaniline, where 0.05 g. was used) in 1 l. of carbon dioxide-free distilled water. All of the other required solutions were prepared from distilled water and analytical grade reagents.

The spectra of the bases were determined with a Beckman DU line-powered spectrophotometer with the same pair of matched 1 cm. silica cells. The solutions in the cells were maintained at 25.0 ± 0.1° by means of thermospacers. Spectra of the bases were measured in approximately 0.1*N* sodium hydroxide, 0.1*N*, 1.0*N*, 2.5*N*, or 5.0*N* sulfuric acid, and buffer solutions containing various proportions of 0.02*N* sodium acetate and 0.02*N* hydrochloric acid. These solutions were prepared by diluting an aliquot volume of stock base solution with the appropriate volume of acid, base, or buffer solution. In each instance, blank cell solutions were prepared in the same manner with distilled water in place of the stock base solution. The spectrum of each base was measured twice in acid and in alkaline solution with fresh solutions each time. The averaged values of the extinction coefficients so obtained were used in the calculations. Beer's law was tested for two compounds of each

(1) Number IV in a program of physicochemical studies of the sense of taste. No. III, *Nature*, in press.

(2) Taken in part from the Ph.D. thesis of A.R.L., Howard University, 1959.

(3) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Amer. Chem. Soc.*, **57**, 2103 (1932).

(4) J. S. Fritz, *Acid-Base Titrations in Non-aqueous Solvents*, The G. Frederick Smith Chemical Co., Columbus, Ohio, 1952, p. 9.

(5) A. R. Lawrence, M.S. Thesis, Howard University, 1957.

(6) F. D. Chattaway, K. J. P. Orton, and R. C. T. Evans, *Ber.*, **33**, 3062 (1900).

(7) A. F. Holleman and J. W. Beekman, *Rec. trav. chim.*, **23**, 237 (1904).

(8) F. Swarts, *Rec. trav. chim.*, **35**, 142 (1916).

type in acid, base, and buffer solution and was found to hold in each case.

Typical spectra are shown in Fig. 1 for 2-methoxy-5-nitroaniline in alkali and in acid.

pH Measurements. The *p*H measurements were made with a Beckman Model G *p*H meter standardized immediately before use at *p*H's of 4.01 and 1.08 by the use of 0.05*M* potassium acid phthalate[9] and 0.1*N* hydrochloric acid, respectively.

Potentiometric titrations in glacial acetic acid.[4] Reagent grade glacial acetic acid[10] was refluxed with 3–5% by weight of potassium permanganate for 2–6 hr., distilled from the reaction mixture, and the fraction boiling at 117–118° collected. Traces of water were removed from this fraction with two to three times the amount of triacetyl borate required for reaction of the estimated amount of water present. The material was then redistilled and the fraction boiling at 117–118° collected. This acetic acid was used throughout the study.

A 0.05*N* perchloric acid solution was prepared by dissolving 4.16 ml. of 72% perchloric acid in 200 to 300 ml. of acetic acid and adding 9.3 ml. of freshly distilled acetic anhydride. This mixture was then made up to 1 l. with acetic acid, allowed to stand overnight, and standardized against potassium acid phthalate dissolved in acetic acid. Solutions of the anilines in acetic acid were prepared by dissolving weighed samples of the bases (about 0.03 g.) in 50.0 ml. each of acetic acid. All of the bases used were readily soluble in this medium.

Titrations[4] were performed by adding perchloric acid solution to the solution of the base in increments of 0.2 ml. except near the equivalence point where 0.1 ml. increments were used. A period of 2 min. was allowed to elapse between each addition and subsequent reading to permit the solution to reach equilibrium. A 5-ml. microburet graduated in 0.02-ml. intervals was used. The cell was a 100-ml. Pyrex glass beaker and stirring was achieved by means of a stream of nitrogen gas bubbling through the solution.[11] Trace amounts of oxygen were removed from the nitrogen by passing it through an alkaline solution of pyrogallol. The cell was immersed in a thermostated water bath maintained at 25.10 ± 0.01°.

The millivolt scale of a Beckman Model G *p*H meter was used to measure the potentials during the titrations. A glass electrode, Beckman Model 40498, was used as the indicator electrode. The reference electrode was a silver–silver chloride electrode, Beckman Model 39261, which was prepared by the electrolysis of a saturated potassium chloride solution. An isolation cell[12] containing acetic acid saturated with potassium chloride connected the silver–silver chloride electrode with the main body of the solution. The equivalence points were determined from a large scale plot of $\Delta MV/\Delta V$ against ΔV, where ΔMV is the change in the millivolt reading and ΔV is the corresponding volume of acid added.

All apparatus was placed upon a large sheet of aluminum foil to provide adequate grounding.[13] Particular care was taken to ground the case of the *p*H meter and the thermostat bath.

A typical titration curve is shown in Fig. 2 for 2-methyl-5-nitroaniline, and the millivolt readings at the half-neutralization points for all compounds are given in Table I.

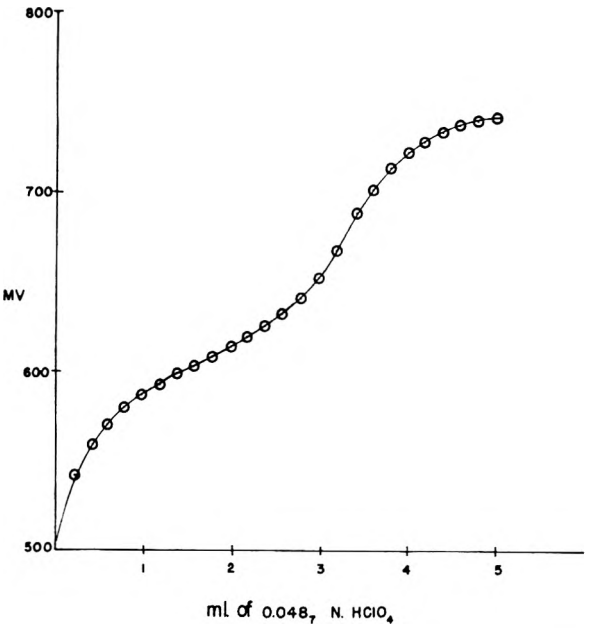


Fig. 2. Graph of the potentiometric titration of 2-methyl-5-nitroaniline in glacial acetic acid

TABLE I

MILLIVOLT READINGS AT HALF NEUTRALIZATION POINTS FOR SUBSTITUTED 5-NITROANILINES

Substituent	$MV_{1/2}$	Mean $MV_{1/2}$
2-CH_3O	601	601
	601	
2-CH_3	605	605
	605	
2-F	700	701
	702	
2-Cl	736	735
	734	
2-Br	739	739
	740	
4-CH_3O	524	523
	523	
4-CH_3	564	565
	565	
4-F	600	602
	603	
4-Cl	641	642
	643	
	642	
4-Br	641	642
	643	
p-Toluidine	502	503
	503	
p-Anisidine	495	500
	500	
1,3-Diphenylguanidine	456	456
	456	

Computation of dissociation constants. The *p*Ka's were calculated from Equation 1[3]

$$pK_a = pH + \log \frac{(e_2 - e_3)}{(e_1 - e_2)} + \log f_{BH^+} \qquad (1)$$

where e_1 and e_3 are the molar absorbancy indexes at a given wave length of the amine in acid and in base; e_2 is the apparent molar absorbancy index in the buffer; and f_{BH^+} is the activity coefficient of the protonated base. The activity

(9) V. E. Bower and R. G. Bates, *J. Research Nat. Bur. Standards*, **59**, 261 (1957).

(10) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath Co., Boston, 1957, p. 281.

(11) R. P. Linstead, J. A. Elvidge, M. Whalley, *A Course in Modern Techniques of Organic Chemistry*, Butterworths Scientific Publications, London, 1955, p. 153.

(12) R. A. Glenn, *Anal. Chem.*, **25**, 1916 (1953).

(13) W. M. Clark, *The Determination of Hydrogen Ions*, 3rd ed., The Williams and Wilkins Co., 1928, p. 357.

coefficient of the nonionic free base is taken as unity.[14] The activity of the protonated base was calculated from the approximate Debye-Hückel relationship,

$$\log f_{BH^+} = -\frac{0.509z^2\sqrt{\mu}}{(1 + a\sqrt{\mu})}$$

where z is the valence of the protonated base, μ is the ionic strength of the medium, and the ionic radius a was given a value of 5.[14]

For the very weak bases 2-fluoro-, 2-chloro-, 2-bromo-, 4-chloro-, and 4-bromo-5-nitroanilines, Equation 2 was used,

$$pK_a = H_0 + \log\frac{(e_2 - e_3)}{e_1 - e_2} \qquad (2)$$

where H_0 is Hammett's acidity function,[15] and the e's have the same meaning as in equation (1). Values of H_0 have been determined by a number of investigators,[16] but for this study the data of Hammett and Deyrup were used. The H_0 values at the particular normalities of interest were determined from a large-scale plot of H_0 *vs.* normality. The normalities of the acid solutions were established by titration against standardized base.

The dissociation constants so determined are given in Table II. It is comforting to observe the good agreement of the pK_a's for *p*-toluidine and *p*-anisidine determined here spectrophotometrically (5.05 and 5.26, respectively) with those determined by other methods (5.07 and 5.29, respectively).[17]

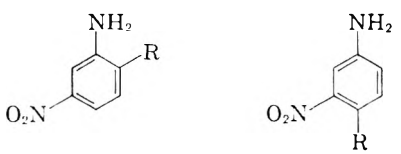
TABLE II

DISSOCIATION CONSTANTS OF 2- AND 4-SUBSTITUTED 5-NITROANILINES FROM SPECTROSCOPIC MEASUREMENTS

Substituent	pK_a	Substituent	pK_a
2-CH_3O	2.49 ± 0.01	4-CH_3O	3.36 ± 0.02
2-CH_3	2.30 ± 0.02	4-CH_3	2.86 ± 0.01
2-F	1.09 ± 0.02	4-F	2.36 ± 0.004
2-Cl	0.64 ± 0.02	4-Cl	1.93 ± 0.02
2-Br	0.52 ± 0.02	4-Br	1.80 ± 0.01
p-Toluidine	5.05 ± 0.01		
p-Anisidine	5.26 ± 0.04		

RESULTS AND DISCUSSION

If a nitro group with its strong electron-withdrawing effect is introduced into the ring of *o*- or *p*-substituted anilines to give I or II, one



I II

might expect 1) the base strengths to decrease, and 2) little or no change in the relative order of base strengths of the monosubstituted anilines.

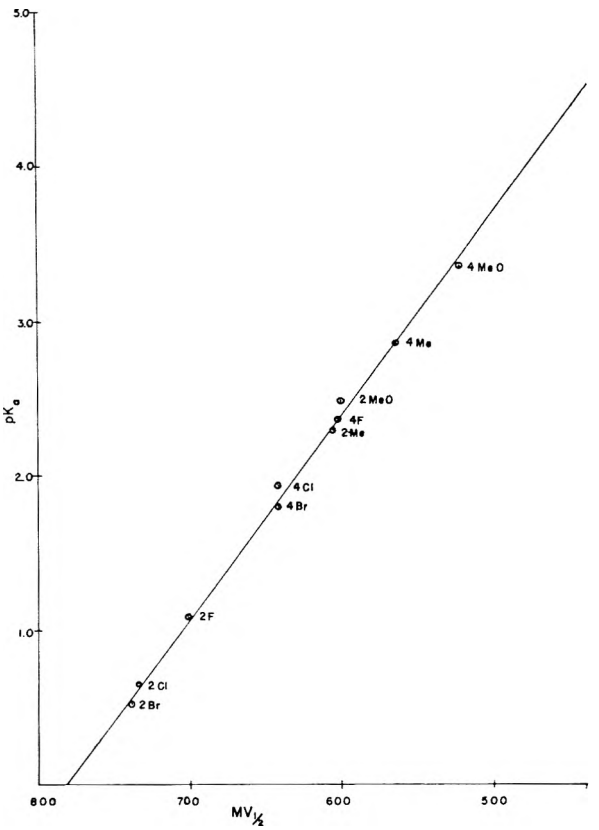


Fig. 3. Plot of pK_a values measured in water *vs.* potentials at half neutralization measured in glacial acetic acid for substituted 5-nitroanilines

Examination of the data of Table III reveals that these expectations are met. This approximate additivity of the effects of the nitro and other substituents indicates that the relative base strengths of the 2- and 4-substituted 5-nitroanilines can be explained on the same bases as are monosubstituted anilines in terms of resonance, steric requirements, inductive effects, and hydrogen bonding.[18]

TABLE III

pK_a VALUES FOR SOME SUBSTITUTED ANILINES

Substituent	pK_a of Aniline	pK_a of 5-Nitroaniline	ΔpK_a
H	4.58	2.54	2.04
2-CH_3O	4.49	2.49	2.00
2-CH_3	4.38	2.30	2.08
2-F	2.96	1.09	1.87
2-Cl	2.62	0.64	1.98
2-Br	2.60	0.52	2.08
4-CH_3O	5.26	3.36	1.90
4-CH_3	5.05	2.86	2.19
4-F	4.51	2.36	2.15
4-Cl	4.00	1.94	2.06
4-Br	3.91	1.80	2.11
		Mean ΔpK_a = 2.05	

(14) S. Glasstone, *The Elements of Physical Chemistry*, D. Van Nostrand Co., Inc., New York, N. Y., 1946, p. 486.

(15) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 267.

(16) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **57**, 2721 (1932); M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(17) *Cf.* H. C. Brown, D. H. McDaniel, and O. Hafliger, in *Determination of Organic Structures by Physical Methods*, edited by E. A. Braude and F. C. Nachod, Academic Press, N. Y., 1955, p. 590.

(18) H. C. Brown, D. H. McDaniel, and O. Hafliger, "Dissociation Constants" in *Determination of Org. Structures by Physical Methods*, edited by F. C. Nachod and E. A. Braude, Academic Press, Inc., N. Y., 1955, chap. 14; B. M. Wepster, *Rec. trav. chim.*, **71**, 1159 (1952).

Fig. 3 is a plot of the pK_a values measured in water for the substituted 5-nitroanilines against the potentials at half-neutralization measured in acetic acid. The equation for this line, computed by the method of least squares, is

$$pK_a = 10.336 - 0.0132\ MV_{1/2}.$$

Such a linear relationship is not unusual[19] and it provides strong support to the order found for the base strengths measured in acetic acid. Also, it indicates that there is not a significant difference in solvation effects for these two solvents for this series of compounds.

The pK_a values for the 4-substituted 5-nitroanilines are plotted against the respective Hammett *sigma* constants in Fig. 4. A reasonably linear relationship exists. The point for the 4-methyl derivative lies slightly above the line. This deviation could be attributed to an effect upon the resonance of the nitro group by the adjacent methyl group, resulting in a decrease of the base strength of the aniline.

In Table IV are listed the pK_a values and the relative sweetnesses of the compounds. Except for the 2-fluoro derivative, whose sweetness was measured by a different group of workers, the relative sweetnesses of the sweet nitroanilines parallel the order of their decreasing basicities. However, no rigid correlation can be made between taste and this single property. Nevertheless, it is hoped that the basicity may later be combined with other properties to give a function which may be used as a single parameter for interpreting or predicting the tastes of compounds.

TABLE IV

pK_a AND RELATIVE SWEETNESSES OF SUBSTITUTED 5-NITROANILINES

Substituent	pK_a	Relative sweetness (Sucrose = 1)
H	4.58	40[20]
2-CH_3O	2.49	167
2-CH_3	2.30	298
2-F	1.09	40[21]
2-Cl	0.64	375
2-Br	0.52	714
4-CH_3O	3.36	tasteless
4-CH_3	2.86	tasteless
4-F	2.36	tasteless
4-Cl	1.93	tasteless
4-Br	1.80	tasteless

It is noteworthy that the spectra of the substituted *m*-nitroanilines in acid solution show a great similarity to the spectra of the corresponding 2- and 4-substituted nitrobenzenes measured in ethanol. This resemblance is not surprising, because in acid solution the lone pair electrons on the amino nitrogen is no longer available for electronic interaction with the nitrophenyl group and, accordingly,

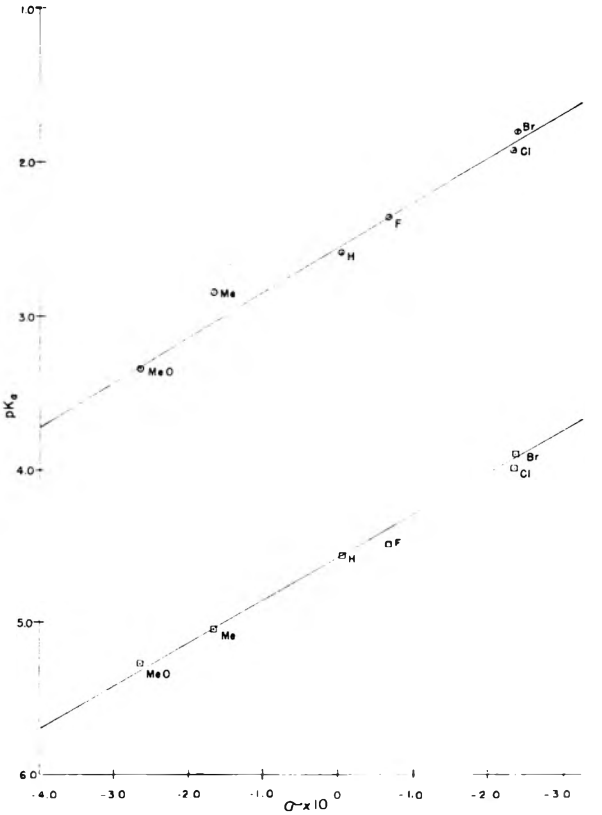


Fig. 4. Plot of pK_a values for 4-substituted 5-nitroanilines (⊙) and *p*-substituted anilines (⊡) against Hammett *sigma* constants

TABLE V

ABSORBANCY INDEXES FOR SUBSTITUTED 5-NITROANILINES IN ACID AND SUBSTITUTED NITROBENZENES IN ETHANOL AT THEIR λ_{max}'S

Substituent	2-Substituted 5-Nitroaniline		*p*-Substituted Nitrobenzenes[22]	
	λ	a_M	λ	a_M
H	256 mμ	7500	257 mμ	8100
F	260	7200	266	7900
CH_3	272	8950	275	10400[23]
Cl	270	9650	272	10000
CH_3O	305	9950	306	10780
Br	275	10300	276	11100
	4-Substituted 5-Nitroaniline		*o*-Substituted Nitrobenzene[22]	
H	256	7500	257	8100
F	248	7000	250	6900
CH_3	255	5350	257	5400
Cl	250	4050	252	3500
CH_3O	259	3850	258.5	3450
Br	250[s]	3400	255	3000

[s] = shoulder

(19) N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930); N. K. Hall, *J. Phys. Chem.* **60**, 63 (1956); S. Viebel, B. J. Nielsen, and S. Refn, *Acta Chem. Scand.* **6**, 1066 (1952).

(20) J. J. Blanksma and P. W. M. van der Weyden, *Rec. trav. chim.* **59**, 629 (1940).

(21) J. J. Blanksma, W. J. van den Broek, and D. Hoegen, *Rec. trav. chim.* **65**, 329 (1946).

(22) W. F. Forbes, *Can. J. Chem.*, **36**, 1350 (1958).

(23) L. L. Green, M.S. Thesis, Howard University, 1959.

the spectra similate those for corresponding compounds not containing the $^{+}NH_3$ group. Furthermore, it is observed that the order of decreasing absorbancy indexes of the λ_{max}'s of the *p*-substituted nitrobenzenes is the same as that of the 2-substituted 5-nitroanilinium ions, where the substituents are *para* to the nitro group, and the order for the *o*-substituted nitrobenzenes is identical with that of the 4-substituted 5-nitroanilinium ions. The values are given in Table V.

WASHINGTON 1, D. C.

Notes

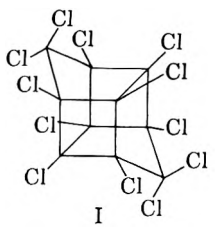
A department for short papers of immediate interest.

Pyrolysis of the Cage Ketone $C_{10}Cl_{10}O$[1]

PHILIP EATON,[2] EMERY CARLSON,[3] PASQUALE LOMBARDO,[3] AND PETER YATES[2]

Received December 28, 1959

Hexachlorocyclopentadiene gives on reaction with aluminum chloride a dimeric chlorocarbon, m.p. 485°,[4-6] and with liquid sulfur trioxide a related chloroketone, m.p. 350°.[6] The structures I and II postulated by McBee[7] for these compounds have recently been corroborated by physical methods, comprising dipole moment,[8-10] infrared[8] and x-ray[10] measurements. Their unusual chemical inertness has led us to investigate their thermal stabilities and behavior on pyrolysis.



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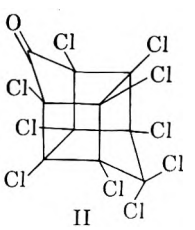


II

It has been reported[7,11] that the chlorocarbon I is remarkably stable to heat, substantial pyrolytic fission occurring only on prolonged heating at or above 500° to produce largely carbonaceous material and chlorine together with a small amount of hexachlorocyclopentadiene.

The thermal stability of the cage system is however markedly reduced by the introduction of the carbonyl group in II. We find that molar equivalents of carbon monoxide and chlorine are readily eliminated at temperatures above 450°. Since the initial organic product was found to be itself thermally labile, a flash pyrolytic technique was developed to permit its isolation. A solution of II in dry carbon tetrachloride was dropped slowly onto the top of a column of ceramic saddles held in a vertical Vycor tube heated by a concentric furnace to 475–500°. The tube was flushed continuously with a rapid stream of dry, oxygen-free, nitrogen. With this apparatus it was possible to effect the pyrolysis and remove the product from the heated zone within approximately ten seconds. The solvent and product were condensed in an ice trap placed immediately below the heated tube. Chromatography of the crude product gave a white crystalline material, C_9Cl_8, m.p. 138–139°, in 80% yield and unchanged II; hexachlorobenzene, arising from pyrolysis of the carbon tetrachloride, was also isolated. Only trace amounts of hexachlorocyclopentadiene were detected, in contradistinction to the observations of Idol[11] who pyrolyzed II under conditions which could lead to the decomposition of the initially formed product. Little or no carbonaceous material was produced; the yield of the C_9Cl_8 product corrected for recovered II was 90–95% in the several pyrolyses carried out. For comparison purposes, I was treated in a similar fashion. At 500° only slight pyrolysis occurred giving trace amounts of hexachlorocyclopentadiene; no carbonaceous material was formed.

The pyrolysis product from II was shown to be octachloroindene, III, by comparison with a sample, m.p. 138–138.5°, prepared by the reaction of phosphorus pentachloride with hexachloroindone (IV), itself prepared by the action of aqueous acetone on octachloro - 3a,4,7,7a - tetrahydro-4,7-methanoindene-1,8-dione (V).[12] The preparation of octachlorindene by this method has been reported previously by Zincke and Gunther,[13] who gave its melting point as 84°; a subsequent report in the patent literature[14] has, however, given a melting point of 132°. Because of this discrepancy it was considered essential to establish the structure of the pyrolysis product independently. Reaction with liquid sulfur trioxide gave the indone IV; chlorination gave a product C_9Cl_{10}, identical with a sample of decachloroindane (VI) prepared by the destructive chlorination of naphthalene in the presence of an iodine/iron catalyst.[14] Treatment of this product with liquid sulfur trioxide gave hexachloroindane-1,3-dione (VII) in

(1) Compound II, decachloropentacyclo[5.3.0.0^{2,6}.0^{4,10}.0^{5,9}]decan-3-one, alternatively named decachlorooctahydro-1,3,4-metheno-2*H*-cyclobuta[cd]-pentalen-2-one; *cf.* H. E. Ungnade and E. T. McBee, *Chem. Revs.*, **58**, 249 (1958).

(2) Harvard University.

(3) Allied Chemical Corporation.

(4) H. J. Prins, *Rec. trav. chim.*, **65**, 455 (1946).

(5) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 952 (1949).

(6) E. E. Gilbert and S. L. Giolito, U. S. Reissue Patent 24,435.

(7) E. T. McBee, C. W. Roberts, J. D. Idol, Jr., and R. H. Earle, Jr., *J. Am. Chem. Soc.*, **78**, 1511 (1956).

(8) D. H. Zijp and H. Gerding, *Rec. trav. chim.*, **77**, 682 (1958).

(9) W. H. Mears, General Chemical Research Laboratory, private communication.

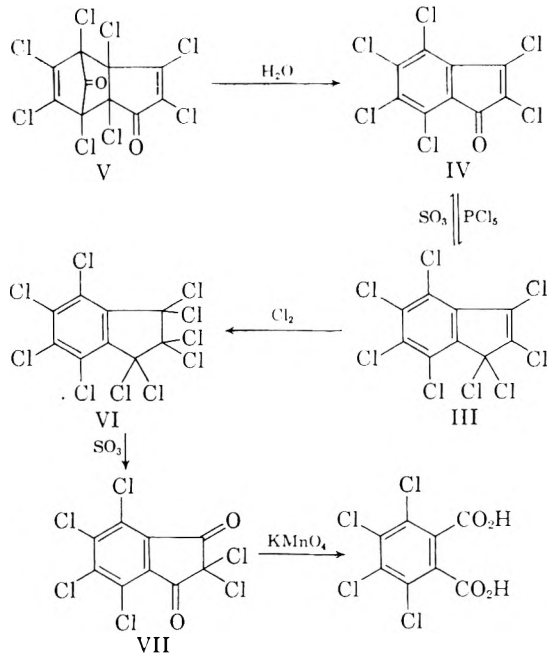
(10) R. Pepinsky and Y. Okaya, Dept. of Physics, Pennsylvania State University, private communication.

(11) J. D. Idol, Jr., Ph.D. Thesis, Purdue, 1954.

(12) T. Zincke and K. H. Meyer, *Ann.*, **367**, 1 (1909).

(13) T. Zincke and H. Gunther, *Ann.*, **272**, 243 (1893).

(14) H. Vollmann, Ger. Patent, **844,143** (1952); *cf. Chem. Abstr.*, **50**, 4227 (1956).



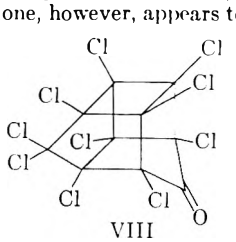
quantitative yield.[15] The diketone was readily oxidized by potassium permanganate to the well known tetrachlorophthalic acid. These reactions provide unambiguous confirmation for the formulation of the pyrolysis product as III.

By analogy with the observed fission of I, it might be considered that octachloroindene is formed from II by cleavage to hexachlorocyclopentadiene and tetrachlorocyclopentadienone, followed by a Diels-Alder recombination with hexachlorocyclopentadiene acting as the dienophile and subsequent decarbonylation and dechlorination. However, hexachlorocyclopentadiene has never been observed to act as a dienophile, while tetrachlorocyclopentadienone is known to undergo very ready dimerization to V[16]; neither V nor its pyrolysis products, octachloroindanone and IV, were detected among the products of the pyrolysis of II under the conditions here described. It seems more likely therefore that the pyrolysis reaction involves the initial loss of the carbonyl group of II as carbon monoxide followed by intramolecular rearrangement and aromatization by loss of chlorine.[17]

(15) *Cf.* J. Bernimolin, *Ber.*, **87**, 640 (1954).

(16) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 946 (1949).

(17) It may be noted that III is more closely related to the unsymmetrical cage structure VIII; such a structure for the $C_{10}C_{10}O$ ketone, however, appears to be ruled out.[8-10]



EXPERIMENTAL[18]

Dodecachloropentacyclo[5.3.0.0^{2,6}.0^{4,10}.0^{5,9}]decane (I). The method of Newcomer and McBee[5] was used. Repeated crystallization of the crude product from benzene gave white cubic crystals, m.p. *ca.* 485° (sealed capillary), showing no absorption in the infrared between 2 and 8.6 μ.

Decachloropentacyclo[5.3.0.0^{2,6}.0^{4,10}.0^{5,9}]decan-3-one (II). Crude material was obtained by the procedure of Gilbert and Ciolito.[6] Decolorization was effected by treatment of a methanolic solution with activated charcoal; addition of water to the filtered solution followed by a preliminary air-drying of the precipitated solid gave hydrated II. Anhydrous material was prepared by prolonged refluxing of a xylene solution of the hydrate under a Dean-Stark water trap; on concentration, this solution deposited large white crystals of pure II, m.p. *ca.* 350° (sealed capillary), $\lambda_{max}^{CCl_4}$ 5.58 μ.

Pyrolysis of I *and* II. Pyrolyses were run by permitting solutions in carbon tetrachloride (50 g./l.) to fall dropwise from a pressure-equalizing funnel onto the top of a 30-cm. column of Berl ceramic saddles held vertically within a Vycor tube, 2.8 cm. in diameter, and heated to 500° by a concentric furnace. The tube was flushed continuously with a rapid stream of dry, oxygen-free, nitrogen. Temperatures were measured by iron-constantan thermocouples contained within thin Vycor tubing, one located at the packing-liquid point of contact and the other at the column center. A maximum temperature difference of 100° between these points was maintained by adjusting the rate of addition of solution. Solvent and products were condensed in an ice trap placed immediately below the heated zone. Test runs indicated that hexachlorobenzene was produced by pyrolysis of the solvent (about 0.2% of solvent converted); it was possible to remove it entirely by volatilization on concentrating the condensates on the steam bath.

The infrared spectrum of the condensate from the pyrolysis of I corresponded to that of unchanged starting material contaminated with small amounts of hexachlorocyclopentadiene; no carbonaceous material was formed.

The condensate from the pyrolysis of II was concentrated to one tenth of its original volume (the distillate contained only hexachlorobenzene in addition to carbon tetrachloride) and was chromatographed on neutral alumina. Evaporation of the fraction obtained by elution with carbon tetrachloride gave white crystalline material, m.p. 138–139°, in 80% yield, identical in all respects to octachloroindene; its melting point was undepressed on admixture with authentic material (*vide infra*). Subsequent elution with methanol gave a fraction which contained unchanged II as its methanol adduct. After correction for recovered starting material (about 15%), the yield of octachloroindene ranged from 90–95%. The unpleasant odor of the concentrated condensates indicated the presence of trace amounts of hexachlorocyclopentadiene.

Hexachloroindone (IV). Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (V; 200 g.), prepared by sulfuric acid hydrolysis of 1,1-dimethoxytetrachlorocyclopentadiene,[12] was dissolved in acetone (500 ml.). Water (*ca.* 350 ml.) was added rapidly to a slight cloudiness. The solution darkened immediately, and yellow crystals of IV separated after 5 min. After standing overnight, the mixture was filtered and the precipitate crystallized from methanol to give 123 g. (82%) of bright yellow crystals, m.p. 149–150°, $\lambda_{max}^{CCl_4}$ 5.77, 6.37 μ.

Anal. Calcd. for C_9Cl_6O: Cl, 63.1. Found: Cl, 63.1.

Octachloroindene (V). A heavy-walled glass pressure bottle was charged with 5.6 g. of IV and 10 g. of phosphorus pentachloride. The mixture was heated in an oil bath under autog-

(18) Melting points are uncorrected. Ultraviolet spectra were recorded on a Cary Dual Beam Spectrometer. Infrared spectra were taken on a Perkin-Elmer Model 21 recording spectrometer.

enous pressure at 190–205° for 2 hr. After cooling, water and ether/acetone were added to dissolve all the solids. The ethereal layer was separated, washed with water, dried over sodium sulfate, and diluted with methanol. Partial evaporation of this solution gave white needles (5 g., 79%) of octachloroindene, which were found to be very sensitive to light. The analytical sample, prepared by repeated crystallization from methanol, melted at 138–138.5°, λ_{max}^{KBr} 6.29 μ, $\lambda_{max}^{C_2H_5OH}$ (ϵ), 236 mμ (19,500), 242 mμ (21,000), 250 mμ (29,000), 259 mμ (31,000).

Anal. Calcd. for C_9Cl_8: C, 27.59; Cl, 72.41. Found: C, 27.52; Cl, 72.23.

Chlorination of V; *decachloroindane* (VI). Chlorine gas was bubbled through a solution of 5 g. of V in 75 ml. of carbon tetrachloride held at 50° for 2 hr. Evaporation of the solvent and crystallization of the residue from methanol gave 4.8 g. (81%) of white crystalline material, m.p. 134–135°, identical with a sample of decachloroindane (VI) prepared by the destructive chlorination of naphthalene as described by Vollmann.[14]

Anal. Calcd. for C_9Cl_{10}: Cl, 76.64. Found: Cl, 76.51.

Hydrolysis of V; *hexachloroindone* (IV). Five grams of V were dissolved in 25 ml. of liquid sulfur trioxide. The excess sulfur trioxide was allowed to evaporate overnight from an open beaker. The remaining sulfuric acid–solid mixture was washed with cold water, and the solid crystallized from methanol to give a nearly quantitative yield (4.4 g.) of IV, m.p. 149–150°.

Hexachloroindane-1,3-dione (VII). Five grams of VI were treated with liquid sulfur trioxide in the same manner as above. A quantitative yield (3.8 g.) of VII was obtained as bright yellow crystals, m.p. 155–156°, $\lambda_{max}^{CCl_4}$ 5.65, 5.75 μ.

Anal. Calcd. for $C_9Cl_6O_2$: Cl, 60.30. Found: Cl, 60.28.

This material was identical with a sample prepared by treatment of VI with anhydrous nitric acid as described by Bernimolin.[15]

Oxidation of VII. Three grams of potassium permanganate in 50 ml. of aqueous 5% sodium hydroxide was added with stirring to 1 g. of VII in 10 ml. of warm acetone. After 4 hr., the solution was acidified with concd. hydrochloric acid, bleached with sulfur dioxide, saturated with ammonium sulfate, and extracted with ether. The ethereal extract was washed with water and evaporated to dryness. Sublimation of the residue gave crystals of tetrachlorophthalic anhydride, m.p. 254–256°, identical with an authentic sample.

Acknowledgment. The authors are indebted to Dr. Everett E. Gilbert for his advice and counsel.

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Macrocyclic Compounds. 2-Methyl-2-azacyclohexadecanone

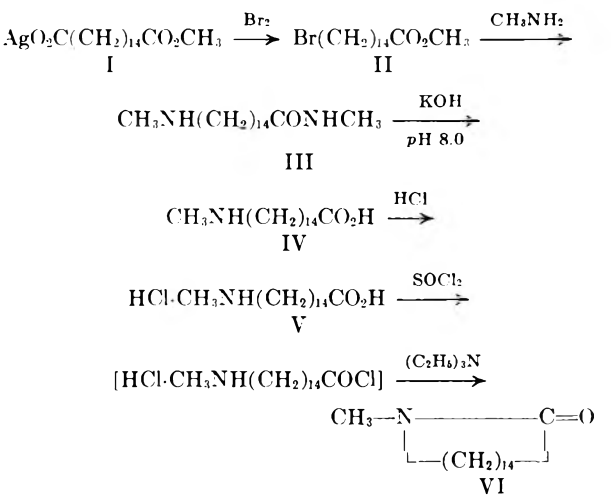
YOSHIO IWAKURA AND KEIKICHI UNO

Received October 1, 1959

Since the structure of natural musk was established as that of a macrocyclic ketone,[1] many macrocyclic compounds have been synthesized. An assumption that cyclic compounds with an approximately 15-membered ring give a musklike odor independent of the type of atoms in the ring skeleton was presented by Ruzicka *et al.*[2] However, in the syntheses of macrocyclic ureas[3] and macrocyclic amides,[4] we found that they gave no odor. Because of the big intermolecular attraction—possibly by H-bonding of the compounds which contain urea- or amide-linkages, it is understood that the melting point becomes high and the volatility becomes low. Assuming that the absence of odor in the macrocyclic ureas and macrocyclic amides was due to their strong intermolecular attraction, we carried out the syntheses of macrocyclic *N*-alkyl amides and *N*,*N*′-dialkyl ureas in which there is no possibility of H-bonding. 2-Methyl-2-azacyclohexadecanone was synthesized from 1,16-hexadecanedioic acid and was found to have a musklike odor.

The sequence of reactions used is shown in Scheme I. In the reaction of the bromoester (II) with methylamine, *N*-methyl-15-methylaminopentadecanamide (III) rather than methyl 15-methylaminopentadecanoate was obtained. 15-Methylaminopentadecanoic acid (IV) was obtained by hydrolysis of III with alcoholic potassium hydroxide, followed by adjusting the *p*H of the solution to 8.0.

Scheme I



When the hydrochloride (V) of the amino acid was treated with thionyl chloride, the amino acid chloride hydrochloride was apparently formed. 2-Methyl-2-azacyclohexadecanone (VI) was prepared by treating the reaction product of amino

(1) L. Ruzicka, *Helv. Chim. Acta*, **9**, 715, 1008 (1926).

(2) L. Ruzicka, G. Salomon, and K. E. Meyer, *Helv. Chim. Acta*, **17**, 882 (1934).

(3) Y. Iwakura, K. Uno, and M. Nakada, *J. Chem. Soc. Japan*, **80**, 78 (1959).

(4) Presented at the 12th meeting of the Chemical Society of Japan, Kyoto, April 1959.

acid hydrochloride V and thionyl chloride with triethylamine in benzene under high dilution.

EXPERIMENTAL

Methyl 15-bromopentadecanoate.[5] Wet silver oxide was added to molten methyl hydrogen 1,16-hexadecanedioate. The silver salt obtained was dried and dispersed in 200 ml. of dry carbon tetrachloride. To the dispersion bromine (82.5 g.) was added gradually while stirring at 40° and the stirring was continued for 2 more hr. at the same temperature. The reaction mixture was filtered, the filtrate was washed with aqueous potassium carbonate and dried with calcium chloride. The solvent was removed and the residue was distilled under reduced pressure to give faint brownish crystals, yield 55 g., b.p. 180°/0.3 mm., m.p. 36–38°.

N-Methyl-15-methylaminopentadecanamide. Thirty-three g. of methyl 15-bromopentadecanoate was dissolved in 100 g. of 30% methylamine solution in methanol and the solution was allowed to stand for 5 days at 30°. After the methanol and excess methylamine were removed, the residue was dissolved in ether. The ethereal solution was washed with aqueous potassium carbonate. The solvent was removed and the residue was distilled under reduced pressure to yield 18 g. of white crystals, b.p. 194–198°/0.05 mm., m.p. 78–79°.

Anal. Calcd. for $C_{17}H_{36}ON_2$: N, 9.85. Found: N, 9.62.

15-Methylaminopentadecanoic acid. *N*-methyl-15-methylaminopentadecanamide (18 g.) was dissolved in a mixture of potassium hydroxide (15 g.), water (20 ml.), and methanol (80 ml.), and heated for 40 hr. under reflux. After the methanol was removed, the residual alkaline solution was poured into 500 ml. of hot water and the *p*H of the solution was adjusted to 8.0 with 1*N* hydrochloric acid. The resulting precipitate weighed 8.3 g. and melted at 132–135°. Recrystallization from 50% ethanol solution gave white leaflets, m.p. 142.5–143.5°.

Anal. Calcd. for $C_{16}H_{33}O_2N$: N, 5.16. Found: N, 5.08.

15-Methylaminopentadecanoic acid hydrochloride. 15-Methylaminopentadecanoic acid was dissolved in hydrochloric acid and excess hydrochloric acid was removed under reduced pressure. Recrystallization of the residue from 90% acetone solution gave white leaflets, m.p. 127–128°.

Anal. Calcd. for $C_{16}H_{34}O_2NCl$: Cl, 11.52. Found: Cl, 11.55.

2-Methyl-2-azacyclohexadecanone. 15-Methylaminopentadecanoic acid hydrochloride (4.4 g.) was dissolved in 20 ml. of thionyl chloride. The excess thionyl chloride was removed under reduced pressure and the residue was dissolved in 50 ml. of absolute tetrahydrofuran. The solution was added to a mixture of triethylamine (35 g.) and dry benzene (3000 ml.) and then stirred at 75° for 15 hr. The reaction mixture was concentrated to about 1000 ml., washed with aqueous potassium carbonate, and the solvent was removed under reduced pressure. The residue was extracted with *n*-hexane, the extract was washed with aqueous sodium hydroxide, and the solvent was distilled. Distillation of the residue gave a clear colorless oil, 1.3 g., b.p. 150–168°/2 mm. Redistilled sample for analysis gave the following values: b.p. 172°/2.5 mm., n_D^{30} 1.4895, d_4^{30} 0.9782.

Anal. Calcd. for $C_{16}H_{31}ON$: N, 5.53. Found: N, 5.49.

Molecular weight. Calcd. for $C_{16}H_{31}ON$: 253. Found: 251.

Molecular refraction. Calcd. for $C_{16}H_{31}ON$: 77.759. Found: 77.234.

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(5) P. Chiut and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

Diels-Alder Adducts of Hexachlorocyclopentadiene with Allyloxyalkanols

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Received February 2, 1960

Many Diels-Alder adducts of hexachlorocyclopentadiene have been reported[1,2] with most classes of dienophiles. Of these adducts there have been a number with reported biological activity. In the field of agricultural chemistry one of the pressing weed control problems is that of aquatic plant life; the destruction of bothersome aquatic plants is particularly important in drainage and other service ditches. Hexachlorocyclopentadiene itself has shown some activity as an aquatic herbicide[3]; it has, however, the disadvantages of low water solubility and relatively high toxicity. Simple Diels-Alder adducts of hexachlorocyclopentadiene have been prepared from olefins possessing water solubilizing groups and these have as a rule been less toxic than the parent diene. For example, adducts have been prepared from allyl glycidyl ether[4] and from divinyl ether[5]; sulfite derivatives have been prepared from the adduct with 2-butyne-1,4-diol.[6] As a rule these have biological activity and possess greater water solubility than hexachlorocyclopentadiene itself.

This report describes the preparation of a series of adducts of hexachlorocyclopentadiene with dienophiles which might display enhanced water compatibility while at the same time retaining herbicidal activity. A series of allyloxy derivatives was prepared from allyl alcohol with ethylene oxide, 1-butylene oxide, and styrene oxide. These compounds (see Table I) were utilized in a standard preparative procedure with hexachlorocyclopentadiene to obtain the Diels-Alder adducts (see Table II). Purified samples of the compounds were tested against the several organisms. It is interesting that the adducts from 2-allyloxyethanol, 2-(allyloxyethoxy)ethanol, and 1-allyloxy-2-butanol were reasonably soluble or emulsifiable in water whereas the adduct from 2-allyloxy-1-phenylethanol was only slightly soluble; the biological activity of the first three adducts against both water weeds and other test organisms is of interest. The 2-allyloxyethanol and 2-(allyloxyethoxy)ethanol adducts both show pronounced activity as insecticides and herbicides as well as inhibition in micro-

(1) C. W. Roberts, *Chem. & Ind. (London)*, 110 (1958).
(2) H. E. Ungnade and E. T. McBee, *Chem. Revs.*, **58**, 249 (1958).
(3) Personal communication, Dr. K. Leasure, The Dow Chemical Company.
(4) W. L. Bressler and J. C. Smith, U. S. Patent, 2,834,790 (May 13, 1958).
(5) A. Goldman, U. S. Patent 2,795,619 (June 11, 1957).
(6) British Patent 810,602 (March 18, 1959).

TABLE I

ALLYLOXYALKANOLS

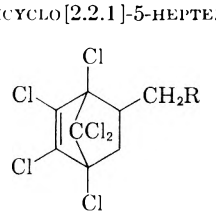
$CH_2{=}CHCH_2OR$

Substituent R	B.P.°	mm.	n_D^{25}	Literature Values B.P.°	mm.	n_D
CH_2CH_2OH	56	10	1.4326	159–160	atm	1.4355(20)[a]
				58–60	20	1.4360(20)[b]
$(CH_2CH_2O)_2H$	106	10	1.4445	98–101	2	1.4440(20)[a]
$CH_2CHOHC_2H_5$	95	60	1.4312	...	...	... [c]
$CH_2CH(C_6H_5)OH$	125	10	1.5193	118–119	4.5	1.5167(30)[d]

[a] A. A. Berlin, A. K. Dubagova, and E. F. Rodionova, *Sbornik Statei Obshchei Khim*, **2**, 1560 (1953); *Chem. Abstr.*, **49**, 5388 (1955). [b] V. N. Kotrelev and I. K. Rubstova, *Khim Prom.*, **1953**, 8; *Chem. Abstr.*, **50**, 6384 (1956). [c] *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.59; H, 10.84. Found: C, 63.91; H, 10.35. [d] D. Swern, G. N. Billen, and H. B. Knight, *J. Am. Chem. Soc.*, **71**, 1152 (1949).

TABLE II

(1,4,5,6,7,7-HEXACHLOROBICYCLO[2.2.1]-5-HEPTEN-2-YL)METHOXYALKANOLS[a]



Substituent R	Yield, %	B.P.°	mm	n_D^{25}	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
OCH_2CH_2OH	72	167	0.3	1.5446	32.03	31.75	2.69	2.51	56.74	57.40
$O(CH_2CH_2O)_2H$	75	185	0.2	1.5335	34.40	34.29	3.37	3.43	50.78	50.55
$OCH_2CHOHC_2H_5$	62	164	0.2	1.5319	35.76	36.21	3.50	3.49	52.79	52.80
$OCH_2CH(C_6H_5)OH$	42	250	0.8	1.5673	42.61	41.97	3.13	3.37	47.17	47.60

[a] Elemental analyses by Dr. S. A. Shrader, Analytical Laboratories, The Dow Chemical Co., Midland, Mich.

biological screening against *S. aureus* whereas the 2-allyloxy-1-phenylethanol adduct shows little or no activity in any of the three latter tests.

EXPERIMENTAL

Typical preparative details are given for only one experiment; the other compounds were prepared under nearly identical conditions (Tables I and II).

Preparation of (2-(1,4,5,6,7,7-hexachlorobicyclo[2.2.1]-5-hepten-2-yl)methoxyethoxy)ethanol. A mixture of 146 g. (1 mole) of 2-(2-allyloxyethoxy)ethanol (see Table I for physical data on starting compounds), 272 g. (1 mole) of hexachlorocyclopentadiene and 500 ml. of *o*-xylene was placed in a 2-l., single-necked, round-bottomed flask equipped with a reflux condenser and heating mantle. The mixture was heated to reflux and maintained at a temperature of 144° for 20 hr. The mixture was distilled to remove xylene and unchanged starting materials and to isolate the pure Diels-Alder adduct, *i.e.*, (2-(1,4,5,6,7,7-hexachlorobicyclo[2.2.1.]-5-hepten-2-yl)methoxyethoxy)ethanol (315 g., 75%), b.p. 185°/0.2 mm., n_D^{25} 1.5335.

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Synthesis of 3,5-Diphenylphenol and a Novel Complex Thereof

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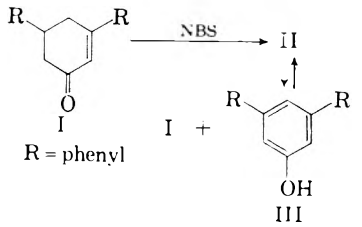
Received December 23, 1959

In the course of a synthetic scheme it was necessary to prepare 3,5-diphenylphenol. 3,5-Diphenylphenol (III) has been prepared by dehydrogenation of 3,5-diphenyl-2-cyclohexen-1-one[1] (I), by decarboxylation of 4,6-diphenylsalicylic acid,[2] and by decarboxylation of 2,6-dicarboxy-3,5-diphenylphenol.[3] In all cases, the yields were too small to be satisfactory in a synthetic scheme. It was reported that bromination of I with bromine followed by dehydrobromination failed to give III.[1] It was felt that repeating the preparation using

(1) A. D. Petrow, *Ber.*, **62**, 642 (1929).
(2) J. Kenner and H. Shaw, *J. Chem. Soc.*, 769 (1931).
(3) W. Deuschel, *Helv. Chim. Acta*, **34**, 168 (1951).

N-bromosuccinimide as the brominating agent might be more successful, as Deuschel reports that bromination of diethyl 2-oxo-4,6-diphenyl-6-cyclohexene-1,3-dicarboxylate with *N*-bromosuccinimide gives the corresponding phenol in excellent yield.



3,5 - Diphenyl - 2 - cyclohexen - 1 - one was prepared by the condensation of benzalacetophenone and acetoacetic ester, followed by hydrolysis and decarboxylation.[4] Bromination was readily effected with *N*-bromosuccinimide and the bromo-3,5-diphenyl-2-cyclohexen-1-one lost hydrogen bromide spontaneously. Recrystallization of the product gave 85–90% yields of a compound (II), m.p. 123–124°. The infrared spectrum indicated bonded hydroxyl (3300 cm.$^{-1}$) and conjugated carbonyl (1645 cm.$^{-1}$). The compound gave analysis corresponding to $C_{36}H_{30}O_2$.

Compound II proved to be an equimolar complex of 3,5-diphenylphenol (m.p. 94°[3]) and 3,5-diphenyl-2-cyclohexen-1-one (m.p. 82,[1] 89°[5]), and was also prepared by recrystallizing a mixture of I and III from hexane or ethanol. Compound formation was demonstrated by the method of Kofler[6] using a hot stage microscope. By heating a slide covered half by the phenol and half by the ketone, melting was observed at 85° and 92° corresponding to the two eutectics, at 89° and 94° for the two pure components, and at 124° for the compound, II.

The solution characteristics of II indicate essentially complete dissociation in dilute solution. The molecular weight, by cryoscopic or ebullioscopic methods, is 246 (theor. 246). The ultraviolet spectrum of II, in ethanol, is equal to the sum of the spectra of its two components. The strongly bonded hydroxyl frequency shifts to shorter wave lengths on dilution in chloroform as would be expected if dissociation occurred. Compound II may be separated into its components by extraction of the phenol from a solution of II in benzene-petroleum ether with Claisen's alkali or by chromatography on Woelm acid alumina grade one. The components may also be separated by the preparation of ketone (2,4-dinitrophenylhydrazone) or hydroxyl (methyl ether) derivatives. The overall yield of the phenol, using the alkali separation, based on I is 75–80%, allowing for recovered ketone. The recovered starting material from the complex may be recycled without further purification.

Apparently the spontaneous dehydrobromination begins when the bromination approaches 40–50% completion and the evolved hydrogen bromide halts further bromination. To circumvent this problem and increase the yield of III, large excesses of *N*-bromosuccinimide and peroxide catalyst were used. In these cases, the overall yield of II was reduced from 90% to 70–80% and some excess phenol was produced.

(4) E. Knoevenagel, *Ann.*, **281**, 59 (1894).

(5) W. Dieckmann, and K. von Fischer, *Ber.*, **44**, 971 (1911).

(6) A. Kofler, *Z. physik. Chem.*, A 187, 201 (1940); A. Kofler, *Z. physik. Chem.*, 363 (1940).

EXPERIMENTAL

3,5-Diphenyl-2-cyclohexen-1-one (I). Ethyl 4,6-diphenyl-2-oxo-3-cyclohexenecarboxylate[4] (9.0 g.) was dissolved in 50 ml. methanol and 50 ml. 10% aqueous sodium hydroxide was added. The solution was refluxed for 2 hr., cooled, and acidified with hydrochloric acid. Carbon dioxide was vigorously evolved. The solution was refluxed for 2 hr. and then concentrated. White crystals separated and were collected and dried. The product was recrystallized from ethanol giving 5.2 g. of I (85%) m.p. 82°.

Compound of 3,5-diphenylphenol and 3,5-diphenyl-2-cyclohexen-1-one (II). 3,5-Diphenyl-2-cyclohexen-1-one (2.0 g.) was dissolved in 25 ml. dry carbon tetrachloride by warming. To the solution was added 1.42 g. *N*-bromosuccinimide. The mixture was refluxed for 3 hr., during which time a red color developed. At the end of this time the reaction turned pale yellow and hydrogen bromide was evolved. After 1 hr additional refluxing the mixture was cooled and filtered to remove the succinimide. The carbon tetrachloride solution was then evaporated to dryness, leaving 2.0 g. reddish crystals, m.p. 95–98°. The product was recrystallized from hexane giving 1.75 g. (87% of theor.) of white crystals m.p. 123–124°.

A small sample recrystallized several times for analysis melted at 123.5–124.5°.

Anal. Calcd. for $C_{36}H_{30}O_2$: C, 87.42; H, 6.11. Found: C, 87.46; H, 6.16.

3,5-Diphenylphenol (III). Compound II (300 mg.) was dissolved in a mixture of 10 ml. benzene and 20 ml. petroleum ether. The solution was extracted with three 10-ml. portions of Claisen's alkali. The extract was diluted with an equal volume of water and acidified with hydrochloric acid. A tan oil separated which solidified on standing. The solid was collected and recrystallized from hexane (135 mg., m.p. 93–94°). Evaporation of the benzene-petroleum ether solution to dryness gave 150 mg. of a tan oil which crystallized from hexane giving 130 mg. I, m.p. 82–83°.

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Preparation of Certain 4-Acylphenols[1]

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Received December 21, 1959

A number of 4-acylphenols have been synthesized in conjunction with a study of ionization constants:

(1) From the M. S. thesis research of R. A. Bragole.

$$ArCOCl + C_6H_5OC_2H_5 \xrightarrow[CS_2]{AlCl_3} \xrightarrow[H_2O]{HCl} ArCO\text{-}C_6H_4\text{-}OH + C_2H_5Cl$$

I. Ar = 3-$CH_3C_6H_4$
II. Ar = 3-$CH_3OC_6H_4$
III. Ar = 3-$CF_3C_6H_4$
IV. Ar = 3,4-$Cl_2C_6H_3$
V. Ar = 3,5-$(NO_2)_2C_6H_3$

$$(CH_3)_2C{=}CHCOOH + C_6H_5OH + (CF_3CO)_2O \longrightarrow (CH_3)_2C{=}CHCO\text{-}C_6H_4\text{-}OH + 2CF_3COOH$$

VI

Three acylation methods were attempted: (a) polyphosphoric acid condensation of phenol with a carboxylic acid,[2] (b) trifluoroacetic anhydride condensation of phenol with a carboxylic acid,[3] and (c) Friedel-Crafts acylation of phenetole.[4] The last of these methods was the most generally successful in these preparations, giving the best yields of compounds I through V. Compound VI was synthesized by the trifluoroacetic anhydride condensation, but it could also be prepared by the Friedel-Crafts reaction, although in poorer yield. Phenyl esters ($C_6H_5OCOC_6H_4R$) rather than acylphenols were formed during the attempted synthesis of compounds I and II by trifluoroacetic anhydride condensation. Polyphosphoric acid condensation was ineffective for these particular compounds (I–VI), although some acylphenols have been prepared by this method, notably I in 19% yield and II in 15% yield.[2b] None of the products, I–VI, was accompanied by the isomeric 2-acylphenol, but in the course of preparing the known 3-nitro-4′-hydroxybenzophenone some of the 2-acylphenol, as its aluminum chelate, precipitated with the desired product when the Friedel-Crafts reaction mixture was hydrolyzed. Such chelates of 2-acylphenols have been reported earlier.[5] The aluminum chelate was insoluble in alkali and dilute acid but was decomposed by cold concentrated sulfuric acid to release the free 3-nitro-2′-hydroxybenzophenone.[6] This 2-acylphenol behaves much like salicylaldehyde and *o*-hydroxyacetophenone, which displace ammonia from the blue tetramminenickel ion to yield pale yellow or pale green solutions, from which stable nickel chelates may be isolated.[5] The 4-acylphenols have no visible effect upon solutions of tetramminenickel ion.

(2) (a) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **77**, 364 (1955); (b) K. Nakazawa and S. Baba, *J. Pharm. Soc. Japan*, **75**, 378 (1955); *Chem. Abstr.* **50**, 2510c (1956).

(3) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, **1951**, 718.

(4) P. J. Montagne, *Rec. trav. chim.*, **39**, 339 (1920).

(5) A. E. Martell and M. Calvin, *Chemistry of Metal Chelates*, Prentice-Hall, Inc., 1956, pp. 184, 185, 216, 228, 423.

(6) D. F. DeTar and D. I. Relyea, *J. Am. Chem. Soc.*, **76**, 1680 (1954).

EXPERIMENTAL

3-Methyl-4′-hydroxybenzophenone (I). Phenetole (4.64 g., 0.038 mole) and aluminum chloride (15.3 g., 0.115 mole) in 165 cc. of carbon disulfide were stirred together for 0.5 hr. at 0–5°. A solution of 6.05 g. (0.039 mole) *m*-toluoyl chloride in 45 cc. of carbon disulfide was added at 0–5° over a 0.5-hr. period with subsequent stirring for 7.5 hr. The mixture was left to stand at room temperature overnight. Upon treating the mixture with ice and hydrochloric acid, a white precipitate consisting largely of the desired 4-acylphenol was obtained. This was dissolved in 10% sodium hydroxide, and the solution treated with activated charcoal and filtered. The product, reprecipitated by acidifying the solution, was collected, washed with sodium bicarbonate to remove any *m*-toluic acid, washed again with water, and dried under vacuum. The yield was 4 g. (50%): m.p. 163–164°. Nakazawa and Baba report m.p. 166°.[2b] Extraction of the carbon disulfide layer with 10% sodium hydroxide yielded a negligible amount of precipitate on acidification of the aqueous layer. A small amount of red oil remained after distillation of the carbon disulfide, but it could not be crystallized.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.2; H, 5.7. Found: C, 79.0; H, 5.6.

3-Methoxy-4′-hydroxybenzophenone (II) was prepared in 51% yield by the same experimental method as I; m.p. 141–142°. Nakazawa and Baba report m.p. 138°.[2b]

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.6; H, 5.4.

3-Trifluoromethyl-4′-hydroxybenzophenone (III) was prepared in 21% yield by an experimental method similar to that used for I; m.p. 144–145°.

Anal. Calcd. for $C_{14}H_9F_3O_2$: F, 21.4. Found: F, 21.3.

3,4-Dichloro-4′-hydroxybenzophenone (IV) was prepared in 40% yield by the same experimental method as I; m.p. 172–174°.

Anal. Calcd. for $C_{13}H_8Cl_2O_2$: Cl, 26.6. Found: Cl, 26.6.

The carbon disulfide residue yielded 3 g. of red solid, m.p. 72–74°. This is most probably 3,4-dichloro-4′-ethoxybenzophenone, for treatment with aluminum chloride in refluxing carbon disulfide, followed by hydrolysis, converted it to the free phenol IV.

3,5-Dinitro-4′-hydroxybenzophenone (V) was prepared in 60% yield by the same experimental method as I; m.p. 196–197° dec.

Anal. Calcd. for $C_{13}H_8N_2O_6$: N, 9.7. Found: N, 9.8.

p-Hydroxyseneciophenone (VI). Senecioic acid (10 g., 0.1 mole) was dissolved in 42 cc. of trifluoroacetic anhydride. Phenol (10.8 g., 0.115 mole) was added, and the resulting mixture was refluxed gently for 4 hr. The mixture was allowed to stand 120 hr. at room temperature and then poured slowly with stirring into excess 10% aqueous sodium bicarbonate. When effervescence subsided, the mixture was extracted with several small portions of ether and the combined ether extract was dried over magnesium sulfate. After the ether was removed, the remaining oil was distilled twice at reduced pressure. The weight of the colorless oil which upon chilling froze to long needles was 9.15 g. (52%); b.p. 96° (12 mm.), m.p. 28–29°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 74.7; H, 7.0.

p-Hydroxyseneciophenone has the effect of a potent local anesthetic. Approximately 10 min. after contact of a drop of the oil with the skin, one begins to feel a numbing sensation at the area of contact. Addition of water to the area of contact seems to promote a striking insensitivity to pain (pin-pricks, hot surfaces, etc.) at the area of contact for a duration of 3 hr. or more, after which complete feeling is restored without any other noticeable effects.

Chelates of 3-nitro-2′-hydroxybenzophenone. The aluminum chelate of 3-nitro-2′-hydroxybenzophenone was isolated during the preparation of 3-nitro-4′-hydroxybenzophenone by a Friedel-Crafts acylation. Upon treating the reaction

mixture with ice and concd. hydrochloric acid, the aluminum complex and the free 4-acylphenol precipitated together. The complex was separated from the 4-acylphenol by treating the mixture with aqueous sodium hydroxide. The complex was decomposed with cold concd. sulfuric acid, and the free 2-acylphenol precipitated upon dilution with water. The aqueous filtrate gave a positive test for the aluminum ion. Upon treating the free 2-acylphenol with alcoholic tetramminenickel (II) chloride solution, a yellow solution resulted. Evaporation of most of the alcohol resulted in the precipitation of the stable nickel chelate, which was pale yellow. There was a striking resemblance of this chelate to that of the known nickel chelate of *o*-hydroxyacetophenone.[3] Treatment of this chelate with cold concd. sulfuric acid released the original 2-acylphenol upon dilution with water. The aqueous filtrate gave a positive test for the nickel ion.

Anal. Calcd. for $(C_{13}H_8O_4N)_2Ni$: Ni, 10.81. Found: Ni, 10.82.

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Condensation of Triethyl Phosphonoacetate with Aromatic Aldehydes

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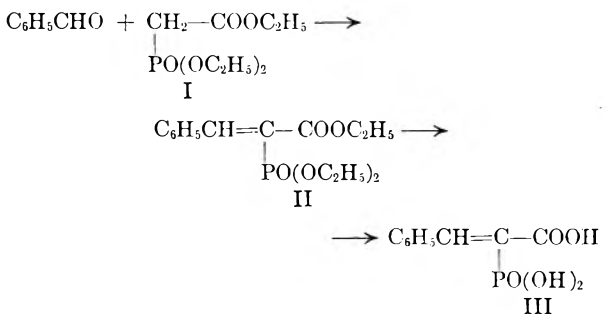
Our interest was attracted by a communication in which benzaldehyde and triethyl phosphonoacetate (I), on heating at 160–170° with acetic anhydride was reported to give triethylbenzylidenephosphonoacetate (II) yielding on acid hydrolysis what was claimed to be the benzylidene phosphonoacetic acid (III).[1]

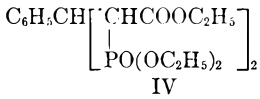


In view of the instability of the arylidenemalonic acids, which lose carbon dioxide rather easily both under acidic and basic conditions, the preparation of benzylidene phosphonoacetic acid by acid hydrolysis of the corresponding triester was somewhat surprising, and as no experimental details or analysis of the final product are given in Pudovik and Lebedeva's paper, we decided to re-investigate this reaction.

(1) A. N. Pudovik and N. M. Lebedeva, *Doklady Akad. Nauk S.S.S.R.*, **90**, 799 (1953) [*Chem. Abstr.*, **50**, 2429^d (1956)], names the final product (III) erroneously benzylidene phosphonic acid instead of benzylidene phosphonoacetic acid, as in the Russian text.

Under the conditions of the Russian authors, which are essentially those of the Perkin reaction, we obtained about 12% of a product, which gave on hydrolysis cinnamic acid, while 83–85% of the aldehyde could be recovered unchanged. The physical constants of the primary condensation product obtained by us, as well as its carbon-hydrogen analysis were in reasonable agreement with that obtained by the Russian authors, although the yield was very much smaller than claimed by them. On the other hand, we were unable to obtain by the hydrolysis of the triester any other product but cinnamic acid (which was identified by melting point, mixed melting point, analysis, and melting point of its bromophenacyl bromide derivative), although widely varied concentrations of both hydrochloric acid and potassium hydroxide were employed in various experiments. Indeed, the acid obtained by Pudovik and Lebedeva was stated by them to have a melting point of 132°, which is practically identical with that of cinnamic acid, and we believe that it actually was cinnamic acid. As no analysis is given in their paper, it may well be that this was identified as benzylidenephosphonoacetic solely on the assumption that hydrolysis of the triester must give the corresponding tribasic acid, without the occurrence of any further reaction.

Using different reaction techniques and basic catalysts, we were able to obtain much better yields of the triethylbenzylidenephosphonoacetate. (See Table I.) Incidentally, by careful fractionation of the reaction product obtained in the ethanol-piperidine mixture, an additional substance could be obtained, which gave the correct analysis for benzylidene bis(triethyl phosphonoacetate) IV, i.e., the condensation product of one mole of



benzaldehyde with two moles of triethyl phosphonoacetate. This product, too, gave cinnamic acid on hydrolysis, and its formation is analogous to the formation of a similar condensation product from two moles of ethyl nitroacetate and one mole of benzaldehyde.[2]

In similar experiments, with *p*-nitrobenzaldehyde and triethyl phosphonoacetate in ethanol as solvent and piperidine as the catalyst, very high yields (83%) of ethyl *p*-nitrocinnamate were obtained. No phosphorus-containing product could be isolated from the reaction mixture.

The relative strength of carbon-carbon and carbon-phosphorus bonds. The strength of carbon-carbon and carbon-phosphorus bonds, other things being equal, is of about the same order.[3]

(2) A. D. Dornow and G. Wiehler, *Ann.* **578**, 117 (1952).

(3) For a review of recent literature see P. C. Crofts, *Quart. Rev.* **12**, 341 (1958), and papers quoted there.

TABLE I

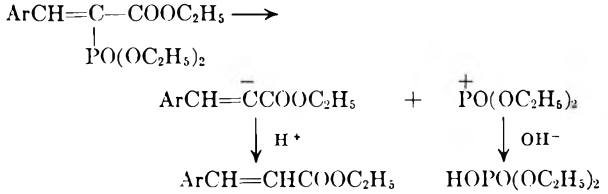
REACTION OF BENZALDEHYDE (BzH) WITH TRIETHYL PHOSPHONOACETATE (TPA)

No.	BzH, mole	TPA, mole	Solvent, Ml.	Catalyst	Temp.	Hr. Heating	Yield, %, of Cinnamic Acid
1.[a]	0.0312	0.0312	50 ml. acetic anhydride	—	160–170	5.5	12
2.[b]	0.0623	0.03	50 ml. ethanol	0.4 g. piperidine	Reflux	5	40
3.[c]	0.0312	0.0312	25 ml. pyridine	0.4 g. piperidine	100	19	22
4.[d]	0.070	0.062	25 ml. benzene	0.002 mole piperidine + 0.001 mole acetic acid	Reflux	44	70

[a] Hydrolysis of condensate by KOH/C_2H_5OH, 84% of the aldehyde recovered. [b] Fraction collected at 140–160°/1 mm: *benzylidenebis TPA* (IV), 10%. Hydrolysis of residue either by HCl or by KOH/C_2H_5OH. Longer heating of reaction mixture resulted in lower yields. [c] Fraction 140–160°/15 mm. hydrolyzed by KOH/C_2H_5OH. [d] Removal of water by azeotropic distillation. Fraction 160–170°/0.02 mm., redist. 140°/0.01 mm., 70% triester; 67% cinnamic acid (after hydrolysis).

In the present case, the question arises, as to why it is that after the hydrolysis of the triester, the elimination of the phosphonic acid group should be so much preferred against the elimination of the carboxyl group. Furthermore, in the case of the reaction between *p*-nitrobenzaldehyde and triethyl phosphonoacetate, the phosphonate group is eliminated already under the mild conditions of the condensation reaction, resulting in ethyl *p*-nitrocinnamate as the first product which can be isolated.

As the nitro group in the *para*-position of the aromatic group can hardly be responsible for any steric acceleration of the elimination, we believe that its effect is mainly the stabilization, by charge distribution, of the intermediate carbanion formed in the elimination. Owing to the rather small partial double-bond character of the phosphorus-oxygen bond,[3] its stabilizing effect will be much smaller than that of the carbonyl group in a dienic system C=C—C=O and therefore the elimination of the phosphonate group will be favored:



This effect seems to be strong enough to make the elimination of the phosphonate group possible under the mild conditions of the piperidine containing ethanol solvent with Ar = *p*-nitrophenyl, whereas in the case of Ar=phenyl, a strong base such as potassium hydroxide, is required.

The steric course of the condensation reaction. In most cases the crude ethyl *p*-nitrocinnamate obtained from the condensation melted at about 80–85° and even after one or two recrystallizations it still melted on rapid heating at 86–87° and on slow heating at 137–138°. Only after three or four recrystallizations did the ester melt both on rapid and on slow heating at 138°. We believe that the interpretation of these results must be that *p*-nitrobenzaldehyde with triethyl phosphonoacetate gives a primary condensation product in which the larger phosphonate group occupies the *trans*-position in reference to the aryl group, giving, on elimination of the phosphonate group, the unstable *cis*-ethyl *p*-nitrocinnamate (not described in the literature), which later isomerizes to the known *trans*-ester (high melting isomer, m.p. 138[4]).

Molecular models support this conclusion, as do also measurements of the C=C stretching frequency of II, which was found to be at 1625 $cm.^{-1}$. The C=C stretching frequency of diethylbenzylidene malonate is at 1650 cm^{-1}. If compound II were more hindered sterically than diethylbenzylidene malonate, it would be expected to give a higher wave number.[5]

EXPERIMENTAL

Materials used. Ethanol, benzene, pyridine, and piperidine were pure commercial products. Benzaldehyde was redistilled immediately before use. *p*-Nitrobenzaldehyde was recrystallized before use (m.p. 107°). Triethyl phosphonoacetate was prepared from diethyl phosphite[6] and ethyl chloroacetate, using a well dispersed suspension of sodium in xylene (instead of in hexane[7]).

(4) E. Bergmann, S. Berkovic, and R. Ikan, *J. Chem. Soc.*, 402 (1936); E. Bergmann, *et al.*, *J. Am. Chem. Soc.*, **78** 6037 (1956).

(5) A less hindered compound, ethylbenzylidene cyanoacetate, gave the same stretching frequency at 1615 $cm.^{-1}$. Measurements of various similar compounds with different substituents in the aryl group showed that polar effects are relatively small and do not interfere with the above conclusion. (Y. Zabicky, personal communication.)

(6) H. McCombie, B. C. Saunders, G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(7) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **68**, 1103 (1946).

Experiments with benzaldehyde are summarized in Table I. The *triethylbenzylidene phosphonoacetate* obtained in experiment No. 4, b.p. 140°/0.01 mm., n_D^{20} = 1.520–1.524, had the correct analysis.

Anal. Calcd. for $C_{15}H_{21}O_5P$: C, 57.7; H, 6.77. Found: C, 57.2; H, 7.1.

The cinnamic acid obtained from all experiments was identified by melting point and mixed melting point of the substance itself and by its *p*-bromophenacyl bromide derivative, m.p. 147.[8]

The substance obtained in experiment No. 2 had the correct analysis for *benzylidenebis(triethyl)phosphonoacetate*), $C_6H_5CH[CH(COOC_2H_5)PO(OC_2H_5)_2]_2$, IV.

Anal. Calcd. for $C_{23}H_{38}O_{10}P_2$: C, 51.57; H, 7.09. Found: C, 51.67; H. 6.85.

No attempt was made to establish the structure of this compound, but its analysis and the fact that it gave cinnamic acid on hydrolysis are strong evidence for its constitution.

The reaction of p-nitrobenzaldehyde with triethyl phosphonoacetate. In a representative experiment, 6 g. (0.0398 mole) of *p*-nitrobenzaldehyde and 5.5 g. (0.0246 mole) of triethyl phosphonoacetate were refluxed for 5 hr. in 60 ml. of pure ethanol containing 0.4 g. of piperidine. After removal of most of the solvent *in vacuo*, the residue solidified and melted at 80–85°. After one recrystallization from dilute ethanol, the substance melted at 86–87° (fast heating) and 90–91° (slow heating). After the second recrystallization the substance melted at 86° (fast heating) and at 138° (slow heating). After the third recrystallization the melting point was 138°, both on fast and slow heating.

The *cis*-ethyl *p*-nitrocinnamate is not described in the literature; the *trans*-ester melts at 138°.[4]

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.8; H, 4.98; N, 6.34. Found: C, 60.2; H, 5.4; N, 6.3.

On hydrolysis the substance yielded *trans-p*-nitrocinnamic acid, m.p. 285° dec., showing no depression with an authentic sample.

Attempted reaction of benzophenone with triethyl phosphonoacetate. Using the same conditions as in the above experiment, over 85% of the benzophenone was recovered unchanged and no other product could be isolated from the reaction mixture.

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(8) J. Reid, *J. Am. Chem. Soc.*, **42**, 1055 (1920).

Substituted γ-Lactones. V.[1] Synthesis of Certain α,β-Disubstituted γ-Lactones. A Route to Lignans of the α, β-Dibenzylbutyrolactone Class

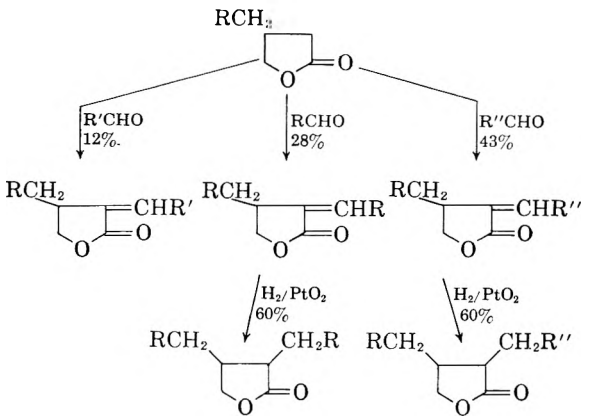
Hans Zimmer, Johannes Rothe,[2] and James M. Holbert

Received December 28, 1959

In our investigations dealing with substituted γ-lactones[3a–c] we became interested in the synthesis of α,β-disubstituted γ-butyrolactones, especially α,β-unsymmetrically substituted γ-butyrolactones. This type of butyrolactones occurs in nature as a class of lignans.[4,5] These are compounds which, at least formally, could be derived from substituted *n*-propylbenzenes which are dimerized by joining the β-carbon atoms of the side chain. Haworth and Woodcock[6] gave a synthesis of such a compound, namely, matairesinol (I), and its dimethylether (II).

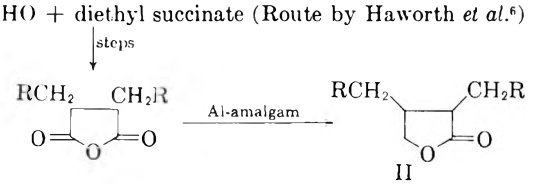
In paper III[3a] of this series we described a method which is generally applicable for the synthesis of β-benzyl-γ-butyrolactones. In paper I[3b] of this series we showed that γ-butyrolactone condenses with a large variety of aldehydes to yield α-benzylidene-γ-butyrolactones. A combination of these two methods resulted in a convenient procedure for synthesizing symmetrically and unsymmetrically α,β-disubstituted γ-butyrolactones. We tested this method in the synthesis of II as a member of a natural occurring lignan and in the synthesis of α-(4-dimethylaminobenzyl)-β-(3,4-dimethoxybenzyl)-γ-butyrolactone as an example for an α,β-unsymmetrically substituted γ-butyrolactone.

The following chart illustrates the route of the syntheses.



R = 3,4-dimethoxyphenyl
R′ = 3,4-dioxymethylenephenyl
R″ = 4-dimethylaminophenyl

2 RCHO + diethyl succinate (Route by Haworth *et al.*[6])



II

II was converted into a dinitro derivative. II and its dinitro derivative synthesized by this route were identical in melting points and infrared spectra with II and dinitro-II prepared by Haworth's method. Both compounds gave no depressions when mixed melting points were determined.

(1) Paper IV of this series, Hans Zimmer, J. Rothe, and Dolores Gracian, *J. Org. Chem.*, in press.

(2) Chattanooga Medicine Company Post-doctorate Research Fellow, 1956–1958. Recipient of a Fulbright Travel Grant.

(3) (a) J. Rothe and Hans Zimmer, *J. Org. Chem.*, **24**, 586 (1959); (b) Hans Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959); (c) Hans Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 100 (1959).

(4) R. D. Haworth, *Nature*, **147**, 225 (1941).

(5) W. M. Hearon and W. S. MacGregor, *Chem. Rev.*, **55**, 957 (1955).

(6) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1939, 154.

As is shown in the condensation between piperonal and β-veratryl-γ-butyrolactone this method is not restricted to a few aldehydes but is obviously a general one for the synthesis of α,β-disubstituted γ-butyrolactones.

We are presently engaged in applying this route in the preparation of other lignans of the α,β-benzylbutyrolactone class.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

The infrared spectra were taken in nujol mulls on a Baird double-beam spectrophotometer.

dl-α-(3,4-Dimethoxybenzylidene)-β-(3,4-dimethoxybenzyl)-butyrolactone. Two grams (8.5 millimoles) of β-(3,4-dimethoxybenzyl)butyrolactone,[3] 1.4 g. (8.5 millimoles) of veratraldehyde, 0.5 g. (9 millimoles) of sodium methoxide, and 16 ml. of benzene were kept in a stoppered bottle for 6 days with occasional shaking. Sulfuric acid, 25 ml. of 2*N*, was added; after some agitating, the layers were separated. The aqueous layer was once more extracted with benzene and the combined organic phase was washed successively with 10% sodium bisulfite and 2*N* sodium carbonate solutions, then with water. After removal of the solvent a brownish oil remained which was taken up in methanol-ether. The compound crystallized after standing in the refrigerator for about 10 days; in later experiments, the process could be accelerated by seeding. The crude first fraction (0.5 g.; m.p. 130–131°) was brownish but could easily be washed colorless with a small amount of methanol. By working up the filtrates, an additional 0.4 g. (m.p. 127–128°) of the compound was obtained; total yield 0.9 g. (28%). The analytical sample melted at 131–131.5°; microcrystalline powder from methanol. The infrared spectrum was as follows: 5.77 μ and 6.08 μ (lactonic C=O, C=C double bond).

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.57; H, 6.19.

dl-α,β-Bis(3,4-dimethoxybenzyl)butyrolactone (dl-Matairesinol dimethyl ether) (II). A. One gram of α,β-bis(3,4-dimethoxybenzyl)succinic anhydride (m.p. 109–111°; lit., m.p. 110–112°) was reduced with amalgamated aluminum according to Haworth and Woodcock.[6] The work-up procedure was changed as follows: After filtration, the alumina was extracted (Soxhlet, 24 hr.) with chloroform; evaporation of the combined extract and filtrate yielded an oil which was refluxed with 5% methanolic potassium hydroxide solution (10 ml.) for 30 min. The methanol was removed, the residue taken up in water (10 ml.), the aqueous solution washed twice with methylene chloride, acidified with hydrochloric acid, and heated on a water bath for 1 hr. The cooled mixture was extracted with chloroform, the extract washed with sodium bicarbonate solution and water, dried (sodium sulfate), and the solvent removed. The residue was taken up in methanol to give 420 mg. (43%) of the lactone, m.p. 111–113°. One recrystallization from methanol raised the melting point to 112–114° (lit., 113–115°).

B. The preceding unsaturated lactone (2.60 g.) was hydrogenated in methanol with platinum oxide (50 p.s.i.). The crude product (2.52 g.) was an almost colorless oil; its methanolic solution did not deposit any crystals, even after standing in the refrigerator for 1 year. Crystallization could easily be induced, however, by seeding with a sample prepared by procedure A; 1.56 g. (60%) of short white prisms, m.p. 102–107°, were obtained. Two recrystallizations from methanol gave material melting at 112–114°, unchanged when mixed with a sample prepared by procedure A. The infrared spectra (5.67 μ) were identical.

The *dinitro derivative* was prepared according to Haworth and Woodcock[6]: (1) from the reduction product of the anhydride (yellow needles from chloroform-methanol, m.p. 193–194°; lit.: 191–192°), and (2) from the crude hydrogenation product (yellow needles from dioxane-methanol, m.p. 190.5–191.5°). Mixed melting point of the two specimens was 191–193°. The infrared spectra (5.69μ) were identical.

Anal. Calcd. for $C_{22}H_{24}N_2O_{10}$: C, 55.46; H, 5.08; N, 5.88. Found: C, 55.45; H, 5.14; N, 5.89.

dl-α-(p-Dimethylaminobenzylidene)-β-(3,4-dimethoxybenzyl)-butyrolactone was obtained from β-(3,4-dimethoxybenzyl)-butyrolactone and *p*-dimethylaminobenzaldehyde as above, with a yield of 43% as pale-yellow short needles from dioxane-methanol, m.p. 193–193.5°; infrared spectrum: 5.74 β and 6.12 β.

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.00; H, 6.73; N, 3.99.

dl-α-(p-Dimethylaminobenzyl)-β-(3,4-dimethoxybenzyl)-butyrolactone was prepared by hydrogenation of the preceding compound in 60% yield, as colorless blocks from methanol, m.p. 115–115.5°. The infrared spectrum was as follows: 5.64 μ (no peak at ~6.1 β, no C=C-unsaturation).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.76; H, 7.47; N, 3.84.

dl-α-(3,4-Methylenedioxybenzylidene)-β-(3,4-dimethoxybenzyl)butyrolactone was prepared from β-(3,4-dimethoxybenzyl)butyrolactone and piperonal as above, yield 12% as pale-yellowish short needles from methanol, m.p. 97–97.5°. The infrared spectrum showed the following bands: 5.75 and 6.10 μ.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; Found: C, 68.40; H, 5.44.

Acknowledgment. The authors appreciate the skillful assistance of Mr. Horst Schmank.

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Esters and Ketones Related to Diphenylacetic Acid

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In order to study the pharmacological properties of ketones and basic esters related to diphenylacetic acid, the preparation of a number of such compounds (Table I) was required. These molecules are of interest since they are structurally related to substances possessing antispasmodic, local anesthetic, anti-adrenal, and analgetic activities.

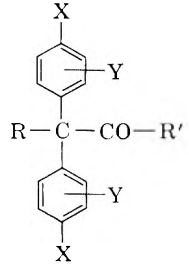
Most of the final compounds prepared in the present study possess nuclear amino groups. 2,2-Bis(*p*-nitrophenyl)propionic acid (I) and 2,2-bis(*p*-nitrophenyl)acetic acid (II)[1,2] were prepared by acid hydrolysis of the respective methyl esters.[3] The reported[1] facile decarboxylation of II

(1) I. M. Hunsberger and E. D. Amstutz, *J. Am. Chem. Soc.*, 71, 2635 (1949).

(2) L. Haskelberg and D. Lavie, *J. Am. Chem. Soc.*, 71, 2580 (1949).

TABLE I

COMPOUNDS RELATED TO DIPHENYLACETIC ACID



No.	R	R'	X	Y	Yield,[a] %	Solvent	Salt	M.P. or B.P. (mm.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	CH_3	OH	NO_2	H	71	80% HOAc	...	175–177[b]	$C_{15}H_{12}N_2O_6$	56.96	57.07	3.82	3.78
2	CH_3	Cl	NO_2	H	63	C_6H_6-PE	...	125–126	$C_{15}H_{11}ClN_2O_5$	53.82	53.85	3.31	3.33
3[c]	CH_3	Cl	CH_3	NO_2	57	C_6H_{14}	...	89–90	$C_{17}H_{15}ClN_2O_5$	56.28	56.59	4.17	4.18
4	H	$(CH_3)_2NCH_2CH_2O$	NO_2	H	67	C_6H_6-PE	...	117–119[b]	$C_{18}H_{19}N_3O_6$	57.90	58.17	5.13	5.29
5	H	$(C_2H_5)_2NCH_2CH_2O$	NO_2	H	64	$(CH_3)_2CO(C_2H_5)_2O$	HCl	164–166	$C_{20}H_{24}ClN_3O_6$	54.86	54.98	5.52	5.73
6	H	C_2H_5O	NO_2	H	...	C_2H_5OH	...	126–128	$C_{11}H_{14}N_2O_6$	58.18	57.99	4.27	4.45
7	CH_3	$(CH_3)_2NCH_2CH_2O$	NO_2	H	...	CH_3OH-$(C_2H_5)_2O$	HCl	222–223[b]	$C_{19}H_{22}ClN_3O_6$	53.84	53.89	5.23	5.29
8	CH_3	$(C_2H_5)_2NCH_2CH_2O$	NO_2	H	45	2-C_3H_7OH	HCl	171–172	$C_{21}H_{26}ClN_3O_6$	55.81	55.82	5.80	5.88
9	CH_3	$(C_2H_5)_2NCH_2CH_2O$	CH_3	NO_2	...	C_2H_5OH	Pier.	105–107	$C_{29}H_{32}N_6O_{13}$	51.78	51.78	4.80	5.00
10	CH_3	$(C_2H_5)_2NCH_2CH(CH_3)O$	NO_2	H	...	CH_3OH-$(C_2H_5)_2O$	HCl	185–187	$C_{22}H_{28}ClN_3O_6$	56.71	56.43	6.06	6.23
11[d]	CH_3	CH_3	NO_2	H	77	95% C_2H_5OH	...	164–166	$C_{16}H_{14}N_2O_5$	61.14	61.31	4.49	4.56
12	CH_3	CH_3	CH_3	NO_2	81	CH_3OH	...	100–101[e]	$C_{18}H_{18}N_2O_5$	63.15	62.17	5.30	5.55
13	CH_3	CH_3	CH_3	NH_2	26	C_6H_6-PE	...	117–118	$C_{18}H_{22}N_2O$	76.56	76.89	7.85	7.98
14[c]	CH_3	$(C_2H_5)_2NCH_2CH_2O$	CH_3	NH_2	35	C_2H_5OH-$(C_2H_5)_2O$	HCl	195–196	$C_{23}H_{31}ClN_3O_2$	65.77	65.54	8.16	8.38
15	H	$(CH_3)_2NCH_2CH_2O$	NH_2	H	67	C_6H_6-PE	...	130–132	$C_{18}H_{23}N_3O_2$	68.98	68.72	7.39	7.07
16	H	C_2H_5O	NH_2	H	...	C_6H_6-PE	...	88–89	$C_{16}H_{18}N_2O_2$	71.09	71.25	6.71	6.84
17	CH_3	$(C_2H_5)_2NCH_2CH_2O$	NH_2	H	70	[f]	...	[g]	$C_{21}H_{29}N_3O_2$	70.95	70.84	8.22	8.30
18	H	OH	$C_6H_5CH_2OCONH$	H	51	...	...	159–162	$C_{30}H_{26}N_2O_6$	70.57	70.34	5.13	5.13
19	CH_3	CH_3	$TsNCH_3$	H	59	EtOH	...	147–149[h]	$C_{32}H_{34}N_2O_5S_2$	65.06	64.97	5.80	6.01
					...	EtOH		170–171[h]			65.13		6.00
20	CH_3	CH_3	$TsNC_2H_5$	H	44	95% EtOH	...	166–167	$C_{34}H_{38}N_3O_9S_2$	65.99	65.89	6.19	6.23
21	CH_3	CH_3	CH_3NH	H	73	EtOH	HCl	203–204	$C_{18}H_{24}Cl_2N_2O \cdot 1/2\ H_2O$	59.34	59.54	6.92	7.03
22	CH_3	CH_3	C_2H_5NH	H	40	EtOH	...	96–97	$C_{20}H_{26}N_2O \cdot 1/2\ H_2O$	75.20	75.23	8.52	8.34
23	CH_3	CH_3	F	H	27	...	...	133 (0.7)	$C_{16}H_{14}F_2O$	73.83	73.81	5.42	5.55

[a] Yields refer to purified products. [b] Melted with decomposition. [c] Ref. 9. [d] M.p. 165.5–167.5° when prepared by a different method: J. Korman and E. C. Olsen, *J. Org. Chem.*, 22, 870 (1957). [e] Further recrystallization failed to improve the analysis, but the impure product could be reduced to No. 13. [f] Purified by chromatography on alumina in benzene. [g] Occurred as an oil. [h] Occurred in interconvertible dimorphic forms.

during acid hydrolysis of its methyl ester and subsequent recrystallization apparently arose from the use of alkali in isolating the product, since we observed no such degradation when using a similar procedure[2] which avoided alkaline conditions. Conversely, I, which lacks an acidic hydrogen atom on the α carbon atom, was stable under basic conditions.

The acids were converted to the respective chlorides and then to the esters. For the preparation of methyl ketones, the acid chlorides were treated with diazomethane and the resulting diazoketones were reduced with hydriodic acid. The use of dimethylcadmium for the conversion to methyl ketones gave no isolable product, although it is reported[4] that dimethylcadmium does not react with aromatic nitro groups.

The aromatic nitro compounds were reduced catalytically to the desired amino derivatives. In some cases, basic esters of I and II could not be reduced in or recrystallized from methanol or ethanol, since transesterified products were obtained; the reductions proceeded normally in dioxane.

In an attempt to avoid the low yield nitration required for the preparation of II, 2,2-bis(*p*-aminophenyl)acetic acid monohydrochloride was prepared directly[5] from aniline and dichloroacetic acid and converted to the carbobenzyloxy derivative. Treatment of the latter with β-diethylaminoethyl chloride[6] did not, however, result in an isolable product.

3,3 - Bis(*p* - *N* - methylaminophenyl) - 2 - butanone and the corresponding *N*-ethyl compound were prepared by a different sequence. 3,3-Bis(*p*-aminophenyl)-2-butanone (III)[7] was tosylated and the resulting sulfonamide was alkylated. Acid hydrolysis gave the desired secondary amines. 3,3-Bis(*p*-fluorophenyl)-2-butanone was obtained by tetrazotization of III, conversion to the fluoborate salt, and pyrolysis.

EXPERIMENTAL[8]

2,2-Bis(p-nitrophenylpropionic acid) (No. 1). A stirred mixture of 302 ml. of sulfuric acid, 71 ml. of water, 163 ml. of acetic acid, and 90.6 g. (0.28 mole) of methyl 2,2-bis(*p*-nitrophenyl)propionate[3] was heated at 95° for 18 hr. and then poured into water. The product was extracted into chloroform and the filtered chloroform solution was washed with 10% sodium hydroxide solution. Acidification of the alkaline wash with concd. hydrochloric acid precipitated the crystalline product, which was collected and recrystallized.

The crystalline *acid chloride (No. 2)* was obtained when a solution of 1.7 g. of the acid in 25 g. of thionyl chloride was refluxed for 1 hr. and the excess thionyl chloride was removed *in vacuo* with the aid of dry benzene.

2,2-Bis(p-methyl-x-nitrophenyl)propionyl chloride (No. 3).[9] A solution of 15 g. (0.04 mole) of 2,2-bis(*p*-methyl-*x*-nitrophenyl)propionic acid[10] in 300 g. of thionyl chloride was heated at 80° until the cessation of hydrogen chloride evolution and then evaporated *in vacuo*. The residue was recrystallized (Darco).

Nitro esters (Nos. 4, 5, 6, 7, 8, 9, and 10). A 10% solution of the appropriate acid chloride (1 mole equivalent) in benzene was treated with the requisite alcohol (2 mole equivalents) and the mixture was refluxed for 1 hr.[11] The cooled solution was washed, dried (sodium sulfate), filtered, and evaporated. The residue was recrystallized or converted to a salt. When 2,2-bis(*p*-nitrophenyl)acetyl chloride was esterified with 2-dibutylaminoethanol and the product was recrystallized from ethanol, transesterification took place and only the ethyl ester (No. 6) was obtained.

Methyl ketones by diazoketone synthesis (Nos. 11, 12). A 10% solution of the requisite acid chloride (1 mole equivalent) in methylene chloride was added dropwise to diazomethane (2 mole equivalents) in methylene chloride. The resulting solution was allowed to stand for 18 hr. and then stirred with excess 58% hydriodic acid. The layers were separated and the methylene chloride was washed successively with water, 10% sodium thiosulfate solution and water. The dried (sodium sulfate) solution was evaporated and the product was recrystallized.

3,3-Bis(p-methyl-x-aminophenyl)-2-butanone (No. 13). A warm solution of 1 g. (0.003 mole) of 3,3-bis(*p*-methyl-*x*-nitrophenyl)-2-butanone and 0.6 g. (0.018 mole) of hydrazine in 10 ml. of absolute alcohol was treated with portions of Raney Nickel from the tip of a microspatula until frothing ceased. The cooled solution was filtered and evaporated and the residue was recrystallized.

Reduction of nitro esters (Nos. 15, 16, and 17). A 10% solution of the nitro ester in pure dioxane was shaken with Adams' catalyst under hydrogen until the theoretical quantity of hydrogen was absorbed. The mixture was filtered and evaporated and the product was recrystallized.

2,2-Bis(p-carbobenzyloxyamidophenyl)acetic acid (No. 18). To a stirred solution of 14.0 g (0.5 mole) of 2,2-bis(*p*-aminophenyl)acetic acid monohydrochloride[5] in 30 ml. (0.12 mole) of 4*N* sodium hydroxide solution there was added, alternately and dropwise, 21.0 g. (0.12 mole) of benzyl chloroformate and 30 ml. (0.12 mole) of 4*N* sodium hydroxide at 5° during 30 min. After 15 min. a gum separated and stirring was continued for 2 hr. Then 150 ml. of ethyl acetate and 150 ml. of 10% hydrochloric acid were added and the layers were separated. The organic phase was washed with water, dried (sodium sulfate), filtered, and evaporated to leave an oil which crystallized on trituration with ether. The product could not be recrystallized but was obtained in pure condition on washing with chloroform.

(3) E. J. Skerrett and D. Woodcock, *J. Chem. Soc.*, 2806 (1952).

(4) C. H. Wang, R. Isensee, A. M. Griffith, and B. E. Christensen, *J. Am. Chem. Soc.*, **69**, 1909 (1947).

(5) G. Heller, *Ann.*, **375**, 261 (1910).

(6) H. Horenstein and H. Pahlicke, *Ber.*, **71**, 1644 (1938).

(7) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 117 (1950); W. L. Bencze and M. J. Allen, *J. Org. Chem.*, **22**, 352 (1957). We thank Dr. D. W. Blackburn and Mr. R. Lange for preparing this material.

(8) All melting points are corrected. Microanalyses were carried out by the Analytical Section.

(9) R. B. Holmes and A. J. Hill, U. S. Patent **2,423,025**, June 24, 1947, disclosed this compound without analytical results.

(10) A. Haiss, *Ber.*, **15**, 1474 (1882).

(11) In later runs it was found that the use of equimolar amounts of the aminoalcohol and 2,2-bis(*p*-nitrophenyl)-acetyl chloride gave cleaner products. It was also found advantageous to add the amino-alcohol slowly to a refluxing solution of the acid chloride. Both of these modifications serve to reduce the possibility of alkaline degradation of the nitro compound.

N-Alkyl derivatives of 3,3-bis(p-toluenesulfonamidophenyl)-2-butanone (Nos. 19 and 20). A mixture of 300 ml. of pyridine, 38.7 g. (0.12 mole) of 3,3-bis(*p*-aminophenyl)-2-butanone dihydrochloride[7] and 57.2 g. (0.3 mole) of *p*-toluenesulfonyl chloride was stirred for 45 min. at 27° and poured into water. The product was extracted into chloroform and the chloroform was washed successively with 20% sulfuric acid, 5% sodium carbonate solution, and water. The dried (magnesium sulfate), filtered chloroform solution was evaporated and the residue was dissolved in 10% sodium hydroxide solution and filtered. The filtrate was acidified with acetic acid to give a pink solid which was collected and dried. There was obtained 86.6 g. (95%) of product, m.p. 75–80°, which could not be recrystallized but which was suitable for use in subsequent reactions.

A 25% solution of the sulfonamide (1 mole equivalent) in ethanol was treated with 1*N* sodium hydroxide (3 mole equivalents) and the requisite alkyl iodide (3 mole equivalents) and stirred at 75° for 3 hr. It was partially evaporated and then extracted with benzene. The benzene layer was washed with water, dried (magnesium sulfate) and evaporated. The residue was recrystallized.

3,3-Bis(p-N-alkylaminophenyl)-2-butanones (Nos. 21 and 22). The appropriate sulfonamide derivative in two volumes of 80% sulfuric acid was heated at 155–160° for 5 min. The cooled solution was poured into water, made alkaline with 20% sodium hydroxide solution, and the product was extracted into ether. The washed, dried (potassium carbonate) ether extract was evaporated and the residue was recrystallized or converted to a salt.

3,3-Bis(p-fluorophenyl)-2-butanone (No. 23). A stirred solution of 16.4 g. (0.05 mole) of 2,2-bis(*p*-aminophenyl)-3-butanone dihydrochloride[7] in 25 ml. of 37% hydrochloric acid and 25 ml. of water was treated dropwise with a solution of 7.2 g. (0.105 mole) of sodium nitrite in 15 ml. of water at 0°. The excess nitrite was neutralized with urea and to the solution there was added 15.2 g. (0.14 mole) of sodium fluoborate in 30 ml. of water. The resulting precipitate was filtered, washed successively with 6 ml. of water, 3 ml. of methanol, and 10 ml. of ether and dried to give 17.0 g. (76%) of salt, m.p. 139° dec.

The diazonium fluoborate was decomposed by heating with a free yellow flame, and the residue was dissolved in chloroform, washed with dilute hydrochloric acid, 10% sodium hydroxide and water, and then dried (sodium sulfate). The filtered chloroform solution was fractionally distilled.

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γ-(*p*-Aminophenyl)butyric Acid

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The preparation of γ-(*p*-aminophenyl)butyric acid was reported by van der Scheer[1] in 1934 through reduction of γ-(*p*-nitrophenyl)butyric acid. The nitrated derivative was obtained from γ-phenylbutyric acid which in turn had been prepared from phenylethyl bromide by the malonic ester synthesis described by Fischer.[2]

Starting with γ-phenylbutyric acid which had been prepared through Clemmensen reduction[3] of ε-benzoylpropionic acid, the procedure of van der Scheer gave the amino acid in an over-all yield of 6%. The nitration of γ-phenylbutyric acid to γ-(*p*-nitrophenyl)butyric acid was accomplished in only 20% yield, the formation of the *ortho* isomer predominating. Although van der Scheer reported a yield of 70% for the preparation of the γ-(*p*-aminophenyl)butyric acid by zinc dust–hydrochloric acid reduction of the nitro compound, the yield obtained in several reactions was not over 40%.

The need for considerable quantities of γ-(*p*-aminophenyl)butyric acid led to the development of the two-step synthesis described herein which affords the amino acid in an over-all yield of 43%. Acetanilide is succinoylated by the procedure described in the literature[4] to give β-(*p*-acetylaminobenzoyl)propionic acid in 60% yield. Treatment of this keto acid by the Huang-Minlon[5] modification of the Wolff-Kishner reaction effected both reduction of the carbonyl group and hydrolysis of the acetamido group in one step to form the γ-(*p*-aminophenyl)butyric acid.

Previous attempts to effect this combined hydrolysis-reduction through the Clemmensen reaction were not successful.

EXPERIMENTAL[6]

A mixture of β-(*p*-acetylaminobenzoyl)propionic acid[4] (77 g., 0.33 mole), 76 g. of potassium hydroxide, 55 ml. of hydrazine hydrate (85%), and 400 ml. of triethylene glycol were heated under reflux for 1.5 hr. The condenser was then removed and the temperature of the solution raised to 195° during which time excess hydrazine hydrate was expelled. (*Caution*—Hood). Refluxing was then continued for an additional 4 hr. at this temperature. The cooled solution was diluted with 400 ml. of water and made weakly acidic (to Alkacid paper) by the addition of 6*N* hydrochloric acid, about 200 ml. being required. The acid which precipitated was removed by filtration, washed with cold water, and dried in a vacuum desiccator over anhydrous calcium chloride; yield 42.8 g., 73%, m.p. 115–120°. Recrystallization of the analytical sample from water gave white plates, m.p. 130–132°. The melting point was not depressed when mixed with an authentic sample of γ-(*p*-aminophenyl)-butyric acid.[7]

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.96; H, 7.55; N, 7.76.

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(1) J. van der Scheer, *J. Am. Chem. Soc.*, **56**, 744 (1934).

(2) E. Fischer, *Ber.*, **39**, 2211 (1906).

(3) E. L. Martin, *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 81.

(4) J. P. English, *et al.*, *J. Am. Chem. Soc.*, **67**, 2263 (1945).

(5) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(6) All melting points are uncorrected.

(7) van der Scheer reported a melting point of 130–131°.

β-Arylglutaconic Acids. III.[1] The Action of Acetic Anhydride and Sodium Acetate on β-(2-Methoxy-4-methylphenyl)glutaconic Anhydride

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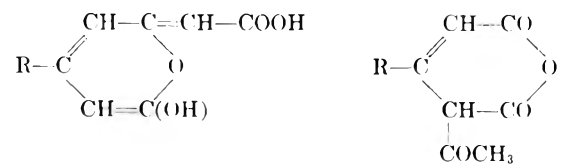
Under the conditions of the Perkin reaction, β-(4-methoxyphenyl)glutaconic anhydride has been shown to give a condensation product thought to be the corresponding glutaconylacetic acid (I).[3] Similar results were obtained earlier by other workers in the case of phthalic anhydride.[4,5] Gogte,[6] however, claims that the condensation product can be represented better by structure II than by structure I,



I II

R = 4-Methoxyphenyl

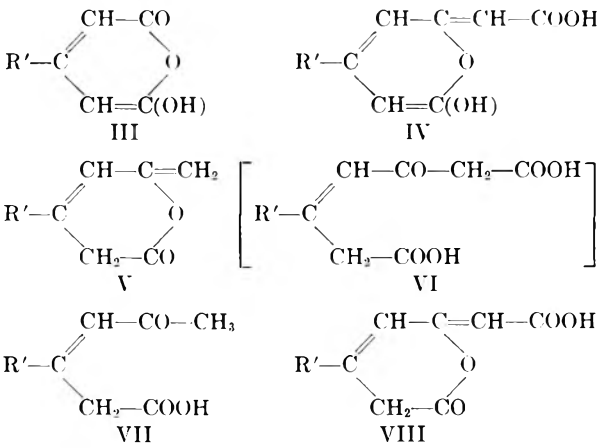
since he also obtained it from β-(4-methoxyphenyl)-glutaconic anhydride under the conditions of Einhorn's acetylation method.[7]

This structural discrepancy has been resolved by Bhave on the basis of chemical evidence,[8] which indicates that the compound is a lactonic acid (I) rather than a ketonic anhydride (II).

In the present studies, we have collected further experimental and physical evidence in support of structure I by preparing similar compounds from an analogous anhydride, namely β-(2-methoxy-4-methylphenyl)glutaconic anhydride, and studying their infrared spectra.[9]

β-(2-Methoxy-4-methylphenyl)glutaconic anhydride (III), the intermediate for the present work, was obtained in 94% yield from the corresponding glutaconic acid[10] by the action of acetic anhydride at reflux temperature. The infrared spectrum of III had strong absorption peaks at 5.65 μ and 5.76 μ, characteristic of unstrained six-membered anhydride attached to an aromatic nucleus.[11] When III was subjected to the action of acetic anhydride in presence of fused sodium acetate, following the general procedure of Bhave,[3] an acidic substance (IV) was obtained in 67% yield. The infrared spectrum of IV does not show absorption attributable to an anhydride linkage, thus indicating the invalidity of structure II, but it has a broad peak between the range 5.69–5.78 μ, probably due to fusing of the carboxylic carbonyl absorption at 5.7 μ and δ-lactonic carbonyl absorption at 5.75 μ.[12] The acid IV gave a positive ferric chloride test (intense violet coloration) suggesting that it is enolic in nature.

When IV was heated above its melting point or treated with mineral acids, it lost a molecule of carbon dioxide affording a neutral compound (V) in 68% yield. The infrared spectrum of V has a single strong peak at 5.75 μ characteristic of δ-lactones.[12] It is apparent that this evidence is not in accord with a ketonic anhydride structure II. Also, IV as well as V failed to give a positive 2,4-dinitrophenylhydrazine test.



R′ = 2-Methoxy-4-methylphenyl

Alkaline hydrolysis of IV was accompanied by decarboxylation giving 3-(2-methoxy-4-methylphenyl)-5-keto-3-hexenoic acid (VII) in 46% yield. This suggests that the intermediate keto dicarboxylic acid (VI) was unstable and readily decarboxylated to a more stable monocarboxylic acid (VII). The presence of a keto function in VII was indicated through the preparation of a phenylhydrazone and semicarbazone. When VII was heated with acetic anhydride at reflux temperature, it gave rise to the lactone V in 58% yield. This lactone failed to give a positive ferric chloride test. Alkaline hydrolysis of V followed by a careful neutralization yielded the parent keto acid (VII). All these observations show a close parallelism between the behavior of IV and phthalylacetic acid[4,5] and thus further support the glutaconylacetic acid structure assigned to IV.

(1) Parts I and II: (a) *J. Org. Chem.*, **24**, 520 (1959); (b) *J. Org. Chem.*, **24**, 2055 (1959).

(2) Present address: Laboratory of Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kan.

(3) D. B. Limaye and V. M. Bhave, *J. Univ. Bombay*, **2**, 82 (1933); [*Chem. Abstr.*, **28**, 6128 (1934)].

(4) S. Gabriel and A. Newman, *Ber.*, **26**, 951 (1893).

(5) S. Gabriel and G. Gieber, *Ber.*, **29**, 25 (1893).

(6) G. R. Gogte, *Proc. Ind. Acad. Sci.*, **7A**, 214 (1938); [*Chem. Abstr.*, **32**, 5389 (1938)].

(7) A. Einhorn and F. Hollandt, *Ann.*, **301**, 95 (1898).

(8) V. M. Bhave, *Rasayanam*, **1**, 127 (1938); [*Chem. Abstr.*, **33**, 1669 (1939)].

(9) Infrared spectra were determined using a Perkin-Elmer Infracord in chloroform solution in the region 5–6 μ.

(10) G. R. Gogte, M.S. thesis, University of Bombay, 1932, p. 72.

(11) B. R. Brown and A. R. Todd, *J. Chem. Soc.*, 1280 (1954).

(12) R. S. Rasmussen and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949).

As mentioned earlier, IV is enolic in nature and we were interested to see if it could be converted into its keto form, an observation made earlier by Bhave in the case of similar compounds.[13] When IV was therefore subjected to the action of concentrated sulfuric acid, an isomeric high melting substance (VIII) was obtained. Unlike IV, VIII did not give any coloration with ferric chloride, but, like IV, it gave the keto acid VII by treatment with alkali and the lactone V by treatment with hydrochloric acid. From these observations and by analogy with previous work,[3,13] the high melting compound VIII can be considered as the keto form of the enolic compound IV. The reverse change, namely, the conversion of the keto VIII to the enol IV has not been observed.

EXPERIMENTAL[14]

3-(2-Methoxy-4-methylphenyl)glutaconylacetic acid (IV). This acid was prepared following the general procedure of Bhave.[3] To an intimate mixture of 11.5 g. (0.05 mole) of β-(2-methoxy-4-methylphenyl)glutaconic anhydride (III) and an equal quantity of powdered fused sodium acetate, 15 ml. of acetic anhydride was added. The mixture was heated on a steam bath for about 10 min. The resulting hot red solution was poured with stirring into 200 ml. water, filtered, and to the clear filtrate, 20 ml. of concd. hydrochloric acid was added. The precipitated solid was collected, washed with several portions of water and the dry solid was crystallized from acetic acid to give 9.5 g. (67% yield) of IV as gray crystals, m.p. 138–139°. A pure sample was obtained by two recrystallizations from alcohol, m.p. 142–142.5°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11; neut. equiv., 274.0. Found: C, 65.37; H, 4.82; neut. equiv., 271.7.

3-(2-Methoxy-4-methylphenyl)-5-keto-3-hexenoic acid (VII). A solution of 13.7 g. (0.05 mole) of IV in 250 ml. of 1*N* sodium hydroxide was kept at room temperature for 12 hr. and then heated on a steam bath for 0.5 hr. to effect complete hydrolysis. After the alkaline solution had been washed with several portions of ether, it was carefully neutralized with dilute hydrochloric acid at ice-bath temperature. The precipitated gummy substance was taken up in ether and the ethereal extracts, after having been washed with several portions of water, were concentrated. The residual gum solidified upon trituration with acetic acid. Recrystallization of the solid from acetic acid gave 5.7 g. (46% yield) of VII as colorless crystals, m.p. 102–104° dec.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45; neut. equiv., 248.0. Found: C, 67.90; H, 6.71; neut. equiv., 250.1.

A *semicarbazone* of VII was prepared in usual manner, m.p. 164–165.5°.

Anal. Calcd. for $C_{15}H_{19}N_3O_4$: neut. equiv., 305.0. Found: neut. equiv., 304.2.

A *phenylhydrazone* of VII was prepared by heating a solution of VII in glacial acetic acid with an equimolar quantity of phenylhydrazine on a steam bath for 15 min. The hydrazone was recrystallized from alcohol to give colorless plates, m.p. 182–183°.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: neut. equiv., 338.0. Found: neut. equiv., 340.0.

3-(2-Methoxy-4-methylphenyl)-5-keto-3-hexenoic acid lactone (V). *Method A.* A hard glass test tube containing 5 g. of IV was heated in an oil bath at 155–160° for 0.5 hr. After the evolution of carbon dioxide had subsided, the contents of the tube was thoroughly washed with 5% sodium bicarbonate solution. The solid residue was collected, washed with several portions of water, and after drying was recrystallized from alcohol to give 2.8 g. (68% yield) of V, m.p. 74–75°.

Method B. A mixture of 5 g. of IV and 10 ml. of concd. hydrochloric acid was heated at reflux temperature on a sand bath for 2 hr. The contents of the flask were poured into water and the solid was collected on a filter. It was washed with several portions of water, dilute sodium hydroxide solution and again with water. After drying, it was recrystallized from alcohol (60%) to give V in 53% yield, m.p. 74–75.5°. A mixed melting point of this sample with the one obtained by method A showed no depression.

Method C. A mixture of 5 g. of VII in 7.5 ml. of acetic anhydride was heated on a steam bath for 2 hr. The contents of the flask was poured into water with stirring and the resulting solid mass was processed as in method B, to give V in 58% yield, m.p. 73.5–74.5°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.05; H, 6.09. Found: C, 73.21; H, 6.37.

3-(2-Methoxy-4-methylphenyl)glutaconylacetic acid (keto form) (VIII). A mixture of 10 g. of finely powdered enolic glutaconylacetic acid (IV) and 10 ml. of concd. sulfuric acid was heated cautiously at 80° for 2 min. The resulting red solution was filtered through a sintered glass funnel and the clear filtrate was slowly poured into 150 ml. of water. The gummy mass that separated was washed with several portions of water and then after drying, was triturated with acetic acid, affording a solid. It was recrystallized from acetic acid to give 6.2 g. (62% yield) of VIII, m.p. 218–220°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11; neut. equiv., 274.0. Found: C, 65.82; H, 5.18; neut. equiv., 275.2.

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(13) V. M. Bhave, M.S. thesis, University of Bombay, 1932.

(14) All melting points are uncorrected.

Bisarene-Chromium Compounds from Aryl Chlorides[1]

RICHARD W. BUSH[2] AND H. R. SNYDER

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Bisarene-chromium compounds of benzene, toluene, *p*-xylene, mesitylene, hexamethylbenzene, tetralin, and biphenyl have been prepared by the action of anhydrous chromic chloride upon the appropriate aromatic hydrocarbon in the presence of anhydrous aluminum chloride and powdered aluminum, the so-called reducing Friedel-Crafts conditions.[3] Only by the alternative synthesis, from arylmagnesium bromides, have bisarene-chromium compounds been prepared that contain substituents other than alkyl and aryl on the aromatic rings. By carbonating the mixture from the reac-

(1) Grateful acknowledgment is made of the partial support of this research by a grant from the National Science Foundation (G6223).

(2) National Science Foundation Fellow, 1956–1957. Phillips Petroleum Co. Fellow, 1957–1958.

(3) (a) E. O. Fischer and W. Hafner, *Z. anorg. u. allgem. Chem.*, **286**, 146 (1956); (b) E. O. Fischer and D. Seus, *Chem. Ber.*, **89**, 1809 (1956).

tion of phenylmagnesium bromide and anhydrous chromic chloride, Zeiss[4] isolated a biscarboxybenzene-chromium complex as the double salt $Ba^{++}(C_6H_5COO^-)_2Cr^+B(C_6H_5)_4^-$. Earlier, Hein[5] had studied the action of anhydrous chromic chloride upon *p*-bromophenylmagnesium bromide and upon *m*-chlorophenylmagnesium bromide. Although the chromium complexes obtained were difficult to isolate and purify, one substance[5a] that Hein isolated in relatively pure state conforms in its analysis to bis(*p*,*p*′-dibromobiphenyl)chromium(I) bromide. This formulation was not suggested by Hein, as the now accepted structure of the aromatic chromium compounds was not known at that time.

In the present study the applicability of the reducing Friedel-Crafts method to the preparation of bisarene-chromium complexes of aromatic chlorides was investigated. In general, the procedure of Fischer[3] was followed, but in agreement with recent reports,[6,7] relatively larger proportions of aluminum chloride improved the yields.

A bisarene-chromium complex was formed in 16% yield by the action of chromic chloride upon chlorobenzene, but the tetraphenylboron salt isolated contained no chlorine and was shown to be a bisbenzene-chromium complex. Dehalogenation of aromatic compounds occurs in the presence of anhydrous aluminum chloride.[8]

A bisarene-chromium complex was formed in 31–36% yield by the action of chromic chloride upon *p*-chlorobiphenyl. From treatment of the product with sodium tetraphenylboron, a salt A was isolated that had the correct composition for bis(*p*-chlorobiphenyl)chromium(I) tetraphenylboron. However, that some dechlorination occurred during the reaction was indicated by the isolation of several samples of tetraphenylboron salt containing less than the expected amount of chlorine. These samples as well as a sample of bisbiphenylchromium(I) tetraphenylboron exhibited infrared peaks at 760 cm.$^{-1}$, attributable to a monosubstituted benzene ring. The infrared spectrum of A possessed no peak at 760 cm.$^{-1}$, a fact which suggests that the molecules of A possess free chlorophenyl rings. The evidence presented requires only that A contain monochlorophenyl rings. The suggestion that A is a bis(*p*-chlorobiphenyl)chromium complex is based upon the assumption that there was a minimum of migration of the chlorine atoms. The bis(*p*-chlorobiphenyl)chromium(I) cation could be reduced to a chromium(O) compound, but this compound could not be isolated in pure state.

That the reducing Friedel-Crafts conditions are not applicable to the preparation of complexes in which the chromium atom is bonded to chlorine-containing rings is suggested by comparison of the results obtained with chlorobenzene and with *p*-chlorobiphenyl. To test this possibility further, *p*,*p*′-dichlorobiphenyl was treated with chromic chloride under the usual conditions. A chromium complex was produced in about half the yield obtained when *p*-chlorobiphenyl was used. The tetraphenylboron salt B was identical in its infrared spectrum with A. The analysis of B was consistent with its formulation as bis(*p*-chlorobiphenyl)chromium(I) tetraphenylboron. Extensive dechlorination would be necessary to allow the formation of a compound with this composition from *p*,*p*′-dichlorobiphenyl. The significance of the experiment is that none of the chromium complex contained more chlorine than the maximum allowed if the chromium is to be bonded only to nonchlorinated rings. This consideration suggests that the chromium atom in the bis(*p*-chlorobiphenyl)-chromium complex is bonded to the phenyl rather than to the chlorophenyl rings.

It is not known whether the dehalogenation occurs before or after the formation of the bisarene-chromium complexes. However, the process that appears best to correlate the results consists of the initial formation of a chromium complex with either chlorinated or nonchlorinated rings. If the chromium bonding weakens the aryl-chlorine bonds, then chlorine should be selectively lost from those rings bonded to the chromium atoms. Such a process would account for the observed formation of bisbenzenechromium from chlorobenzene, of bis(*p*-chlorobiphenyl)chromium from *p*,*p*′-dichlorobiphenyl, and of bis(*p*-chlorobiphenyl)chromium, along with dehalogenated derivatives, from *p*-chlorobiphenyl.

EXPERIMENTAL[9,10]

Bisbenzenechromium tetraphenylboron from chlorobenzene. In a 12 × 100 mm. Pyrex tube were placed 0.50 g. (3.15 mmoles) of anhydrous chromic chloride (Fisher Scientific Co.), 0.17 g. (6.30 mmoles) of aluminum powder, 0.84 g. (6.30 mmoles) of anhydrous aluminum chloride, and 2.3 ml. (23 mmoles) of chlorobenzene (Eastman white label, redistilled). The tube was evacuated, sealed, and shaken vigorously to mix the reagents. The tube was heated with rotation for 16 hr. at 150° in a small electric furnace. The mixture was hydrolyzed with 5 ml. of methanol and 20 ml. of ice water. Ammonium hydroxide was added, the mixture was heated to 70°, and the chromium and aluminum hydroxides were removed by filtration. The filtrate was treated with 5*N* sodium hydroxide and boiled until free of ammonia. The yellow solution, containing chromium(I)

(4) H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.* **78**, 5959 (1956).

(5) (a) F. Hein and R. Späte, *Ber.*, **59**, 751 (1926); (b) F. Hein and W. Retter, *Ber.*, **71**, 1966 (1938).

(6) F. Hein and K. Eisfeld, *Z. anorg. u. allgem. Chem.*, **292**, 162 (1957).

(7) E. O. Fischer and H. P. Fritz, *Advances in Inorganic Chemistry and Radiochemistry*, **1**, 99 (1959).

(8) C. A. Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corp., New York, N. Y., 1941, pp. 610, 692–696.

(9) All melting points are corrected.

(10) Microanalyses by Mr. Josef Nemeth and his associates. Infrared spectra by Mr. Paul McMahon and Mrs. Mary Verkade.

complex in 16% yield,[11] was acidified with acetic acid and treated with 0.1*M* sodium tetraphenylboron. The resulting yellow precipitate was recrystallized from acetone, and 0.1 g. of yellow crystals was obtained, m.p. *ca.* 298° dec. The sample gave a negative Beilstein test and was recrystallized for analysis.

Anal. Calcd. for $C_{36}H_{32}CrB$: C, 81.97; H, 6.12. Found: C, 81.63; H, 6.29.

The infrared spectrum was identical with that of bisbenzenechromium(I) tetraphenylboron, m.p. *ca.* 290° dec., prepared from benzene by the method of Fischer.[3a]

Bis(p-chlorobiphenyl)chromium complex from p-chlorobiphenyl. In a 125-ml. Erlenmeyer flask were mixed 5.0 g. (0.0315 mole) of anhydrous chromic chloride,[12] 1.7 g. (0.063 mole) of aluminum powder, 8.4 g. (0.063 mole) of anhydrous aluminum chloride, and 17.5 g. (0.093 mole) of *p*-chlorobiphenyl (Monsanto Chemical Co., recrystallized from ethanol). The mixture was kept under a nitrogen atmosphere and was stirred occasionally while heating for 5 hr. at 145–160°. The mixture was hydrolyzed with 50 ml. of methanol and 200 ml. of ice water, then treated with excess 5*N* sodium hydroxide and *ca.* 50 g. of sodium hydrosulfite. The mixture was extracted with benzene, and the red-black benzene, solution was added to distilled water and placed under an air stream to re-oxidize the chromium complex. When the benzene had evaporated, the aqueous mixture was heated to 70° and filtered, and the residue was re-extracted with hot water. The aqueous filtrates were combined to give an orange solution C that contained chromium(I) complex in yields of 31–36%.[11]

Bis(p-chlorobiphenyl)chromium(I) tetraphenylboron. Upon cooling, solution C afforded a voluminous yellow precipitate. The precipitate was dissolved in water and the solution was washed with benzene, acidified with acetic acid, and treated with 0.1*M* sodium tetraphenylboron. When the resulting yellow precipitate was recrystallized from acetone, 1.32 g. (6%) of orange plates was obtained. After a second recrystallization the sample melted at 200.5–202° dec.

Anal. Calcd. for $C_{48}H_{38}Cl_2CrB$: C, 77.01; H, 5.12; Cl, 9.48. Found: C, 76.93; H, 5.06; Cl, 9.43.

In experiments in which the reaction mixture was heated for 16 hr. instead of 5 hr., and the tetraphenylboron salts were precipitated directly from solution C, the salts contained less than the calculated amount of chlorine.

Bis(p-chlorobiphenyl)chromium(0). All operations were conducted under a blanket of nitrogen. Solution C, after cooling and refiltering, was treated with a basic solution of sodium hydrosulfite. The mixture was extracted with benzene, and the black benzene extract was dried over anhydrous magnesium sulfate and filtered. The benzene was removed by vacuum freeze drying, which left 4.4 g. (33%) of voluminous orange powder. It was washed with anhydrous ether, dried *in vacuo*, and stored in an evacuated tube. The purified product melted at 105–108° dec.

Anal. Calcd. for $C_{24}H_{18}Cl_2Cr$: C, 67.14; H, 4.23; Cl, 16.52; Cr, 12.12. Found: C, 68.33; H, 5.00; Cl, 13.65; Cr, 12.8.

In preliminary experiments, attempted sublimation of the crude product was accompanied by extensive decomposition. Sublimates were obtained in maximum yields of 6% and contained only 8–9% chlorine.

Bis(p-chlorobiphenyl)chromium tetraphenylboron from p,p'-dichlorobiphenyl. In a 12 × 100 mm. Pyrex tube were placed 0.50 g. (3.15 mmoles) of anhydrous chromic chloride (Fisher Scientific Co.), 0.17 g. (6.30 mmoles) of aluminum powder, 0.84 g. (6.30 mmoles) of anhydrous aluminum chloride, and 2.79 g. (12.5 mmoles) of *p,p'*-dichlorobiphenyl (Federal Phosphorus Co., recrystallized from ethanol, m.p. 146–148.5°). The tube was evacuated, sealed, and shaken vigorously to mix the reagents. The tube was heated with rotation for 5 hr. at 155–160° in a small electric furnace. The mixture was hydrolyzed and extracted as in the procedure for bis(*p*-chlorobiphenyl)chromium complex from *p*-chlorobiphenyl. The aqueous filtrate contained chromium(I) complex in 16% yield.[11] Acidification of the filtrate with acetic acid and treatment with 0.1*M* sodium tetraphenylboron afforded a precipitate which was recrystallized from acetone to give 0.2 g. of orange crystals, m.p. 196–198° dec. After a second recrystallization, the compound melted at 197.5–198.5° dec.

Anal. Calcd. for $C_{48}H_{38}Cl_2CrB$: C, 77.01; H, 5.12; Cl, 9.48. Found: C, 77.43; H, 5.32; Cl, 9.72.

The infrared spectrum was identical with that of bis(*p*-chlorobiphenyl)chromium(I) tetraphenylboron prepared from *o*-chlorobiphenyl.

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(11) The amount of chromium(I) ion in solution was determined from an aliquot containing 0.05 to 0.2 mmole of chromium. The complex was decomposed by boiling with concd. sulfuric acid. The chromium was oxidized by sodium peroxide to chromium(VI) and was titrated as dichromate.

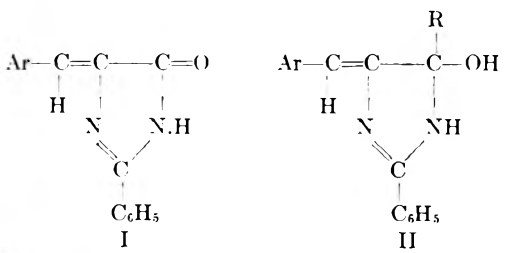
(12) The authors wish to thank Dr. John H. Wotiz of the Research Center of the Diamond Alkali Co., Painesville, Ohio, for the gift of anhydrous chromic chloride.

Action of Grignard Reagents on Heterocyclic Compounds. III.[1] Action of Arylmagnesium Halides on 2-Phenyl-4-benzylidene-2-imidazoline-5-one

William Ibrahim Awad and Abd Elaziz Ali Gad Allah

Received November 12, 1959

Mustafa and Harhash[2] claimed that methyl-, and phenylmagnesium halides react with 2-phenyl-4-benzylidene-2-imidazoline-5-one (Ia) to give colorless products believed to have structures IIa and IIb respectively. No proof was given for such structures.



I

Ia. Ar = C_6H_5
Ib. Ar = *p*-$CH_3OC_6H_4$

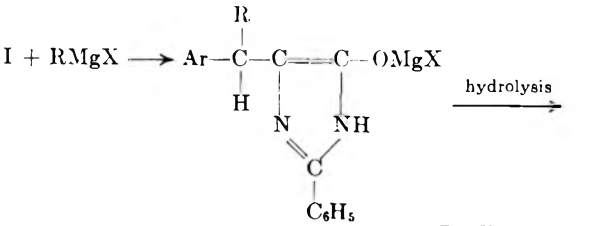
II

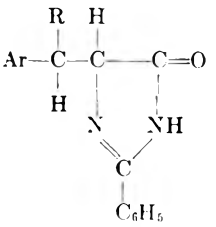
IIa. Ar = R = C_6H_5
IIb. Ar = C_6H_5, R = CH_3

We have now reinvestigated the action of phenyl-, and naphthylmagnesium halides on Ia and Ib and we believe that the products have structure III: *i.e.*, 1,4-addition followed by ketonization according to the following scheme:

(1) W. I. Awad and M. S. Hafez, *J. Org. Chem.*, in press.

(2) A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, **21**, 575 (1956).





III

IIIa. Ar = R = C_6H_5
IIIb. Ar = C_6H_5, R = α-$C_{10}H_7$
IIIc. Ar = p-$CH_3OC_6H_4$, R = C_6H_5
IIId. Ar = p-$CH_3OC_6H_4$, R = α-$C_{10}H_7$

Actually there are three possibilities for such a reaction: 1) ring opening which would necessitate the addition of two molecules of the Grignard reagent and which disagreed with the analytical data—in reality the analysis shows that I adds one mole of the Grignard reagent; 2) 1,2-addition as suggested by Mustafa,[2] in which case the carbonyl group would disappear; and 3) 1,4-addition which leads to III as suggested here, in which case the carbonyl group is still present.

Infrared spectra of the Grignard products show clearly that the carbonyl stretching frequency of amide I and amide II is present (*cf.* Table I), both in the starting materials and in the Grignard products. This favors structure III. A similar 1,4-addition was observed by Panizzi[3] when phenylmagnesium bromide reacted with 3-methyl-4-benzyliden-isooxazolone.

TABLE I[a]

INFRARED SPECTRA OF STARTING MATERIAL AND PRODUCTS

Compound	Stretching Frequency, Cm.$^{-1}$[b]	
	Amide I	Amide II
Ia	1709	1605
IIIa	1723	1587
IIIb	1723	1587
Ib	1681	1587
IIIc	1681	1612
IIId	1723	1587

[a] The infrared measurements were carried out on Perkin-Elmer infrared Model 137, in nujol medium. [b] For the comparison of the stretching frequencies of amide I and amide II see Bellamy[4] and Awad.[5]

EXPERIMENTAL

Microanalyses were carried out by Alfred Bernhardt, Max Planck Instutit, Mülheim (Ruhr), Germany. Melting points are not corrected.

Action of phenylmagnesium bromide on 2-phenyl-4-benzylidene-2-imidazolin-5-one.[6] (Ia). A solution of Ia (2 g.) in dry benzene (50 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 3.8 g., and magnesium, 0.72 g.) and the reaction was carried out as described by Mustafa.[2] Recrystallization of the product from benzene gave 0.5 g. of IIIa as colorless needles, m.p. 220–221°.

Anal. Calcd. for $C_{22}H_{18}ON_2$: C, 81.0; H, 5.52; N, 8.58. Found: C, 81.52; H, 5.55; N, 8.48. The product gave an orange color with concd. sulfuric acid.

Action of naphthylmagnesium bromide on Ia. A solution of Ia (2 g.) in dry benzene (50 ml.) was added to an ethereal solution of naphthylmagnesium bromide [from α-bromonaphthalene (5 g.) and magnesium (0.72 g.)] and the reaction mixture was completed as usual. Recrystallization of the product (IIIb) from benzene gave 0.5 g. as colorless needles, m.p. 218–219°.

Anal. Calcd. for $C_{26}H_{20}ON_2$: C, 82.9; H, 5.32; N, 7.47. Found: C, 82.39; H, 5.37; N, 6.88. The product gave a pink color with concd. sulfuric acid.

Preparation of 2-phenyl-4-(p-methoxybenzylidene)-2-imidazolin-5-one (IB). Hippuric acid (9 g.) and fused sodium acetate (4.9 g.) were mixed with acetic anhydride (5.3 g.) and anisaldehyde (13.7 g.). The reaction mixture was heated on a water bath for 30 min. It was then filtered, washed with hot water, and finally with a little alcohol.

The above product (40 g.) was mixed with water (100 ml.), alcohol (200 ml.), and concd. ammonia (20 g.). The mixture was refluxed until all the solid was completely soluble. Concentrated ammonia (20 ml.) and potassium carbonate (20 g.) were then added and heating was continued for 1 hr. more, during which time some more ammonia was added. A yellow crystalline product (Ib) was obtained, filtered, and washed with hot water, alcohol, and finally with hot benzene. It was then recrystallized from acetic acid as yellow needles m.p. 285–286°, yield 30 g. Erlenmeyer and Wittenberg[7] reported a melting point of 283°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 72.82; H, 5.14; N, 10.02.

Action of phenylmagnesium bromide on 2-phenyl(p-methoxybenzylidene)-2-imidazolin-5-one. (IB). A solution of Ib (2 g.) in dry benzene (50 ml.) was added to an ethereal solution of phenylmagnesium bromide [from bromobenzene (3.4 g.) and magnesium (0.72 g.)] and the reaction was completed as usual. Recrystallization from benzene gave 0.5 g. of IIIc as colorless needles; m.p. 203–204°.

Anal. Calcd. for $C_{23}H_{20}O_2N_2$: N, 7.86; Found: N, 7.40. The product gave a yellow color with concd. sulfuric acid.

Action of naphthylmagnesium bromide on Ib. A solution of Ib (2 g.) in dry benzene (50 ml.) was added to an ethereal solution of naphthylmagnesium bromide [from α-bromonaphthalene (5 g.) and magnesium (0.72 g.)] and the reaction was completed as usual. Recrystallization of the product from benzene gave 0.5 g. of IIId as colorless needles, m.p. 239–240°.

Anal. Calcd. for $C_{27}H_{22}O_2N_2$: N, 6.36. Found: N, 6.44. The product gave a permanganate color with concd. sulfuric acid.

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(3) L. Panizzi, *Gazz. chim. ital.*, **76**, 44 (1946).
(4) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, London, 1957, pp. 180 and 185.
(5) W. I. Awad, A. A. Raouf, and A. M. Kamel, *J. Org. Chem.*, **24**, 1777 (1959).
(6) D. L. Williams and A. R. Ronzio, *J. Am. Chem. Soc.*, **68**, 647 (1946).
(7) von E. Erlenmeyer, Jr., and Wittenberg, *Ann.*, **337**, 298 (1904).

Preparation of 2,4,6-Trinitrazaheptane

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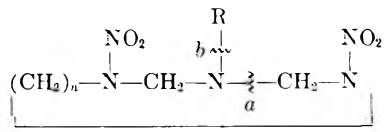
Chapman, Owston, and Woodcock[1] found that in the nitrolysis of aminomethylnitramines, I,

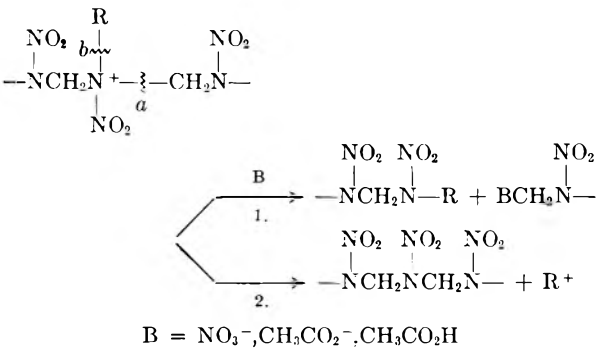


I

R = CH_3, C_2H_5, $(CH_3)_2CH$, $CH_3(CH_2)_3$, $CH_2(CH_2)_4CH$
n = 1, 2

cleavage always occurred at *a* when the nitrolyzing medium was acetic anhydride and nitric acid. When ammonium nitrate was added to the acetic anhydride-nitric acid medium cleavage occurred at *b* when R = isopropyl or cyclohexyl and at *a* when R = methyl and butyl. With R = ethyl a little cleavage was detected at *b* but most of it occurred at *a*. The authors did not offer any explanation for the change in cleavage site, in the case of R = isopropyl and cyclohexyl when ammonium nitrate was added to the system.

By analogy with the mechanism expressed for the von Braun reaction,[2] the initial step in the nitrolysis reaction would be the formation of a complex between the amine and a nitronium ion. The next step, (Path 1), when using only acetic anhydride and nitric acid, would be the attack of

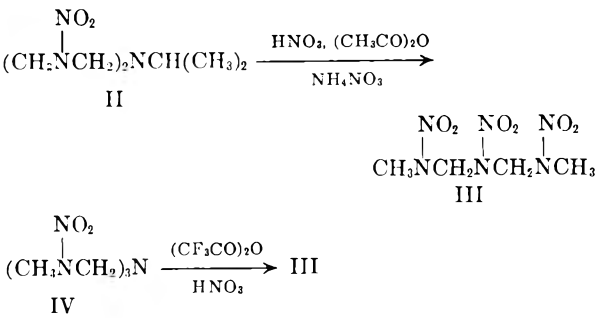


B = NO_3^-, $CH_3CO_2^-$, CH_3CO_2H

a nucleophile, B, on one of the adjacent methylenes to break the carbon-nitrogen bond. The methylenes, because of the adjacent electron withdrawing nitramine groups,[3] would be attacked in preference to the alkyl R groups. The addition of ammonium nitrate to the reaction medium increases the ionizing power of the system sufficiently so that the carbon-nitrogen bond of the secondary alkyl group in the nitronium ion-amine complex is ionized partially or completely resulting in preferential cleavage at *b* (Path 2).

Lamberton[4] suggests that nitrolysis reactions in general may proceed by Path 2. However, it appears that this mechanism is operative only where R may readily form a carbonium ion.

When nitrolysis reactions were conducted with acyclic systems the same effects were noted as with the cyclic systems. The nitrolysis of uncharacterized bis-(*N*-nitro-*N*-methylaminomethyl)-2-propylamine (II) with nitric acid, acetic anhydride, and ammonium nitrate gave 2,4,6-trinitrazaheptane (III). Here the reaction proceeds according to Path 2.



The nitrolysis of tris(*N*-nitro-*N*-methylaminomethyl)amine (IV) with nitric acid and trifluoroacetic anhydride also gave III. As all three groups on the central amino nitrogen are the same, the nitrolysis product would be the same regardless of whether the reaction went by Path 1 or 2. However, in consideration of the reactions of I with acetic anhydride and nitric acid, compound IV probably reacts by Path 1 under the conditions used. Acetic anhydride and nitric acid did not yield III from IV. The success of the trifluoroacetic anhydride–nitric acid medium may have been due to the high concentration of dinitrogen pentoxide that can be achieved from these two reagents.[5]

2,4,6-Trinitrazaheptane is a white crystalline compound which melts to a clear liquid, without visible decomposition, at 168–169°. The cyclic analog, 1,3,5-trinitrazacycloheptane is reported by Myers and Wright to melt with decomposition at 165–165.5°.[6] No immediate explanation accounts for this difference in thermal stability between the two compounds.

It was not possible to nitrolyze a group from the central amino nitrogen of tris[*N*-nitro-*N*-(β-cyanoethyl)aminomethyl]amine (V). The failure of V to nitrolyze may be due to the lesser basicity of V compared with IV, thereby preventing formation of sufficient nitronium ion-amine complex to allow the reaction to proceed in the desired manner.

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EXPERIMENTAL

Preparation of 2,4,6-trinitrazaheptane (III) *from* IV. Six and three-tenths grams (0.10 mole) of 99% nitric acid and 31.5 g. (0.15 mole) of trifluoroacetic anhydride were mixed at −10°, then allowed to warm to 10°. Two and eight-tenths grams (0.010 mole) of tris(*N*-nitro-*N*-methylaminomethyl)amine[7] (IV), m.p. 116–117°, was added portionwise with stirring and cooling. The temperature was maintained at 10°. After addition was complete the temperature was raised to 20° for 5 min. The volatile materials were then removed under reduced pressure and the viscous residue treated with ether. One gram of solid, m.p. 150–160°, was filtered. This was recrystallized from butanone to give 0.5 g. (21% yield) of 2,4,6-trinitrazaheptane, m.p. 166–168°. Another recrystallization from butanone raised the melting point to 168–169°. The compound melts to a clear liquid with no apparent decomposition.

Anal. Calcd. for $C_4H_{10}N_6O_6$: C, 20.17; H, 4.23; N, 35.29; mol. wt. 238. Found: C, 20.26; H, 4.21; N, 35.56; mol. wt. 246 (Rast).

The infrared spectrum showed nitramino absorption at 6.40 μ (broad), 6.55 μ, and 7.80 μ, and a strong band at 13.07 μ.[8]

Preparation of 2,4,6-trinitrazaheptane (III) *from* II. Two and one-half grams (0.008 mole) of crude bis(*N*-nitro-*N*-methylaminomethyl)(2-propyl)amine (II) was dissolved in 20 ml. of acetic anhydride and heated to 55°. To this was added a solution of 3.4 g. (0.042 mole) of ammonium nitrate in 4.6 g. (0.073 mole) of 99% nitric acid. After 15 min. at 55° the solution was poured into 500 ml. of ice and water. One-half gram of solid, m.p. 110–120°, separated. This was recrystallized from chloroform to give 0.3 g. of material, m.p. 155–160°. Recrystallization from butanone gave 0.1 g. of material, m.p. 166–168°. The infrared spectrum of this material was identical with the spectrum of III prepared in the previous experiment.

Anal. Calcd. for $C_4H_{10}N_6O_6$: C, 20.17; H, 4.23; N, 35.29. Found: C, 20.43; H, 4.67; N, 36.02.

Treatment of IV with acetic anhydride and nitric acid. Three and six-tenths grams (0.013 mole) of IV was added to a solution of 8.8 ml. (0.21 mole) of 99% nitric acid and 24 ml. (0.26 mole) of acetic anhydride at 0°. After addition was complete, the solution was warmed to 30° and maintained there 25 min. The slightly yellow solution was poured into 250 ml. of ice and water. No insoluble material separated.

Treatment of tris-[N-nitro-N-(β-cyanoethyl)aminomethyl]-amine (V) with trifluoroacetic anhydride and nitric acid. Six and three-tenths grams (0.10 mole) of 99% nitric acid was added to 31.5 g. (0.15 mole) of trifluoroacetic anhydride at 0°. The solution was warmed to 10°. Four grams (0.010 mole) of V was added, with stirring, to the solution. There was no noticeable temperature rise. The temperature was raised to 15° where the solid dissolved. The solution was then poured into 250 ml. of ice and water. About 2 g. of oil separated. The oil was dissolved in 25 ml. of methylene chloride and 0.025 g. of solid separated, m.p. 135–138°. A mixed melting point with a sample of V gave no depression; hence, the solid was starting material. The oily material, soluble in methylene chloride, was not investigated but probably was not the desired 1,9-dicyano-3,5,7-trinitrazanonane, as this compound should be a relatively high melting, insoluble material as judged by the character of other 2,4,6-trinitrazaheptane derivatives.

Preparation of bis(N-nitro-N-Methylaminomethyl)(2-propyl)amine (II). Two grams (0.026 mole) of methylnitramine was added to 2.1 g. (0.026 mole) of 37% formaldehyde solution. This solution was cooled to 0° and 0.77 g. (0.013 mole) of isopropylamine was added. After a few minutes an oil separated and settled to the bottom. The reaction mixture was warmed to 25°. After 30 min. the water was evaporated under reduced pressure to leave 2.5 g. of material, m.p. 27–30°. The material was not characterized but was assumed to be II on the basis of the analogous preparation of bis(*N*-nitro-*N*-methylaminomethyl)methylamine.[9]

Preparation of tris[N-nitro-N-(β-cyanoethyl)aminomethyl]-amine (V). Eleven and one-half grams (0.10 mole) of β-cyanoethylnitramine was dissolved in 8.33 g. of 37% aqueous formaldehyde solution and chilled to 0°. Then 2.02 g. (0.33 mole) of 28% aqueous ammonia was added to the solution. The solution was poured into a shallow dish and left uncovered at room temperature until the water had evaporated. There was 12.9 g. (97% yield) of white solid remaining, m.p. 100–120°. Two recrystallizations from acetonitrile gave 7 g. of V, m.p. 136–138°.

Anal. Calcd. for $C_{12}H_{18}N_{10}O_6$: C, 36.18; H, 4.55; N, 35.17; mol. wt. 398. Found: C, 36.03; H, 4.51; N, 35.11, 35.30; mol. wt. 354 (cryoscopic method using ethylene carbonate).

The low value for the experimentally determined molecular weight may be due to partial dissociation of the compound. After V was kept in a closed bottle for any length of time, the odor of formaldehyde was evident when the bottle was opened. Also the melting point always dropped when the material was stored for several months.

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Orientation in the Nitration of 2′,5′-Dimethoxyacetophenone[1]

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The nitration of 2′,5′-dimethoxyacetophenone has been studied under a variety of conditions and found to lead to the formation of a mixture of the 4′- and 6′-nitro isomers, with the 6′-nitro isomer accounting for approximately 50 to 80% of the product, depending on the conditions. Extensive substitution in the 6′ position has previously been reported for several compounds of similar structure;[4] this behavior has been considered to be anomalous.[4a,b] The high proportion of substitution in the 6′ position is consistent with the predicted relative stabilities of the transition states. Only in the case of substitution in this position is the tran-

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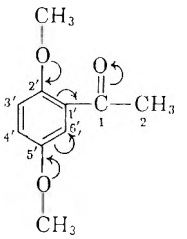
(2) This paper is based partly on a thesis submitted by C. R. Hamel in partial fulfillment of the requirements for the degree of Master of Science at Clarkson College of Technology, January 1959.
(3) Participant, National Science Foundation Research Participation Program for High School Science Teachers, Clarkson College of Technology, June–August, 1959.
(4) (a) G. S. Hammond, F. J. Modic, and R. M. Hedges, *J. Am. Chem. Soc.*, **75**, 1388 (1953); (b) K. A. Kobe and T. B. Hudson, *Ind. Eng. Chem.*, **42**, 356 (1950); (c) L. Rubenstein, *J. Chem. Soc.*, **127**, 1998 (1925).

sition state stabilized by conjugation of the 2′-methoxy group with the carbonyl side chain.



The relative stabilities of the transition states for substitution in the 3′ and 4′ positions are not obvious from a consideration of their resonance structures, although it appears reasonable that electrons should be released more readily to the 4′ position by the 5′-methoxy group than to the 3′ position by the 2′-methoxy group, since the latter is conjugated with the carbonyl side chain.[5] Considerably more of the 4′-nitro isomer was obtained with a mixture of nitric acid and sulfuric acid than with nitric acid alone. If the attacking reagents in the two media are nitronium ion and nitric acidium ion respectively,[6] the difference in isomer distribution can be attributed to higher activation energies and resultant greater selectivity in the case of the latter. An alternative explanation suggested on the basis of results with compounds of somewhat analagous structure involves the effect of the degree of solvation of the nitronium ion on transition state stabilities.[4a] That the carbonyl group plays the determining role in substitution in the 6′ position was demonstrated by the exclusive formation of the 4′-nitro compound on the nitration of 1-ethyl-2,5-dimethoxybenzene.[7]

EXPERIMENTAL[8]

Nitration of 2′,5′-dimethoxyacetophenone. Run A. To 40 ml. of concd. nitric acid (sp. gr. 1.42) at −20° was added with stirring 8.0 g. of 2′,5′-dimethoxyacetophenone[9] over a period of 4 hr. The mixture was stirred for an additional 2.5 hr. at −20°, then poured into 500 ml. of ice water. The product was isolated by filtration, washed free of acid and dried. The yield was 9.7 g. (97% assuming mononitration) of a yellow powder.

Run B. The procedure was the same as in *Run A* except that the addition and aging periods were shortened to 90 and 15 min. respectively. The yield was 8.4 g. (84%) of a yellow powder exclusive of a small amount of gummy material adhering to the stirrer.

Run C. The procedure was the same as in *Run B* except that the nitrating medium consisted of a mixture of 40 ml. of nitric acid and 20 ml. of concd. sulfuric acid (sp. gr. 1.84). The yield was 8.6 g. (86%) of a yellow powder exclusive of a small amount of gummy material adhering to the stirrer.

Run D. To a solution of 8.65 g. of 2′,5′-dimethoxyacetophenone in 30 ml. of glacial acetic acid was added with stirring a mixture of 6.1 ml. of concd. nitric acid and 18.3 ml. of glacial acetic acid over a 5-hr. period. The temperature was kept close to the freezing point of the mixture (5° to 12°) throughout the addition. The mixture was maintained at 5° for 22 hr., then quenched with 200 ml. of ice water. The resulting suspension was stirred for several hours to break up lumps, then chilled and the product isolated by filtration, washed, and dried. No attempt was made to isolate additional product from the filtrate. The yield was 8.4 g. (78%) of an orange-yellow powder.

In addition to the above runs, a number of nitrations were attempted which resulted in the formation of intractable dark gums or tars, presumably because of oxidation. In these experiments 2′,5′-dimethoxyacetophenone was added dropwise to concd. nitric acid at 5°, and to 4:1, 2:1, and 1:1 mixtures (by volume) of concd. sulfuric acid and concd. nitric acid at −20°.

Determination of isomer distribution. Activated alumina (Merck reagent aluminum oxide, suitable for chromatographic adsorption) was partially deactivated by slurrying with methanol and air-drying overnight. The alumina was charged in benzene to a bed depth of 90 mm. in a 110 × 10 mm. column. A solution of 0.2000 g. of nitration product in 3 ml. of benzene was fed to the top of the column and development effected with benzene at a rate of approximately 35 ml. per hr. Two well-resolved yellow bands were eluted separately and analyzed spectrophotometrically (Beckman DU) after appropriate dilutions with ethanol. A small, immobile red band containing less than 2% of the charge was also obtained. The more mobile yellow band represented 2′,5′-dimethoxy-4′-nitroacetophenone, the less mobile yellow band 2′,5′-dimethoxy-6′-nitroacetophenone (3′,6′-dimethoxy-2′-nitroacetophenone). The analytical peaks employed for the determination of the two compounds were 365 mμ and 335 mμ respectively. Samples of the pure isomers obtained by fractional crystallization of the nitration product from methanol were used as standards. A third yellow band, less mobile than the 6′-nitro isomer and representing an extremely small amount of material was observed in analyzing the product from *Run D*. The material balances based on the spectrophotometric analyses of the eluates and the weights charged to the column ranged from 95 to 105%. In the analysis of the product from *Run A*, the column eluates were not assayed spectrophotometrically but evaporated to dryness to yield the individual isomers in a high state of purity. The material balance in this case was 102%. The results of the isomer distribution determinations were as follows:

Run	Medium	Temp.	%,4′-	%,6′-
A	HNO_3	−20°	21	79
B	HNO_3	−20°	23, 23	77, 77
C	HNO_3-H_2SO_4	−20°	51, 47	49, 53
D	HNO_3-HOAc	5 to 12°	34	66

1-Ethyl-2,5-dimethoxybenzene.[10] Mossy zinc (140 g.) was amalgamated by a standard procedure[11] and the amalgam refluxed with 263 ml. of concd. hydrochloric acid and 175 ml. of water while 35 g. of 2′,5′-dimethoxyacetophenone was added over a 1-hr. period. Reflux was continued for 22 hr., during which time 97 ml. of additional concd. hydrochloric

(5) For a discussion of an analagous situation see G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 505–507.

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acid was added in 10-ml. increments. The oily upper layer was then separated, dried with calcium chloride and fractionated under reduced pressure. The main fraction, b.p. 65–67.5°/5 mm., consisted of 15.7 g. (49%) of a pale yellow liquid. Refractionation gave a colorless analytical sample, b.p. 68–70°/7 mm., n_D^{25} 1.5148, f.p. −4 to −6.5°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 72.6; H, 8.4.

1-Ethyl-2,5-dimethoxy-4-nitrobenzene. 1-Ethyl-2,5-dimethoxybenzene (8.0 g.) was nitrated by the procedure used in *Run D* for 2′,5′-dimethoxyacetophenone with the exception that the mixture was quenched immediately after completion of the acid addition. The reaction was considerably more vigorous than in the case of 2′,5′-dimethoxyacetophenone. The yield was 9.2 g. (92%) of yellow needles, m.p. 79–80°. Recrystallization from either methanol or benzene–petroleum ether did not raise the melting point.

Anal. Calcd. for $C_{10}H_{13}O_4N$: N, 6.6. Found: N, 6.7.

Attempts at nitration with concd. nitric acid at −18° and −35° resulted in the formation of dark tars.

Determination of structure of the nitro compounds. The structure of 1-ethyl-2,5-dimethoxy-4-nitrobenzene was established by its oxidation to 2,5-dimethoxy-4-nitrobenzoic acid followed by demethylation of the latter to 2,5-dihydroxy-4-nitrobenzoic acid, a known compound.[12] The structure of 2′,5′-dimethoxy-4′-nitroacetophenone was determined by its conversion to 2,5-dimethoxy-4-nitrobenzoic acid; that of 2′,5′-dimethoxy-6′-nitroacetophenone by its conversion to 2,5-dimethoxy-6-nitrobenzoic acid, a compound also obtained from 2-bromo-2′,5′-dimethoxy-6′-nitroacetophenone.[13] The position of the nitro group in the latter compound has been established by its conversion to 4,4′,7,7′-tetramethoxyindigotin by treatment with ammonium sulfide.[13]

1-Ethyl-2,5-dimethoxy-4-nitrobenzene (3.0 g.) was refluxed for 6 hr. with a solution of 9.0 g. of potassium permanganate and 34.5 ml. of 5% sodium hydroxide in 500 ml. of water. Following removal of manganese dioxide by filtration, the solution was extracted with ether, then acidified to *p*H 1 with 10% sulfuric acid. The material thus precipitated was recrystallized from hot water, yielding orange-red crystals of 2,5-dimethoxy-4-nitrobenzoic acid, m.p. 192–193° dec.

Anal. Calcd. for $C_9H_9O_6N$: N, 6.2; neut. equiv., 227. Found: N, 6.3; neut. equiv., 231.

A mixture of 0.23 g. of 2,5-dimethoxy-4-nitrobenzoic acid, 0.20 ml. of glacial acetic acid and 1.49 ml. of 49% hydrobromic acid was heated at 125–160° for 18 hr. The acetic acid was then removed under reduced pressure and the residue extracted with ether. The solid obtained on evaporation of the ether was recrystallized from hot water, yielding orange-red needles of 2,5-dihydroxy-4-nitrobenzoic acid, m.p. 244–245 dec. (no depression on mixing with an authentic sample prepared by an independent, unambiguous procedure[12,14]; identical ultraviolet and visible absorption spectra with maxima at 278 mμ and 425 mμ in benzene; deep violet color with alkali[12]).

2′,5′-Dimethoxy-4′-nitroacetophenone was isolated as yellow needles, m.p. 122–123°, from the fractional crystallization of the crude nitration product from *Run A*.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9; N, 6.2. Found: C, 53.4; H, 5.1; N, 6.2.

Treatment of this material with hypohalite yielded 2,5-dimethoxy-4-nitrobenzoic acid, m.p. 192–193° dec. (no depression on mixing with a sample of the product obtained from the oxidation of 1-ethyl-2,5-dimethoxybenzene; identical ultraviolet absorption spectra with maxima at 277 mμ and 360 mμ in benzene).

2′,5′-Dimethoxy-6′-nitroacetophenone was also isolated from the fractional crystallization as pale yellow needles, m.p. 72–73°.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9; N, 6.2. Found: C, 53.0; H, 4.9; N, 6.3.

Treatment of this material with hypohalite yielded 2,5-dimethoxy-6-nitrobenzoic acid, m.p. 192–193° dec. (no depression on mixing with a sample prepared from 2-bromo-2′,5′-dimethoxy-6′-nitroacetophenone by the haloform reaction[13]; identical ultraviolet absorption spectra with maxima at 325 mμ in benzene; large depression in melting point on mixing with a sample of 2,5-dimethoxy-4-nitrobenzoic acid).

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(14) The authors are grateful to Smith & Nephew Research, Ltd., Hunsdon, England for this sample.

Chalcones. IV. Synthesis of Chloro- and Nitrochalcones

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Syntheses of some methylchalcones have been reported.[1b,2] The present communication records the synthesis of isomeric chloro- and nitro- substituted chalcones obtained by the Claisen-Schmidt condensation of resacetophenone, resacetophenone dimethyl ether, and *o*-hydroxyacetophenone with isomeric chlorobenzaldehydes and of resacetophenone and *o*-hydroxyacetophenone with *m*-nitrobenzaldehyde.

Condensation of *o*-chlorobenzaldehyde with resacetophenone, taken in stoichiometric proportion, at room temperature for eight days, gave the 2′,4′-dihydroxy-2-chlorochalcone in a good yield (58.7%) and without the formation of any resinous products. The same condensation could also be effected by heating at 60° for three hours, and subsequently leaving the reaction mixture at room temperature for twenty-two hours to give the above chalcone in 55% yield.

In the synthesis of 2′,4′-dihydroxy-3-chlorochalcone the yield was found to increase from 18–33% by using four times the stoichiometric amount of *m*-chlorobenzaldehyde. But a considerable amount of *m*-chlorobenzoic acid was formed in this condensation.

It is interesting to find that the isomeric 2′,4′-dihydroxy-4-chlorochalcone is pyrochromatic—becomes orange on heating and yellow on cooling.

Condensation of isomeric chlorobenzaldehydes with resacetophenone, under similar experimental conditions, gave significant differences in the yields

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(2) D. N. Dhar and J. B. Lal, in press.

TABLE I

CHALCONES

Chalcone	Color and Crystalline Shape	Solvent for Crystallization	M.P.°	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
2′,4′-Dihydroxy-2-chloro	Yellow micro-needles	Chloroform	166–167	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.52	3.98
2′,4′-Dihydroxy-3-chloro-	Yellow micro-needles	Aqueous methanol	161–162	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.70	3.84
2′,4′-Dihydroxy-4-chloro-	Yellow lozenge shaped plates	Acetone	190–191	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.20	4.24
					Cl		Cl	
2′,4′-Dimethoxy-2-chloro-	Pale yellow silky needles	Ethanol	107–107.5	$C_{17}H_{15}O_3Cl$	11.7		11.6	
2′,4′,-Dimethoxy-4-chloro-	Pale yellow silky needles	Ethanol	117.5	$C_{17}H_{15}O_3Cl$	11.7		11.8	
					N		N	
2′,4′-Dihydroxy-3-nitro-	Lemon yellow micro-needles	Ethanol–acetic acid	214–215	$C_{15}H_{11}O_5N$	4.91		5.09	
2′-Hydroxy-3-nitro-	Yellow micro-crystalline powder	Ethanol	153–154	$C_{15}H_{11}O_4N$	5.20		5.5	

TABLE II

FLAVANONES

Flavanone	Color and Crystalline Shape	Solvent	M.P.,°	Formula	Calcd. C	Calcd. H	Found C	Found H
7-Hydroxy-2′-chloro-	Pinkish white plates	Benzene–petroleum ether	208–209	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.32	4.2
7-Hydroxy-3′-chloro-	Colorless flat micro-needles	Benzene	184–185	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.42	4.28
7-Hydroxy-4′-chloro-	Colorless hexagonal prisms	Acetone	209–210	$C_{15}H_{11}O_3Cl$	65.57	4.0	65.07	4.31
					N		N	
7-Hydroxy-3′-nitro-	Yellowish white micro-plates	Ethanol	240–241	$C_{15}H_{11}O_5N$	4.91		5.21	

TABLE III

CHALCONE 2,4-DINITROPHENYLHYDRAZONES

	Color and Crystalline Shape	Solvent	M.P.,°	Formula		
					N	N
2′,4′,-Dihydroxy-2-chloro-	Orange-red micro-needles	Ethyl acetate	253–254.5	$C_{21}H_{15}O_6ClN_4$	12.32	12.48
2′,4′,-Dihydroxy-3-chloro-	Red micro-needles	Ethyl acetate	263° dec.	$C_{21}H_{15}O_6ClN_4$	12.32	12.39
2′,4′,-Dihydroxy-4-chloro-	Deep red micro-needles	Ethanol	245–247	$C_{21}H_{15}O_6ClN_4$	12.32	12.13

of isomeric chlorochalcones, *e.g.*, 2′,4′-dihydroxy-2-chlorochalcone (64%) and 2′,4′-dihydroxy-3 (and 4)-chlorochalcones (17.8% and 19.4%). The high yield of 2′,4′-dihydroxy-2-chlorochalcone may be explained on the basis of combined inductive and direct effects (I+D) of the chloro substituent in the aldehyde component which makes the latter more electropositive and hence facilitates the condensation.

It has been found that in the condensation of resacetophenone with isomeric nitrobenzaldehydes, the presence of high concentration of alkali causes much resinification of the latter. No chalcone could be secured from either *o*- or *p*-nitrobenzaldehyde. Condensation with *m*-nitrobenzaldehyde, at 60° for forty-five minutes, however, gave 2′,4′-dihydroxy-3-nitrochalcone in 14% yield by the use of a larger quantity of the solvent as a diluent. The reaction is clean although resinification ensues on prolonged condensation.

On acid isomerization, the chloro- and nitrochalcones readily yield their corresponding flavanones. In the isomerization of 2′,4′-dihydroxy-4-chlorochalcone a large quantity of red coloring matter was produced with the 7-hydroxy-4′-chloroflavanone. This flavanone was found to

isomerize partly into its corresponding chalcone when heated above its melting point.

On prolonged reduction with magnesium and hydrochloric acid 7-hydroxy-4′-chloroflavanone develops a deep red color. The rest of the chloro and nitroflavanones, *e.g.*, 7-hydroxy-2′(and 3′)-chloroflavanones and 7-hydroxy-3′-nitroflavanone, however, fail to respond to this color reaction.

All the flavanones described here failed to impart any coloration to ethanolic ferric chloride.

EXPERIMENTAL

All the melting points are uncorrected. The chalcones were prepared according to the procedure of Schraufstätter and Deutsch.[3] The flavanones were secured by the acid isomerization[4] of the appropriate chalcones. The compounds prepared are listed in Tables I–III below.

Acknowledgment. The author wishes to thank the Government of India, Ministry of Scientific Research and Cultural Affairs, for the award of a Senior Research Scholarship and to Dr. J. B. Lal for his interest in this work.

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Formation of Chloranil During Chlorination of Certain Nitroaromatic Compounds

Robert E. Miller and William A. White

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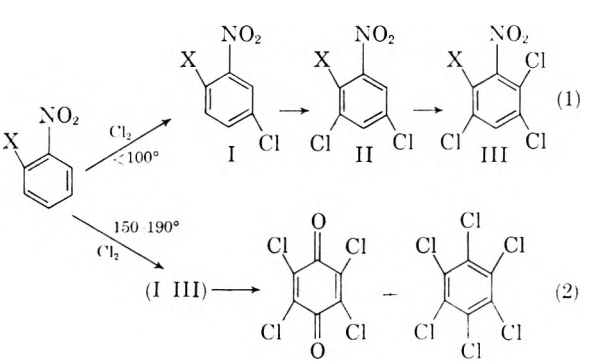
The chlorination of nitrobenzene, *o*-chloronitrobenzene, and *o*-nitrophenol with ferric chloride-chlorine at high temperatures results in the formation of hexachlorobenzene and chloranil together with a variety of chlorinated nitroaromatic derivatives. Hexachlorobenzene has been prepared from nitrobenzene[1] by a ferric chloride-catalyzed chlorination at temperatures above 100°, and from *o*-chloronitrobenzene[2] with antimony pentachloride–chlorine at 120°. The reaction of 1,4-dichloro-2,5-dinitro- or 1,5-dichloro-2,4-dinitrobenzene[3] with ferric chloride and chlorine at 140–180° also yields hexachlorobenzene. However, the formation of chloranil during these reactions was not described.

During the present investigation the conversions of the nitroaromatic compounds to chloranil amounted to 17–29%. Hexachlorobenzene conversion ranged from 7–89%. Although no attempt was made to establish optimum conditions, several observations are pertinent. Denitration of the ring is best accomplished at temperatures of 170–190°. The chlorination reaction is slow—to obtain significant yields of hexachlorobenzene and/or chloranil, a rapid flow rate of chlorine was used over a seven to ten hour period. No direct effects of ferric chloride concentration upon the course of the reaction were observed. Both catalytic and molar quantities of the metallic halide were used with similar results.

The experimental data are recorded in Table I.

Essentially, the formation of chloranil from the chlorination of a nitroaromatic compound represented in the equation below must proceed such that the position *para* to the nitro group is not substituted prior to denitration.



where X=H,OH,Cl.

To establish that denitration of the ring is temperature dependent, the chlorination of *o*-nitrophenol was conducted under mild conditions. Hexachlorobenzene and chloranil were not formed at 72°; 4,6-dichloro-2-nitrophenol (69%) and a mixture of monochloronitrophenols (28%) were the major products. The formation of the 4,6-dichloro isomer from the chlorination of *o*-nitrophenol has been reported earlier.[4] Page[1] has reported the formation of 2,3,5,6-tetrachloronitrobenzene from the chlorination of nitrobenzene below 100°.

While an ionic mechanism for the initial stages of the chlorination reaction would be valid at lower temperatures (Equation 1) complications arise under drastic conditions (130–200°). Thermally-initiated free radical reactions involving chlorination, nitration, denitration and/or oxidation may occur simultaneously. Cohen and Bennett,[5] for example, have reported that chlorination of 2,5-dichloronitrobenzene—the predominant isomer obtained on monochlorination of *o*-chloronitrobenzene[2]— at 130° with antimony pentachloride–chlorine does not give the expected 2,3,5-trichloronitrobenzene, but rather the 2,4,5-isomer.

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(2) A. F. Holleman, *Rec. trav. chim.*, **23**, 360 (1904); **31**, 280 (1912).

(3) E. Hüffer, *Rec. trav. chim.*, **40**, 452 (1921).

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TABLE I

CHLORINATION OF NITROAROMATIC COMPOUNDS

X	X-ArNO$_2$, mole	FeCl$_3$, g.	Cl$_2$, c.f.m.	Temp., °	Time, hr.	% Conv.[a] C_6Cl_6	% Conv.[a] $C_6Cl_4O_2$
H	0.05	16.2[b]	...	190–195	1	7.1	Trace
o-Cl	0.1	49.0	...	175–193	6	7.0	20.0
o-Cl	0.31	0.1	5	147–170	5	89.5	Trace
				180–196			
o-HO	0.57	0.1	5	150–180	5	17.1	29.6[c]
				190–200	2.5		
o-HO	0.23	0.1	5	72[d]	2.5	...	...[e,f]
o-HO	0.13	0.1	2	60–120	5	....	17.0[g,h]
				150–178	1		

[a] The infrared spectra of hexachlorobenzene and chloranil were identical with reference spectra (4545 and 6634 Sadtler Standard Spectra, respectively). [b] 94.5% of ferric ion converted to ferrous ion during reaction as determined by titration of aqueous washings with 0.05*N* potassium dichromate. [c] A complex mixture of chlorinated nitrophenols also resulted. [d] Carbon tetrachloride (100 ml.) used as solvent. [e] 4,6-Dichloro-2-nitrophenol (39%), m.p. 124–125°. R. L. Datta and H. Mitter, *J. Am. Chem. Soc.*, **41**, 2035 (1929) give 122–123°. *Anal.* Calcd. for $C_6H_3Cl_2NO_3$: C, 34.56; H, 1.44; Cl, 34.13; N, 6.73. Found: C, 34.91; H, 1.41; Cl, 32.21; N, 6.58. [f] A crude mixture of monochloronitrophenols (28%), m.p. 62–70° also obtained. *Anal.* Calcd. for $C_6H_4ClNO_3$: C, 41.50; H, 2.30; Cl, 20.45. Found: C, 39.59; H, 2.09; Cl, 21.98. [g] *Anal.* Calcd. for $C_6Cl_4O_2$: C, 29.25; Cl, 57.78. Found: C, 29.41, 29.43; Cl, 57.29, 57.28. [h] 4,6-Dichloro-2-nitrophenol (54.6%) also isolated, m.p. 124–126°. Infrared analysis shows absorptions due to hydroxyl, nitro and chloro groups; no adjacent hydrogen atoms on aromatic ring.

In view of the drastic conditions used in the present investigation, it would be difficult to predict the chlorinated intermediates, or the point at which the oxidation reaction occurs. It was shown, however, that the formation of hexachlorobenzene under the present reaction conditions could be derived from the chlorination of chloranil at 155–175°. The formation of hexachlorobenzene from chloranil has previously been reported[6] under somewhat different and even more drastic conditions.

Since nitrogen oxides were evolved during this chlorination reaction of nitroaromatics, the alternate possibility existed that oxidation and/or nitration of hexachlorobenzene may take place. It has been stated[7] that hexachlorobenzene is resistant to substitution by electrophilic reagents, and that when conditions are drastic enough to bring about a reaction with such reagents, it is not one of substitution. Although we were unable to isolate chloranil from the reaction of hexachlorobenzene with nitrogen tetroxide at 150–160°, the quinone has been obtained (21%) from the reaction of hexachlorobenzene with a sulfuric acid–nitric acid mixture at 90°.[8] No nitrated products were isolated.

EXPERIMENTAL

A typical experiment was conducted in the following manner. A cylindrical flask, fitted with a gas inlet tube, stirrer, thermometer, and condenser was charged with 80.0 g. (0.57 mole) of *o*-nitrophenol and 0.1 g. of anhydrous ferric chloride. The mixture was heated to 150° by means of a silicone oil bath. Chlorine gas was introduced at the rate of 5 c.f.m. After 5 hr. at 150–180°, the gas flow was interrupted, the mixture cooled and weighed. A gain of 45.0 g. had resulted. The mixture was reheated to 190° and chlorine passed through the mixture at 190–200° for an additional 2.5 hr. At this stage sublimation of a yellow solid was observed. The total gain in weight was 86.7 g. The mixture was washed with hot water and then extracted with ether. The ether extracts were discarded. The solids were extracted with chloroform; a yellow solid (41.7 g.) remained insoluble. After two recrystallizations from chloroform, the chloranil melted at 290–291° (sealed tube).

The solvent was removed from the chloroform soluble material (126.0 g.). The solids were extracted with ethanol to give 27.8 g. of insoluble material. This was recrystallized from chloroform to yield hexachlorobenzene, white needles, melting at 230–231°.

Anal. Calcd. for C_6Cl_6: C, 25.28; Cl, 74.80. Found: C, 25.15, 25.20; Cl, 74.36, 74.43.

The ethanol soluble material (73.8 g.) was not further investigated; it is probably a mixture of chlorinated nitrophenols.

Chloranil from hexachlorobenzene. Hexachlorobenzene (10.0 g., 0.03 mole) was placed in a flask and heated to 90° for 8 hr. with 23 ml. of 96% sulfuric acid and 78 ml. of fuming nitric acid. The mixture was cooled, diluted with water, and filtered. The solids were extracted with water and dried. Fractional crystallization of the solids from chloroform gave 1.6 g. (21.6%) of chloranil, yellow needles, m.p. and mixed m.p. 290–291° (sealed tube) (lit.,[9] m.p. 290–291° sealed tube).

Hexachlorobenzene from chloranil. Chloranil, 5.0 g. (0.02 mole) and ferric chloride (0.1 g.) were placed in a test tube and heated to 155–175° while passing chlorine through the mixture for 2.5 hr. at the rate of 5 c.f.m. The cooled mixture was extracted with chloroform to give 1.0 g. (17.5%) of hexachlorobenzene, white needles, m.p., and mixed m.p., 230–232°.

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(7) A. L. Rocklin, *J. Org. Chem.*, **21**, 1478 (1956).
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Observations on the Bromination of Phenylmercaptoacetic Acid

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In view of the preparation of 4-bromophenyl methyl sulfide by bromination of phenyl methyl sulfide in yields of greater than 90%,[1,2] it was surprising that 4-bromophenylmercaptoacetic acid could be obtained in yields of only about 60% by bromination of phenylmercaptoacetic acid in acetic acid. During the search for other possible products, 2-bromophenylmercaptoacetic acid, 3-bromophenylmercaptoacetic acid, 4-bromophenylmercaptoacetic acid, bis(2-bromophenyl) disulfide, bis(3-bromophenyl) disulfide and bis(4-bromophenyl) disulfide were prepared for comparison. It was found that 4-bromophenylmercaptoacetic acid was the only solid, nonvolatile, bromine-containing acid produced by bromination of phenylmercaptoacetic acid and that water in the reaction mixture led to the production of disulfides.

As the reaction proceeded, water was introduced as (a) water vapor in the air used to evaporate the reaction mixture, which contained unreacted bromine, and (b) water into which the acetic acid solution of the residue was poured. In order to determine the effect of water introduced while bromine was still present, the reaction was conducted in a solvent mixture, acetic acid and water. The solid product obtained was diphenyl disulfide. To illustrate the same effect, a solution of glacial acetic acid, 4-bromophenylmercaptoacetic acid and bromine was not evaporated but was poured into water and allowed to stand for an hour; bis(4-bromophenyl) disulfide was isolated from the insoluble solid. The negligible effect of water in the absence of bromine was demonstrated by the observation that phenylmercaptoacetic acid could be recrystallized from water with good recovery.

A possible reaction pathway, which will account for products found, is outlined below. We have not attempted to isolate bromoacetic acid from the reaction mixture.

(a) $H_2O + Br_2 \longrightarrow HBr + HOBr$

(b) $ArSCH_2CO_2H + HBr \longrightarrow ArSH + BrCH_2CO_2H$

(c) $2\ ArSH + HOBr \longrightarrow ArSSAr + H_2O + HBr$

or

$2\ ArSH + Br_2 \longrightarrow ArSSAr + 2\ HBr$

The mild conditions for the cleavage of this particular carbon - sulfur bond may be compared with conditions required for cleavage of aryl alkyl sulfides.[3] Such a facile room temperature cleavage as this might explain the low herbicidal activity of arylmercaptoacetic acids.[4-6]

EXPERIMENTAL

Materials. Phenylmercaptoacetic acid was obtained from Evans Chemetics, Inc. 2-, 3-, and 4-Bromoanilines were purchased from Distillation Products Industries. These compounds were purified by recrystallization or by distillation before use. Acetic acid was purified by repeatedly discarding eutectic compositions from partially melted commercial glacial acetic acid.

Bromination of phenylmercaptoacetic acid. To a solution of 4.00 g. (0.024 mole) of phenylmercaptoacetic acid and 100 ml. of glacial acetic acid in a flask protected by a drying tube was added 4.8 g. (0.030 mole) of bromine. The solution was allowed to remain out of direct sunlight for 5 days. Volatile constituents were removed from the orange solution by passing a gentle stream of air over the surface at ambient temperature; evaporation was continued until a dry residue remained. The dry, colorless, solid residue was dissolved in 25 ml. of hot acetic acid. The hot solution was poured into 100 ml. of cold water. The colorless precipitate was removed by filtration and dried *in vacuo*. The weight of the dried solid was 4.89 g.

The solid was recrystallized from water and then from an ethanol-water mixture. There was obtained 3.66 g. (62%) of 4-bromophenylmercaptoacetic acid.

The filtrates from the recrystallizations were extracted with ether. The extracts were combined, dried, and evaporated to dryness. The solid residue (melting range 90–113°) was analyzed with the infrared spectrophotometer.[7] Its spectrum consisted of contributions by phenylmercaptoacetic acid and 4-bromophenylmercaptoacetic acid.

The reaction was repeated several times. In the spectrum of one residue a very weak absorption at 14.05 μ indicated the presence of 2-bromophenylmercaptoacetic acid. However, attempts to estimate its concentration by infrared analysis were fruitless.

Bromophenylmercaptoacetic acids. 2-, 3-, and 4-Bromophenylmercaptoacetic acids were prepared from the corresponding bromoanilines. The bromoanilines were converted to the bromobenzenethiols by the method of Schwarzenbach and Egli.[8] The thiols were subsequently treated with sodium hydroxide and chloroacetic acid in a manner similar to that employed by Gabriel[9] for the synthesis of phenylmercaptoacetic acid. The bromophenylmercaptoacetic acids were recrystallized from ethanol-water mixtures. Physical constants of the previously known bromobenzenethiols and 4-bromophenylmercaptoacetic acid were comparable with literature values.[10,11]

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(7) Infrared spectra of solids were of potassium bromide disks and the spectrum of bis(3-bromophenyl) disulfide was of the pure liquid film between potassium bromide plates; all were recorded with a Perkin-Elmer Model 21 spectrophotometer.

(8) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).

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(11) H. F. Wilson and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 5200 (1950).

2-Bromophenylmercaptoacetic acid crystallized as colorless platelets from an ethanol-water mixture, m.p. 117–118°.

Anal. Calcd. for $C_8H_7O_2BrS$: Br, 32.34; neut. equiv., 247. Found: Br, 32.52; neut. equiv., 247.

3-Bromophenylmercaptoacetic acid crystallized from an ethanol-water mixture as colorless needles, m.p. 85–86°.

Anal. Calcd. for $C_8H_7O_2BrS$: Br, 32.34; neut. equiv., 247. Found: Br, 32.63; neut. equiv., 247.

Disulfides. Diphenyl disulfide, bis(2-bromophenyl) disulfide, bis(3-bromophenyl) disulfide, and bis(4-bromophenyl) disulfide were prepared by oxidation of the corresponding sodium thiophenoxides with air. The disulfides, recrystallized from ethanol or distilled, exhibited physical properties consistent with values reported in the literature.[11,12]

Infrared spectra. Infrared spectra of phenylmercaptoacetic acid, the bromophenylmercaptoacetic acids, and the disulfides were recorded. Prominent absorption bands in the region of out-of-plane CH deformations, which were used in analysis of residues obtained from recrystallization filtrates, are listed. Wave lengths are in microns and the most prominent band(s) in each spectrum is in italics. Phenylmercaptoacetic acid, 12.35, *13.55*, 14.3, 14.58; 2-bromophenylmercaptoacetic acid, 12.4, *13.3*, 14.05; 3-bromophenylmercaptoacetic acid, *12.9*, *13.3*; 4-bromophenylmercaptoacetic acid, *12.45*; diphenyl disulfide, *13.5*, *13.6*, 14.58; bis(2-bromophenyl) disulfide, *13.44*, 14.19; bis(3-bromophenyl) disulfide, 12.35, *12.95*, *13.44*; bis(4-bromophenyl) disulfide, *12.32*, 13.84.

Bromination in acetic acid–water mixture. To a solution of 4.00 g. of phenylmercaptoacetic acid, 75 ml. of glacial acetic acid, and 25 ml. of distilled water was added 4.8 g. of bromine. Conditions and isolation procedure were the same as described for the reaction in acetic acid. The crystalline product obtained after recrystallization consisted of 1.53 g. (67%) of diphenyl disulfide. No pure chemical individual could be isolated from extracts of the filtrates.

Cleavage of 4-bromophenylmercaptoacetic acid. A solution of 2.96 g. of 4-bromophenylmercaptoacetic acid, 100 ml. of glacial acetic acid, and 2.4 g. of bromine in a flask equipped with a drying tube was kept in the dark for 5 days. The reaction mixture was poured into 500 ml. of cold water, this resulting in formation of a colorless precipitate. After an hour the precipitate was removed by filtration. The dried solid weighed 1.45 g. and exhibited a melting range of 85–105°. Acidic and neutral fractions were separated. By recrystallization of these fractions there were obtained 1.02 g. (34% recovery) of 4-bromophenylmercaptoacetic acid and 0.11 g. (6.7% yield) of bis(4-bromophenyl) disulfide.

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(12) H. Hubner and J. Alsberg, *Ann.*, **156**, 308 (1870).

Acid-Catalyzed Rearrangement of Diethyl Ketone and Diisopropyl Ketone[1]

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Acid-catalyzed ketone rearrangements have received considerable attention in the past few years[2–4] and the mechanism of the reaction appears to be well established.[2] The ketone conjugate acid rearranges to an isomeric carbonium ion by an alkyl or aryl group shift, which in turn reverts to the original ketone conjugate acid or rearranges to the conjugate acid of the isomeric ketone by a second alkyl or aryl group shift. All mechanisms involving oxygen function migration (oxide conjugate acid formation, hydroxide shift or reversible pinacol formation) are excluded by the work of Barton and Porter[5] and the observation[6] that 3,3-dimethyl-2-butanone-1-2-C^{14} does not rearrange to 3,3-dimethyl-2-butanone-3-C^{14} under conditions where 3,3-dimethyl-2-butanone-1-C^{14} rearranges to an equilibrium mixture with 3,3-dimethyl-2-butanone-4-C^{14}.

Barton and Porter[5] and Zook, Smith, and Greene[7] studied the acid-catalyzed rearrangements of a number of aliphatic ketones, including in both cases, diisopropyl ketone, for which no rearrangement was observed.[8] Barton and Porter conclude that only those ketones whose carbonyl groups are attached to at least one quaternary carbon can rearrange. In terms of the established mechanism, the conclusion could be stated that rearrangement would take place only when a tertiary carbonium ion can be formed in the migration of an alkyl group to the carbonyl carbon.

The results of the present research demonstrate that ketone rearrangements do occur, not only where such tertiary carbonium ions would be formed, but also where secondary and primary carbonium ions would be required, assuming the same rearrangement mechanism.

Upon treatment with perchloric or sulfuric acid at 90° for three hours diisopropyl ketone rearranges to the extent of 70% to 3,4-dimethyl-2-pentanone. No other rearrangement products could be detected by gas chromatography. The rearranged ketone was identified by gas chromatographic and chemical comparison with an authentic sample of 3,4-dimethyl-2-pentanone.

(1) This research was supported by the Atomic Energy Commission.

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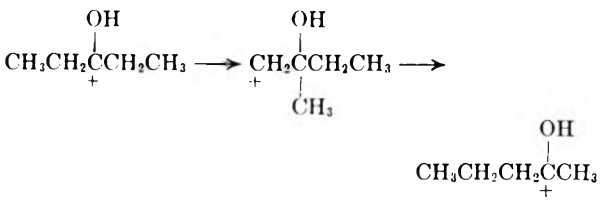
(8) The conditions used by both groups of workers were much less conducive to rearrangement than those used in most cases in the work reported here, and the small amount of rearrangement which does occur under conditions used by Zook, Smith, and Greene[7] might well have gone undetected, since it is within the limits of accuracy claimed for their analytical method. Barton and Porter state that they did not look for minor rearrangement products.

When diethyl ketone was heated on the steam bath for three hours with 70% perchloric acid, it rearranged to the extent of approximately 63% to methyl propyl ketone. Since the boiling points of diethyl ketone and methyl propyl ketone are almost identical, no attempt was made to fractionate the recovered ketone mixture.[9] Instead, the mixture was degraded by the haloform reaction, and iodoform and butyric acid were isolated and characterized.

The simplest interpretation of these rearrangements involves rearrangement of the conjugate acid of the ketone as illustrated here for diethyl ketone.[10]



The scope of ketone rearrangement reactions is being investigated further.

EXPERIMENTAL

Diethyl ketone. Ten grams of diethyl ketone dissolved in 50 ml. of 70% perchloric acid were heated on the steam bath for 3 hr. The solution, which had turned yellow, was poured onto ice, neutralized with sodium hydroxide, and extracted with ether. The combined ether extract was washed and dried, and the ether evaporated. The residue was distilled under vacuum and a wide cut was taken centering on the boiling point of a mixture of diethyl ketone and methyl propyl ketone. The gas chromatograph of this material was essentially identical with that of the starting material. Sodium hypoiodite was added to 1.6 g. of the mixed ketones and 2.1 g. of iodoform of characteristic odor and m.p. 115–119°, reported[11] m.p. 119° was obtained. The filtrate was acidified with sulfuric acid, treated with excess silver sulfate and distilled, extra water being added several times. The acid in the distillate was identified as butyric acid by titrating with standard sodium hydroxide (10.3 mmoles), evaporating the solution to dryness and weighing the sodium salt, and by preparation of the *p*-toluide, m.p. 73–75°, reported[12] m.p. 74–75°, mixed melting point with an authentic sample 73–74°. The yield of sodium butyrate corresponded to 1.015 g. of methyl propyl ketone, indicating that approximately 63% of the diethyl ketone had rearranged. A sample of the diethyl ketone used was subjected to the same degradation procedure and neither iodoform nor butyric acid was obtained. A known mixture of diethyl ketone and methyl propyl ketone gave exactly the expected results when subjected to the degradation procedure.

Diisopropyl ketone. Ten milliliters of diisopropyl ketone and 50 ml. of concd. sulfuric acid (or, in a separate experiment, 3 ml. of ketone and 50 ml. of 70% perchloric acid) were heated at 90° for 3 hr. The mixed ketone fraction was recovered as above and shown by gas chromatography to consist of 30% of diisopropyl ketone and 70% of another compound which was identified as 3,4-dimethyl-2-pentanone by comparison with an authentic sample prepared by the acetoacetic ester synthesis following the procedure of Willstatter and Hatt.[13] No other rearrangement product could be found from the gas chromatograph. The 3,4-dimethyl-2-pentanone from the rearrangement was also characterized as the semicarbazone, m.p. 112°, reported[14] m.p. 112°, mixed melting point with an authentic sample 112°. Under milder conditions comparable to those previously used[7] (5 g. of ketone and 50 g. of concd. sulfuric acid at room temperature for 8 days) a small amount (about 3–4%) of rearrangement was observed.

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(9) Even gas chromatography failed to separate the two ketones; however only a fifty-foot polyester column was tried, and separation might be possible with other columns.

(10) A mechanism whereby the movement of the methyl and ethyl groups is concerted is not ruled out, although the geometrical requirements of such a mechanism are such that it is not attractive; however, see ref. 4.

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Acetolysis and Trifluoroacetolysis of *tert*-Butyl Nitrate[1]

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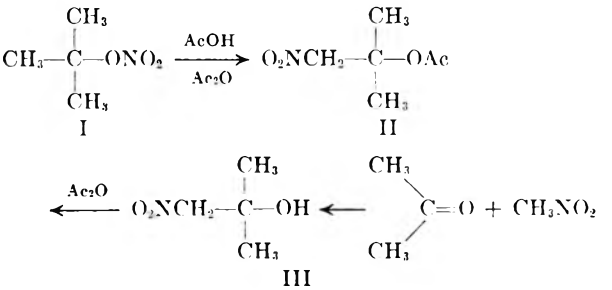
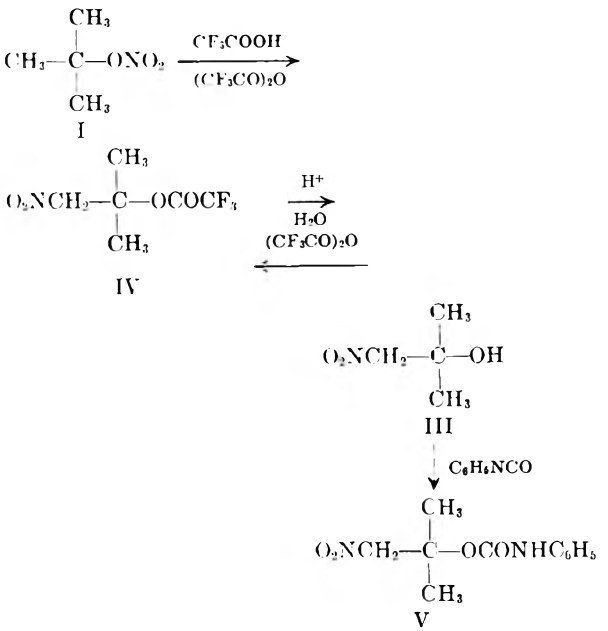
In the course of a polarographic study of the acetolysis of *tert*-butyl nitrate (I), it was observed (see Table I) that the diffusion current increased markedly during the course of a run when acetic anhydride was present in the acetolysis medium. In the absence of acetic anhydride, however, the diffusion current changed very little. I, therefore, appeared to be converted into a much more readily reducible species, possibly a nitro compound. A large scale acetolysis of I yielded, in very low yield, a high boiling ester, suspected to be nitro-*tert*-butyl acetate (II). Independent synthesis of II showed that the acetolysis product was indeed II, as shown by comparison of infrared spectra.



In the hope that solvolysis in trifluoroacetic acid would give a better yield of a product similar to II,

(1) Reported in part at the Pacific Southwest Regional Meeting of the American Chemical Society, Redlands, California, October 25, 1958, p. A-7 of abstracts.

the trifluoroacetolysis of I in the presence of trifluoroacetic anhydride was attempted. This solvolysis was quite rapid and exothermic, the reaction apparently being over in a few minutes. A 36% yield of the expected product, nitro-*tert*-butyl trifluoroacetate (IV), was isolated upon work-up of the reaction mixture.



The structure of IV was verified by its independent synthesis from III, and by its hydrolysis to III and conversion to the phenyl urethane(V).

One can only speculate as to the mechanism of the conversion of I to II (or IV). A likely possibility is the elimination of nitric acid from I to isobutylene, followed by the addition of acetyl nitrate (or trifluoroacetyl nitrate) to give the observed products. The formation of isobutylene seems to be a reasonable explanation for the low product yields and poor product balances, as this gas could be easily lost during either the reaction period or the work-up.

A number of attempts were made to see whether the increase in polarographic wave height (see Table I) would conform to some simple rate law. Simple first and second order rate laws, and consecutive first and second order rate laws were tried, but without success.

EXPERIMENTAL

Polarographic study. tert-Butyl nitrate produces a polarographic wave with an $E_{1/2}$ *vs.* Hg. pool of -1.00 volts in a 50% ethanol solution of tetramethylammonium chloride. However, a solution of *tert*-butyl nitrate in acetic anhydride that has stood for several hours produces a polarographic wave with an $E_{1/2}$ *vs.* Hg. pool of -0.90 volts when placed in a 50% ethanol solution of tetramethylammonium chloride.

The acetolysis solution was prepared as follows: 1.0 Ml. of *tert*-butyl nitrate and 1 ml. of acetic anhydride were placed in a 25-ml. volumetric flask and diluted to volume with glacial acetic acid. This solution was heated in a constant temperature bath at 52.17°. For the polarograms, a 1-ml. aliquot of the *tert*-butyl nitrate-acetic anhydride solution was placed in a 25-ml. volumetric flask. Fifteen milliliters of a 50% ethanol solution of 0.1*M* tetramethylammonium chloride was added to the flask. Five drops of a 0.1% solution of methyl red were added and a 10*M* sodium hydroxide solution was slowly added with stirring until the solution just turned yellow. The solution was then diluted to volume with the 50% ethanol solution of tetramethylammonium chloride. Approximately 15 ml. of this solution was introduced into a polarographic cell, held at a constant temperature (25° ± 0.1°), and flushed with nitrogen for 5 min. The polarogram was then recorded from -0.30 to -1.50 volts.

The change in the wave height with time at $E_{1/2} = -0.90$ volts for a typical experiment is summarized in Table I. In this table the polarographic wave height at 0 hr. is for the original *tert*-butyl nitrate–acetic anhydride solution ($E_{1/2}$ vs. Hg. pool = -1.00 volts).

TABLE I

POLAROGRAPHIC STUDY OF THE ACETOLYSIS OF *tert*-BUTYL NITRATE AT 52.17°

Time (min.)	Polarographic Wave Height (μa)
0	0.60
64	9.03
93	14.88
110	17.32
191	20.40
249	30.70
304	33.20
451	34.20
1347	47.00

Nitro-tert-butyl alcohol and nitro-tert-butyl acetate. Nitro-*tert*-butyl alcohol, b.p. 56–60° (2 mm.), n_D^{25} 1.4256, and nitro-*tert*-butyl acetate, b.p. 45° (1.5 mm.) n_D^{24} 1.4352, were prepared according to the directions of Lambert and Lowe.[2]

Nitro-tert-butyl phenyl urethane. To 2.00 g. (0.0168 mole) of nitro-*tert*-butyl alcohol was added 2.00 g. (0.0168 mole) of phenyl isocyanate and the mixture was heated 20 hr. on the steam bath. After this heating period, the mixture was very viscous, and crystals appeared when the side of the tube was scratched gently with a stirring rod. The mixture was taken up in benzene and petroleum ether (b.p. 60–80°) was added. An oil appeared which readily crystallized to yield 2.26 g. of crystals, m.p. 81°; m.p. 82° after six recrystallizations.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.23; H, 5.96.

Nitro-tert-butyl trifluoroacetate. To 12.0 g. (0.10 mole) of nitro-*tert*-butyl alcohol (cooled in ice) was added gradually 30 ml. of trifluoroacetic anhydride. The mixture was allowed to warm gradually to room temperature and then was refluxed for 2 hr. Removal of excess trifluoroacetic acid and anhydride and distillation of the residue yielded 14.79 g. (65%) of nitro-*tert*-butyl trifluoroacetate, b.p. 42° (1 mm). The infrared spectrum of this material was nearly identical with that of the product from the trifluoroacetolysis of *tert*-butyl nitrate.

Trifluoroacetolysis of tert-butyl nitrate. To a mixture of 20 ml. of trifluoroacetic anhydride and 50 ml. of trifluoroacetic acid (cooled in Dry Ice until crystals of trifluoroacetic acid appeared) was added 10 ml. (*ca.* 10 g., 0.0926 mole) of *tert*-butyl nitrate. The mixture was allowed to warm very gradually to nearly room temperature until a slight discoloring was observed. As long as an exothermic reaction seemed to take place, the mixture was kept cool. After the reaction appeared to be over, the mixture stood at room

(2) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

temperature for 2 hr. The solvent mixture of acid and anhydride was removed by distillation at aspirator pressure and the residue was collected at 60° (2 mm.) to yield 6.43 g. (36%) of nitro-*tert*-butyl trifluoroacetate. The infrared spectrum of this material was virtually identical with that of authentic nitro-*tert*-butyl trifluoroacetate.

Hydrolysis of nitro-tert-butyl trifluoroacetate. To 2.0 g. (0.0168 mole) of nitro-*tert*-butyl trifluoroacetate were added 10 ml. of water and 3 drops of concd. sulfuric acid. The mixture was refluxed for *ca.* 5 min., and then solid sodium bicarbonate was added in sufficient quantity to neutralize the sulfuric and trifluoroacetic acids. The product was extracted with ether and the dried ether extract evaporated; 1.5 ml. of phenyl isocyanate was added to the residue and the mixture was heated overnight on the steam bath. The mixture was worked up as in the preparation of the phenyl urethane of nitro-*tert*-butyl alcohol to yield 2.39 g. of crude product, m.p. 80–85° after one recrystallization.

Characterization of the tert-butyl nitrate trifluoroacetolysis product. Two grams of the trifluoroacetolysis product was worked up as in the hydrolysis of nitro-*tert*-butyl trifluoroacetate to yield 2.17 g. of urethane, m.p. 80–81°, after one recrystallization. The mixture melting point with nitro-*tert*-butyl phenyl urethane was 81–82°. The infrared spectra of the two samples were identical.

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Studies of the Cyclization of *o*-Benzoylbenzoic-Carboxyl-C^{14} Acid

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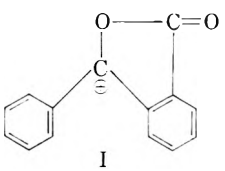
Newman and co-workers[1,2] have presented strong arguments that when *o*-benzoylbenzoic acid is dissolved in concentrated sulfuric acid, the organic acid is almost entirely converted to a cyclic positive ion, I. According to their views the cyclization of

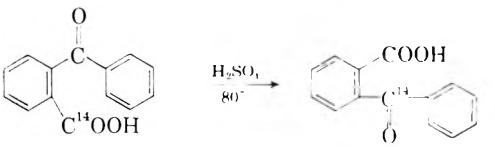


I

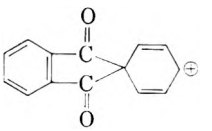
the dissolved *o*-benzoylbenzoic acid upon heating this sulfuric acid solution involves a rate-determining conversion of the cyclic positive ion to anthraquinone with the ejection of a proton.

Studies of the cyclization of *o*-benzoylbenzoic-carboxyl-C^{14} acid have provided additional information bearing on the mechanism of the cyclization in concentrated sulfuric acid.

Hayashi rearrangement[3,4] accompanies cyclization of certain substituted *o*-benzoylbenzoic acids. This rearrangement is exemplified by the reaction[3]: It is apparent that any Hayashi rearrangement accompanying the cyclization of *o*-benzoylbenzoic acid could be detected only by the use of isotopic labeling. A sample of *o*-benzoylbenzoic-*carboxyl*-C^{14} acid was cyclized to the extent of 16% at 80° in concentrated sulfuric acid. The 84% unchanged acid was recovered, purified, and degraded by decarboxylation at 275° to benzophenone. As the pure 2,4-dinitrophenylhydrazone prepared from this benzophenone contained little more than background activity, no measurable degree of Hayashi rearrangement could be detected. Hayashi rearrangement of *o*-benzoylbenzoic-*carboxyl*-C^{14} acid would lead to carbon-14 in the keto group:



This result also eliminates any intermediate in the cyclization reaction in which the two nonaromatic carbon atoms are equilibrated with each other and with the unchanged acid at a rate which is rapid in comparison with the overall reaction rate. The symmetrical ion, for example, is not a



significant part of the reaction path. The present result is in accord with the Newman[1] mechanism, inasmuch as the latter does not provide a path for Hayashi rearrangement during cyclization of *o*-benzoylbenzoic acid to anthraquinone.

It now appears that the 3.5% carbon-14 isotope effect[5] in the cyclization of *o*-benzoylbenzoic-carboxyl-C^{14} acid is *not* an effect of carbon-14 substitution on the pre-rate equilibrium between *o*-benzoylbenzoic acid and the oxocarbonium ion, $C_6H_5COC_6H_4CO^+$ (II), as was suggested earlier.[5] Rather, this carbon-14 isotope effect, being of *intermediate magnitude*, appears to be either (a) an isotope effect on a pre-rate equilibrium between I and II or (b) a kinetic isotope effect on a concerted process which converts I directly to anthraquinone with ejection of a proton.

(1) M. S. Newman, *J. Am. Chem. Soc.*, **64**, 2324 (1942).
(2) M. S. Newman, H. G. Kuivala, and A. B. Garrett, *J. Am. Chem. Soc.*, **67**, 704 (1945).
(3) M. Hayashi, *J. Chem. Soc.*, 2516 (1927).
(4) R. B. Sandin, R. M. Melby, R. Crawford, and D. McGreer, *J. Am. Chem. Soc.*, **78**, 3817 (1956).
(5) Gus A. Ropp, *J. Chem. Phys.*, **23**, 2196 (1956).

EXPERIMENTAL

Partial conversion of o-benzoylbenzoic-carboxyl-C^{11} acid to labeled anthraquinone. In 25 ml. of C.P. sulfuric acid, 850 mg. of *o*-benzoylbenzoic-carboxyl-C^{11} acid was dissolved at room temperature to form a clear, red solution. This was heated in an oil bath 20 min. at 80°. The solution was poured onto ice, warmed to room temperature, and digested for 15 min. on a steam bath. The mixture was cooled in ice and the precipitated solid was collected on a filter and washed with water. The solid was extracted with 4*N* sodium hydroxide. The alkali-insoluble residue was washed with water and dried to give 130 mg. (16.5%) of labeled anthraquinone which was identified by its melting point after a recrystallization from ethanol. The alkaline solution was acidified and the recovered *o*-benzoylbenzoic-carboxyl-C^{14} acid was collected on a filter, washed with water, dried, and recrystallized from a hexane-benzene solution. Degradation of the purified, recovered acid was performed by the method of Dougherty.[6] Radioassays were performed by a modification of the method described by Neville.[7]

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(6) G. Dougherty, *J. Am. Chem. Soc.*, **50**, 571 (1928).
(7) O. K. Neville, *J. Am. Chem. Soc.*, **70**, 3501 (1948).

2,4′-Biquinolyl

I. W. ELLIOTT

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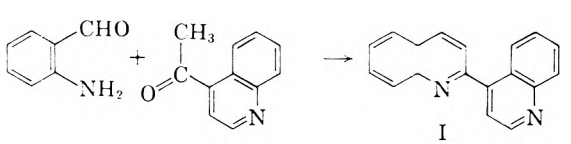
2,4′-Biquinolyl (I) is not among the series of known biquinolyls. The possibility that derivatives of this diquinolyl system might be formed in certain reductive coupling reactions that are currently under investigation prompted us to prepare the parent heteroaromatic compound for reference and for comparison with other known biquinolyls.

The intermediates for the synthesis of I were all known compounds. Starting from isatin, the sequence included 1-acetylisatin, 4-carboxycarbostyril, 2-chlorocinchoninic acid, cinchoninic acid, ethyl cinchoninate, and methyl 4-quinolyl ketone.[1] The last stage involved a Friedländer condensation of the ketone with *o*-aminobenzaldehyde to give 2,4′-biquinolyl.



I

The structure I for the final base is shown by the method of synthesis, its absorption spectra, and the preparation of salts. Spectroscopically, the base shows absorption in the ultraviolet like quinoline and other biquinolyls.[2] 2,4′-Biquinolyl forms a monopicrate salt in accord with the pattern observed by Abramovitch in the pyridylquinoline series.[3] Even with perchloric acid, the stable salt obtained was the monoprotonated derivative. Although a high-melting salt (m.p. 274°) was obtained from 2,4′-biquinolyl and concentrated perchloric acid, recrystallization from acidic methanol repeatedly afforded only a lower-melting monoperchlorate (m.p. 239–240°).[4]

Further evidence for the 2,4′-biquinolyl structure (I) is obtained from the infrared spectrum. There is no band in the region of 3.0 μ(N–H) nor in the range 5.8–6.0 μ (ketone or aldehyde carbonyl). There is a series of bands (6.20, 6.28, 6.35, 6.40, and 6.43 μ) of weak to medium intensity that show a general similarity to the spectra of other quinoline derivatives. However, the strongest bands appear in the region 11–14 μ where the C—H out-of-plane deformation vibrations arise. This portion of the spectrum has been widely used to study substitution in aromatic compounds, and it has been proposed that the correlations of the band positions with the number of adjacent hydrogens can be extended to pyridine and quinoline if the nitrogen is regarded as a substituted ring atom and, in the case of a bicyclic aromatic compound, if the two rings are considered separately.[5] For 2,4′-biquinolyl, however, there were only three strong bands observed within the usually accepted region. These were found at 11.96, 13.27, and 13.53 μ. The first of these is like the band in *p*-disubstituted benzenes and may, as a single band, be ascribed to vibrations involving two adjacent hydrogens on both pyridine rings. The other two bands are like those found in the spectra of *o*-disubstituted benzenes and may arise from the C–H deformation frequencies associated with the two benzenoid rings. Moreover, the spectrum of 2,4′-biquinolyl is generally similar in the 11–14 μ region to a composite spectrum of quinaldine and lepidine.[6]

(1) (a) T. L. Jacobs, *et al.*, *Org. Syntheses*, **Coll. Vol. III**, 456 (1955); (b) K. N. Campbell and J. F. Kerwin, *J. Am. Chem. Soc.*, **68**, 1837 (1946); (c) C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 2460 (1943).

(2) M. Crawford and I. F. B. Smyth, *J. Chem. Soc.*, 1433 (1952).
(3) R. A. Abramovitch, *J. Chem. Soc.*, 3839 (1954).
(4) P. Krumholz, *J. Am. Chem. Soc.*, **73**, 3487 (1951) observed that the second dissociation constant for those dipyridyls in which one ring was linked at the 2-position was high compared to other isomers and that no biacid salt was formed for 2,2′-bipyridyl.
(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1958, p. 281. The principal limitation of this technique is that frequently the number of bands present exceeds that expected on the basis of the formulated rules, even in the carbocyclic series; *cf.* L. Cencelj and D. Hudzi, *Spectrochim. Acta*, **7**, 274 (1955); R. F. Curtis and G. Viswanath, *J. Chem. Soc.*, 1670 (1959); C. G. Cannon and G. B. B. M. Sutherland, *Spectrochim. Acta*, **4**, 373 (1951).
(6) Although the biquinolyl spectrum was recorded from a mulled sample and the two methylquinoline spectra were taken with liquid films, our examination of other closely related compounds does not indicate that there are appreciable variations from the two sampling techniques.

TABLE I

INFRARED ABSORPTION BANDS IN 11–14 μ REGION

2,4′-Biquinolyl (nujol mull)	2,2′-Biquinolyl (nujol mull)	Quinaldine (liquid)	Lepidine (liquid)
11.35 m[a]	—	11.35 w	—
11.50 w	11.50 m	11.52 vw	—
11.59 w	—	—	11.67 s
11.96 s	11.93 s	—	11.93 vs
11.28 w	12.05 s	12.22 vs	12.32 m
12.51 w	—	—	—
12.71 m	12.71 m	12.80 s	12.78 w
13.05 w	13.08 w	13.05 vw	—
13.13 w	—	—	—
13.27 s	13.45 i	13.38 s	13.25 vs
13.53 vs	13.52 s	—	—

[a] Vs = very strong; s = strong; m = medium; w = weak; vw = very weak.

EXPERIMENTAL[6]

Methyl 4-quinolyl ketone. Ethyl cinchoninate was prepared from 14 g. of cinchoninic acid in 75 ml. of absolute ethanol and 5 ml. of concd. sulfuric acid. The ester (12 g.) was distilled at 106–107° (0.2 mm.) [lit.,[1b] b.p. 120–123 (1 mm.)], with the following infrared bands (liquid film) (μ): 5.72, (C=O), 12.50, 13.10. The picrate from the ester melted at 187–188° (lit.,[1c] m.p. 183–188°). The ester was condensed with ethyl acetate in toluene solution with sodium ethoxide and the condensation product was isolated as the sodium salt. To 6 g. of the sodio-derivative of ethyl 3-keto-3-(4-quinolyl)propanoate was added 75 ml. of water and 12 ml. of concd. sulfuric acid, and the solution was heated on the steam bath for 3 hr. The cooled solution was made weakly alkaline with sodium carbonate solution and extracted five times with ether. Evaporation of the dried ether extracts left only a small amount of a dark viscous oil that was distilled to give 0.9 g. of methyl 4-quinolyl ketone, b.p. 108–110° (0.2 mm.) (lit.,[7] b.p. 138°/2 mm.). Significant infrared bands follow (liquid film) (μ): 5.86 (ketone C=O). 6.31, 11.75, 13.05. The ketone formed a picrate, m.p. 165–167° (lit.,[7] m.p. 165–167°).

2,4′-Biquinolyl. A solution of 0.72 g. of methyl 4-quinolyl ketone in 50 ml. of ethanol was treated with 0.70 g. of freshly prepared 2-aminobenzaldehyde[8] and 0.20 g. of potassium hydroxide. On warming a solid began to form, but this redissolved in hot ethanol. The solution, which turned red, was heated on a steam bath for 1 hr., filtered from a small amount of insoluble residue, and allowed to cool. From the solution 0.8 g. of a pink voluminous solid separated. Passage of the ethanolic solution of the biquinoline through a short column of alumina gave a colorless product, m.p. 153–154°; $\lambda_{max}^{C_2H_5OH}$ (log ϵ) 3.17 (4.04), 230 mμ(4.56).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.40; H, 4.93; N, 10.69.

2,4′-Biquinolyl monopicrate was prepared in ethanol solution and recrystallized from acetonitrile as yellow plates, m.p. 261–262°.

Anal. Calcd. for $C_{24}H_{15}N_5O_7$: C, 59.35; H, 3.12. Found: C, 60.10; H, 3.35.

2,4′-Biquinolyl perchlorate was prepared in methanol solution and recrystallized from a mixture of methanol and water as pale yellow needles, m.p. 239–240°.

Anal. Calcd. for $C_{18}H_{13}N_2O_4Cl$: C, 60.60; H, 3.67; N, 7.85. Found: C, 60.77; H, 3.08; N, 7.99.

When 2,4′-biquinolyl or the monoperchlorate was treated with concd. perchloric acid, a salt melting at 274–276° was obtained, but recrystallization of this salt from acidic methanol gave only the salt melting at 239–240°.

Acknowledgment. The author wishes to thank Mr. Marion S. Barry, who prepared certain intermediate compounds, and Drs. Nelson Fuson and James R. Lawson for suggestions and criticism of the infrared spectral interpretation. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corporation for partial support of this research.

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(6) Melting points were taken in a Drechsel melting point apparatus and are otherwise uncorrected. Analyses are by Schwarzkopf Microanalytical Laboratory. The infrared spectra were recorded on a Beckman IR-4 spectrophotometer with sodium chloride optics, and the ultraviolet spectrum was taken on a Beckman DK-1 instrument.

(7) A. Kaufmann, H. Peyer, and M. Kunkler, *Ber.*, **45**, 3090 (1912).

(8) F. G. Mann and A. J. Wilkinson, *J. Chem. Soc.*, 3346 (1957).

2,4-Diamino-5-formylpyrimidine and 2,4-Diamino-5-hydroxymethylpyrimidine[1]

HOWARD TIECKELMANN, ROBERT GUTHRIE, AND J. GRAHAM NAIRN[2]

Received December 11, 1959

In a study of the catalytic hydrogenation of heterocyclic nitriles,[3a,b] Huber has prepared a compound described as 2,4-diamino-5-hydroxymethylpyrimidine (I), which was formed from the hydrochloride of an amine characterized as di-(2,4 - diamino - 5 - pyrimidylmethyl)amine (II) on treatment with aqueous sodium hydroxide. This latter amine was formed along with 2,4-diamino-5-aminomethylpyrimidine (III) on hydrogenation of 2,4-diamino-5-cyanopyrimidine.[3a]

We have hydrogenated 2,4-diamino-5-cyanopyrimidine using a W-4[4] Raney nickel catalyst. Substances were formed which gave the approximate properties of the compounds previously described as the hydrochlorides of II and III. Treatment of the compound, presumed to be II, with aqueous sodium hydroxide gave a compound with properties different from those shown by a sample of I which had been prepared by Nairn and Tieckel-

(1) Supported by a Grant, CY-2857, from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Present address, University of Toronto, Faculty of Pharmacy, Toronto, Ontario.

(3) (a) W. Huber, *J. Am. Chem. Soc.*, **65**, 2222 (1943). (b) W. Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).

(4) H. Adkins and A. A. Pavlic, *J. Am. Chem. Soc.*, **69**, 3039 (1947).

mann.[5] The latter report a melting point of 231–234° compared with a melting point of 265° dec., previously reported.[3a] The most striking difference between the two materials was in their inhibitory effects on *Bacillus subtilis* ATCC-6051. It has been observed[6] that many 2-substituted 4-amino-5-hydroxymethylpyrimidines inhibit the growth of this organism and that this inhibition is reversed by the thiamin pyrimidine 2-methyl-4-amino-5-hydroxymethylpyrimidine. The compound prepared by the method of Huber had little effect on this organism, whereas I, prepared by Nairn and Tieckelmann, produced a strong inhibition that was specifically prevented by the thiamin pyrimidine, thiamin, or cocarboxylase.

In the present work elementary analyses indicated that the compound previously described as I was 2,4-diamino-5-formylpyrimidine (IV). The structure was confirmed by the formation of the oxime and by reduction to I with sodium borohydride. Prepared by this method, I was identical with the substance prepared by Nairn and Tieckelmann in melting points, infrared and ultraviolet absorption spectra, and specific inhibition of *Bacillus subtilis*.

Although the 5-aldimine also can be predicted to give the aldehyde IV by hydrolysis, evidence indicates that the substance formed along with III in our hydrogenation was the Schiff's base V of III and IV. We did not characterize this material. It was isolated as a hydrochloride but it was not possible to obtain consistent chlorine analyses after crystallization from aqueous alcohol. The values ranged from 25–33%, depending on conditions, and most probably were due to hydrolysis during recrystallization. A small amount of this material was hydrolyzed in 10% sodium hydroxide. Paper chromatography of the hydrolysate with water-saturated *n*-butyl alcohol containing ammonia revealed two spots, when observed under ultraviolet light, corresponding in Rf and inhibition of *B. subtilis* to III and IV (Table I). When the spots were excised and extracted with water, ultraviolet absorption spectra indicated approximately equal amounts of III and IV. In subsequent experiments, III and IV were formed in reasonable yield by hydrolysis of the crude Schiff's base.

TABLE I

PAPER CHROMATOGRAPHY OF PYRIMIDINES

	Rf[a]	λ Max. (mμ)	Inhibition by *B. subtilis*
III	0.05	284	+[b]
I	0.17	275	+
IV	0.29	299 265	−
Hydrolysate of V	0.04	284	+
	0.29	299 265	−

[a] One ml. of concd. ammonium hydroxide was added to a solution of 1 l. of *n*-butyl alcohol saturated with water. After shaking and standing overnight the butyl alcohol layer was used as the solvent. [b] The ultraviolet light absorbing spots on the paper were marked. A strip was cut and placed on solid agar medium seeded with *B. subtilis*. Following a suitable growth period, the marked spot was observed at the center of a symmetrically shaped inhibitory area.

EXPERIMENTAL[7,8]

2,4-Diamino-5-formylpyrimidine (IV). Seven grams of 2,4-diamino-5-cyanopyrimidine was hydrogenated according to the method previously described[3a] employing a W-4[4] Raney nickel catalyst. The resulting mixture gave 2.3 g. of the dihydrochloride of III and 5.6 g. of the hydrochloride of V. Crude V was dissolved in 100 ml. water and the solution made basic to litmus with 10% sodium hydroxide. The precipitate was collected and washed with water to give 1.6 g. (85%) of IV. The analytical sample was recrystallized from water; m.p. 263–264° dec. Ultraviolet absorption was as follows: *p*H 1.0 λ_{max} 279 mμ ($\epsilon = 7.5 \times 10^3$). *p*H 6.2, 300 ($1.6 \times 10^4$), 264 ($1.2 \times 10^4$).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.37; H, 4.38; N, 40.56. Found: C, 43.70; H, 4.51; N, 40.40.

2,4-Diamino-5-aminomethylpyrimidine (III) *from* V. The filtrate from the previous experiment was treated with 6 ml. of concd. hydrochloric acid and evaporated to dryness at reduced pressure. The residue, consisting of the dihydrochloride of III and sodium chloride, was treated with 30 ml. of absolute alcohol and filtered. The 5.5 g. of solid collected was recrystallized from water-alcohol to give 2.24 g. of the dihydrochloride of III, dec., 278–281°, (lit.,[3a] dec. 278–280°). The ultraviolet spectra showed the following bands: *p*H 1.0 λ_{max} 269 mμ ($\epsilon = 4.7 \times 10^3$), *p*H 6.1 273 ($4.3 \times 10^3$), *p*H 11.4 285 ($6.8 \times 10^3$).

2,4-Diamino-5-hydroxymethylpyrimidine (I). A solution of 0.1 g. of sodium borohydride in 10 ml. of water was added to a suspension of 0.5 g. of 2,4-diamino-5-formylpyrimidine in 20 ml. of water. After standing for 15 min. with occasional shaking, the mixture was heated to 50–55° until the solid dissolved. After cooling and standing overnight 0.35 g. (69%) of 2,4-diamino-5-hydroxymethylpyrimidine had precipitated; m.p. 231–233° dec. The analytical sample, m.p. 234–236° dec., was recrystallized from water. Ultraviolet absorption was as follows: *p*H 0.9, λ_{max} 269 mμ ($\epsilon = 5.1 \times 10^3$), *p*H 7.7 283 ($6.7 \times 10^3$), *p*H 11.2 233 ($1.1 \times 10^4$), 284 ($7.0 \times 10^3$).

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 43.02; H, 5.79; N, 40.11.

2,4-Diamino-5-pyrimidylaldoxime. A solution of 0.3 g. of 2,4-diamino-5-formylpyrimidine in 10 ml. of hot ethyl alcohol was added to a solution of 5 g. of hydroxylamine hydrochloride in 10 ml. of water made basic with 20 ml. of 10% sodium hydroxide. The solution was heated on a steam bath for 30 min., concentrated to one half the original volume, and allowed to cool. The precipitate was crystallized four times from water. The oxime melted at 290–291° dec. and was soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_5H_7N_5O$: C, 39.21; H, 4.61; N, 45.73. Found: C, 39.36; H, 4.99; N, 45.92.

(5) J. G. Nairn and H. Tieckelmann, *J. Org. Chem.*, **25**, 1127 (1960).

(6) R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exp. Biol. and Med.*, **94**, 792 (1957).

(7) Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

(8) Microanalyses by Galbraith Laboratories, Knoxville, Tennessee.

Acknowledgment. The authors are indebted to Miss Arlyn Meininghaus of the University of Buffalo and Mr. Joseph Stanford of Williamsville High School, Williamsville, N. Y., for technical assistance and to Dr. James M. Sprague of Merck, Sharp and Dohme for his interest.

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3-Amino-4-phenylpyrazole as an Intermediate

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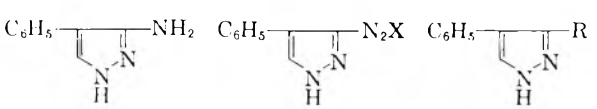
The displacement of the amine group in 3-amino-4-phenylpyrazole (I) by other groups,



I

II a. R = H
b. R = Br
c. R = NO_2
d. R = N=N—S—C_2H_5
e. R = S—C_2H_5

through the intermediate diazonium salt, has been found to be a useful preparative scheme for 3-substituted pyrazoles. The amine was diazotized in aqueous mineral acid by reaction with sodium nitrite, and the intermediate diazonium salt was converted into 4-phenylpyrazole (IIa, 93% yield) by reaction with hypophosphorous acid, and into 3-bromo-4-phenylpyrazole (IIb, 85.6% yield) by reaction with cuprous bromide. Pyrolysis of the corresponding diazofluoroborate in the presence of sodium nitrite and copper bronze afforded 3-nitro-4-phenylpyrazole in 22.4% yield.

Reaction of diazotized 3-amino-4-phenylpyrazole with ethyl mercaptan proceeded abnormally,[3] giving the diazonium sulfide (IId, 72.5% yield) instead of the expected 3-ethylmercapto-4-phenylpyrazole (IIe). The diazonium sulfide (IId) was relatively stable and was recrystallized from hot ethanol; however, prolonged boiling in methanol resulted in its reduction to 4-phenylpyrazole (52% yield). The diazonium sulfide gave colored products by reaction with phenol, β-naphthol, and dimethylaniline.

It is of interest to note that 3-amino-4-phenylpyrazole (I) can be diazotized in aqueous solution. This behavior is in contrast to the special conditions[4] required for the diazotization of 2-aminopyridine, which also contains the amidine function (—N=C(—NH$_2$)—).

It has been known for some time that 3- and 5-aminopyrazoles form diazonium salts; however, most of the cases studied have involved derivatives bearing a substituent on the pyrazole nitrogen atom, and relatively little attention has been directed to replacement reactions.[5a] 4-Aminopyrazoles from typical diazonium salts which undergo the usual coupling[5a,6] and replacement[3] reactions.

Electrophilic substitution of the pyrazole ring in other than the 4-position is rare.[5b] If a phenyl group is at C_4, nitration will occur in the benzene ring.[7] The availability of certain 3-aminopyrazoles[8] and their subsequent conversion to 3-substituted pyrazole by the procedure described appears to be an attractive synthetic procedure in this series.

EXPERIMENTAL

4-Phenylpyrazole from I. 3-Amino-4-phenylpyrazole[8] (2.3 g., 0.0414 ml.) was added to boiling concd. hydrochloric acid (4.5 ml.) and, when solution was complete, an additional portion of concd. hydrochloric acid (5 ml.) was added. The mixture was cooled (0–5°) and sodium nitrite (1.5 g.) in water (3.5 ml.) was added dropwise over a 5-min. period. The resulting solution was stirred and hypophosphorous acid (15 ml., 50% aqueous) was added dropwise (5 min.) while the temperature was maintained at 0°. The resulting solution was stirred for an additional 10 min. at 0°, and then placed in a refrigerator (24 hr.). Crude IIa (1.78 g., 93% yield, m.p. 225–227°) was collected and recrystallized from methanol-water. Pure IIa melted at 227–228° and did not depress the melting point of an authentic sample (m.p. 228°).[9]

3-Bromo-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole 1.5 g., 0.0095 ml.) was dissolved in hot hydrobromic acid (10%, 5 ml.) and an excess of sodium nitrite (2.5 g.) in water (5 ml.) was added. Excess urea (~2 g.) was added to destroy excess sodium nitrite; the solution was filtered, and concd. hydrobromic acid (48%, 5 ml.) and cuprous bromide (~0.5 g.) were added. The solution was boiled to complete the reaction and then allowed to stand in an ice bath. The product weighed 2.0 g. (94.8% yield, m.p. 142–144°) and melted at 146–146.5 (1.8 g., 85.6% yield) after recrystallization from methanol. This product caused no depression in melting point when mixed with authentic IIb.[8]

3-Nitro-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole (1.8 g., 0.0113 ml.) was dissolved in fluoboric acid solution (10 ml.) in a 250-ml. beaker. The mixture was kept

(1) Now Mrs. Thomas Rouse.

(2) From the M.S. Thesis of Iive Mae Aldre, University of Minnesota, 1958.

(3) *Cf.* O. Stadler, *Ber.*, **17**, 2078 (1884).

(4) *Heterocyclic Compounds*, R. C. Elderfield, ed., Vol. I, Ch. 8, Harry S. Mosher, p. 444, John Wiley & Sons, New York, 1950.

(5) (a) *Cf. Heterocyclic Compounds*, R. C. Elderfield, ed., Vol. V, Ch. 2, Thomas L. Jacobs, p. 141. John Wiley and Sons, New York, 1957; (b) Ref. 5a, p. 99.

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(9) E. Buchner and A. Papendieck, *Ber.*, **28**, 223 (1890).

in an ice-salt bath and the solution was stirred efficiently. A cold (0°) solution of sodium nitrite (1 g.) in water (3 ml.) was added dropwise. The resulting mixture was maintained at 0°, and stirring was continued for an additional 5 min. The solid diazonium fluoborate was filtered by suction on a sintered glass filter, washed several times with cold fluoboric acid and then with water. It was very soluble in 95% ethanol.

Then sodium nitrite (20 g.) was dissolved in water (40 ml.) and copper filings (4 g.) were added. The mixture was stirred efficiently and a suspension of the fluoborate salt in water (10 ml.) was added very slowly. Frothing occurred and a few drops of ether was added from time to time to break the foam. The reaction was complete when all of the salt was added.

The crude product was filtered by suction and washed a few times with water and dilute (10%) sodium hydroxide. The product, 3-nitro-4-phenylpyrazole, weighed 0.48 g. (0.0025 mole; 22.4% yield; m.p. 205–208°). Recrystallization of this material from chloroform gave pale yellow needles melting at 209–210°. This product caused no depression in melting point when mixed with authentic IIc.[8]

Reaction of 4-phenylpyrazole-3-diazonium chloride with ethyl mercaptan. The diazotization of I (1.8 g., 0.011 ml. was carried out as described above for the preparation of 4-phenylpyrazole. The resulting mixture was maintained at 0° and ethyl mercaptan (7.2 g., 0.0113 ml.) was added dropwise with swirling. A few drops of ethyl mercaptan was added in excess. The reaction mixture containing a yellow solid was maintained at ice-salt temperature for 24 hr. The solid was then collected, washed with water, and dried by vacuum. Crude IId (1.9 g., 72.5%, m.p. 98–100°) was recrystallized from aqueous methanol which afforded pure IId as long yellow needles (m.p. 101–101.5°).

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.89; H, 5.17; N, 24.13. Found: C, 56.47; H, 5.25, N, 24.05.

The reaction of IId *with methanol.* A solution of IId (0.56 g., 0.0024 ml.) in methanol (50 ml.) was heated at the reflux temperature for 7.5 hr. The methanol was removed, and the pale yellow solid (0.18 g., 52% yield, m.p. 222–225°) was collected and recrystallized from chloroform. The pure product (m.p. 227–228°) was identified as 4-phenylpyrazole (m.p. and mixed m.p. 227–228°).

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Practical Synthesis of 5α-Androstan-17β-ol[1]

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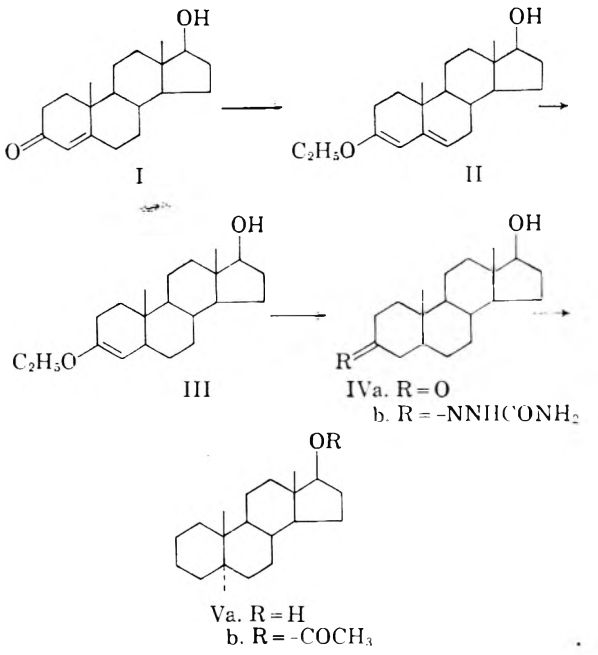
Under a contract with the Cancer Chemotherapy National Service Center, this laboratory was asked to prepare a number of steroids not available commercially. One such compound was 5α-androstan-17β-ol (Va). This latter compound has been prepared by a number of investigators from testosterone (I)[2]; however, none of the published methods appeared attractive for the preparation of V on a large scale.

In this paper a procedure is described for the preparation of V which is amenable to large scale operation. The reaction sequence is as follows:



Testosterone (I) was smoothly converted to 3-ethoxy-3,5-androstadien-17β-ol (II) by reaction with triethyl orthoformate in ethanolic hydrogen chloride. Reduction of the 5,6-double bond of II to give the enol ether (III) was effected catalytically with 5% palladium on charcoal in ethanol. The enol (III) was reversed to the 3-keto compound with acid and the 17β-hydroxyandrostan-3-one (IVa) was converted *in situ* to the sparingly soluble 3-semicarbazone (IVb).[3] The overall yield for the three steps was 64%. Since the completion of this work, the direct reduction of I to IVa in high yield has been reported using lithium in liquid ammonia.[4] This reduces the present scheme to a three-step synthesis. The semicarbazone (IVb) was reduced in 93% yield by the method of Wolff-Kishner as modified by Huang-Minlon.[5] Excess hydrazine hydrate was employed in the reduction to prevent the formation of the epimeric 3-ol compounds.[6]

The product obtained was identical with material obtained from IVa by the procedure of Kagi and Miescher.[2a]

EXPERIMENTAL

3-Ethoxy-3,5-Androstadien-17β-ol (II). Testosterone (100 g., 0.347 mole), 864 ml. of dry benzene, 86.4 ml. of ethyl

(1) This work was done under Contract #SA-43-ph-1948 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

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(5) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(6) J. D. Dutcher and O. Wintersteiner, *J. Am. Chem. Soc.*, **61**, 1992 (1939).

orthoformate, 172 ml. of absolute ethanol, and 8.6 ml. of 4*N* ethanolic hydrogen chloride were heated at reflux for 2 hr. The cooled solution was made slightly alkaline by the addition of a solution of sodium methoxide and then washed three times with 500 ml. of water. The dried benzene solution (potassium carbonate) was concentrated *in vacuo*. Residual benzene was removed by flushing *in vacuo* with 100 ml. of absolute ethanol. The crude residue was used without further purification for the next step.

The crude product may be purified by trituration with petroleum ether until crystalline, followed by recrystallization from methanol, m.p. 116–118° (solvated); 132–137° (desolvated). $[\alpha]_D^{23}$ −130° (ethanol).

Anal. Calcd. for $C_{21}H_{32}O_2$ (316.47); C, 79.69; H, 10.19. Found: C, 79.61; H, 9.99.

Semicarbazone of 17β-hydroxyandrostan-3-one (IVb). The crude dienol ether (II) was dissolved in 1875 ml. of absolute ethanol and hydrogenated with 8 g. of 5% palladium-charcoal catalyst under a hydrogen pressure of 40 p.s.i. The theoretical amount of hydrogen (0.347 mole) was absorbed in 10 hr. Hydrogenation was continued for a total of 19 hr., 104% of the theoretical amount of hydrogen being absorbed.

Two hundred milliliters of 2.5*N* hydrochloric acid[7] was added to the hydrogenation solution and the catalyst removed by filtration through a filter aid. The filtrate was refluxed for 20 min. A solution of 50 g. of sodium acetate in 100 ml. of water was added and the mixture stirred at 50–60° for 45 min., and to the warm (50–60°) solution of the steroid was added a warm solution of 37.5 g. (0.5 mole) of semicarbazide in 600 ml. of ethanol. The mixture was allowed to cool slowly to 20° and the filtered semicarbazone was washed with ethanol, then with ether, and dried *in vacuo*, yield 76.7 g. (64% from I), m.p. 249–251° dec., $\lambda_{max}^{CH_3OH}$ 228 mμ, ε 13,400. The melting point, mixed melting point and spectral data agreed with a sample of IVb prepared from authentic IVa.

5α-Androstan-17β-ol (V). Seventy four grams of semicarbazone, (IVb), 520 ml. of diethylene glycol, 52 ml. of 85% hydrazine hydrate, and 49 g. of powdered potassium hydroxide were heated in a round bottomed flask equipped with a thermometer, mechanical stirrer, and a vertical air condenser. The temperature was increased slowly to 200–210° and held at this temperature until the evolution of nitrogen had ceased (approximately 45 min.). The mixture was allowed to cool to 180–190° and poured into a well stirred mixture of 2 l. of water and 2 kg. of ice. The product was filtered and washed with water to neutrality. After drying at 70°, 54.8 g. (93%) of Va were obtained, m.p. 164–166.5. Recrystallization from ethanol and from heptane gave material, m.p. 165.5–166.5, $[\alpha]_D^{24}$ +12 ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{32}O$ (276.45): C, 82.54; H, 11.66. Found: C, 82.48; H, 11.48.

The infrared spectrum in carbon disulfide corresponded favorably with the published spectrum.[8]

5α-Androstan-17β-ol acetate (Vb). Forty-one grams of Va and 185 ml. of acetic anhydride were heated and stirred on the steambath for 1 hr. The hot solution was diluted slowly with water until the excess acetic anhydride was decomposed. More water (total 750 ml.) was then added to precipitate the product. After filtration and drying, the crude acetate was dissolved in ether, treated with charcoal, and the ether removed *in vacuo*. The residue was recrystallized from 110 ml. of methanol to give 43 g. (91%) of Vb, m.p. 81–82.5, $[\alpha]_D^{24}$ +5 ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{34}O_2$ (318.48): C, 79.19; H, 10.76. Found: C, 79.14; H, 10.84.

The physical properties of samples of Va and Vb made via the Clemmensen reduction of IVa[2a] were identical with those reported above.

Acknowledgment. The authors are indebted to Dr. N. R. Trenner and Mr. R. Walker for the infrared spectra and to Mr. R. N. Boos and staff for the analytical data reported.

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(7) The addition of acid before filtration coagulates the catalyst and prevents colloidal catalyst from passing into the filtrate.

(8) K. Dobriner, E. R. Katzenellenbogen, and R. N. Jones, *Infrared Absorption Spectra of Steroids*, Vol. I, Interscience Publishers, Inc., New York 1953, Spectrum No. 29.

Halochromism Studies on Prodigiosin

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Recently it was reported that prodigiosin perchlorate reacts with alcohols[1] causing spectral shifts from 536 to 542 mμ and that the solvent functioned as a Lewis base toward the pigment. During the course of experimentation in this laboratory it was observed that the pigment free base, which was yellow in nonpolar solvents or acetone, became red when shaken with water, acids, or alcohols. When red aqueous pigment solutions were extracted with water-insoluble solvents, the reaction seemed to reverse and the yellow base was extracted into the organic phase. Consequently, a determination of the acid dissociation constant was undertaken in an attempt to resolve this phenomenon. It was found that $K_a = 3.23 \times 10^{-8}$ ($pK_a = 7.51$) at 25°. This would indicate that protonated prodigiosin is about as weak an acid as hydrogen sulfide or hypochlorous acid, but still considerably stronger than water or alcohols whose pK_a values are 16 or greater. The halochromism phenomenon was finally traced to carbon dioxide in the water ($K_a = 3.5 \times 10^{-7}$ for carbonic acid) and to acid impurities in the solvents. Thus, if distilled water is boiled and cooled by passage of pure nitrogen or oxygen gas through it and an acetone solution of prodigiosin is added, there is no color change from yellow to red. If the solution is shaken or if the water is shaken or carbon dioxide passed through before addition of the pigment, the red color forms immediately because of reaction with protons derived from carbonic acid. Moreover, alcohols purified carefully in the usual fashion by drying with aluminum isopropoxide do not cause halochromism when used to dissolve the pigment.

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Prodigiosin, however, has a great affinity for water and will partially remove water of crystallization from such materials as magnesium sulfate heptahydrate or copper sulfate pentahydrate. Thus an acetone solution of prodigiosin to which crystals of these materials have been added exhibits immediate reddening or color shift from yellow toward the red part of the spectrum. The effect is apparently related to the ability of the salt in question to ionize with formation of protons, as the color shift is strongest with salts like copper, ammonium, or zinc sulfate, intermediate with magnesium sulfate, and scarcely preceptible with sodium sulfate. On prolonged standing over a week with the exclusion of moisture, copper sulfate pentahydrate was dehydrated to the grey anhydrous salt.

These observations lead us to conclude that the halochromism is independent of the nature of the solvent and is caused by the oxonium ion which functions as a Lewis acid towards the pigment.

EXPERIMENTAL

Various methods for the extraction of the pigment were examined. Cells undergo lysation completely in formic or acetic acids, or pyridine within a matter of minutes. This lysate can be rapidly extracted with immiscible solvents to obtain the free prodigiosin. Thus colonial growth of *S. marcescens* on Difco Peptone agar slants was dissolved by addition of 90% formic acid. The lysate was poured into distilled water, extracted three times with petroleum ether, and the organic phase dried over anhydrous sodium sulfate. The aqueous phase contains a blue pigment, R_f 0.2, previously reported and chromatographed by Williams and Green[2] and is identical with their material. An accompanying purple pigment is an artifact caused by acid decomposition of prodigiosin. The organic phase was evaporated and the residue extracted with warm water giving a red aqueous phase and an orange residue which was not further characterized. The red aqueous phase was re-extracted with petroleum ether, evaporated, and taken up into acetone giving yellow prodigiosin, identified by paper chromatography[2] (R_f 0.7, ether-petroleum ether 1:2) and ultraviolet and visible spectra.[1]

Sufficient acetone prodigiosin solution was added to Sorenson buffers of gradient *p*H from 6 to 8 to given an optical density from 1 to 1.5. The visible region absorption curves as a function of *p*H were determined using a Cary Model 14 spectrophotometer. Two other absorbancies, at *p*H 2 and *p*H 10, were also determined over a concentration range to verify Beers Law, but the absorption in strong base was inconstant because of destruction of the pigment. Consequently a solution of free prodigiosin in acetone was used for the Beers Law verification in the basic region. These data were treated as described by Tobey[3] to obtain the pK_a and K_a.

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(2) R. P. Williams, J. A. Green, and D. A. Rappoport, *J. Bacteriology*, **71**, 115 (1956).

(3) S. W. Tobey, *J. Chem. Ed.* **35**, 514 (1958).

Aspidofiline, the Phenolic Alkaloid of Aspidosperma Pyrifolium Mart

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Received April 30, 1959

Aspidosperma pyrifolium Mart., a member of the family *Apocynaceae*, is a tree reaching a height of (5 m.).. with grey bark, and a fruit resembling that of the European pear tree. It is found in certain places in the drought region in the north-east of Brazil, generally the most arid part, and is commonly called "pereiro." The plant material was collected by J. Santa Rosa in the Municipio of Acari, Rio Grande do Norte, and botanically identified by the late J. G. Kuhlmann. From the leaves a new base, Aspidofiline, was isolated, m.p. 186–187°, picrate, m.p. 146°.

Aspidofiline and its picrate analysed very well for a $C_{20}H_{22}N_2O_2$ compound. The new base is closely related to other *N*-acetyldihydroindoles, such as aspidospermine[2] and spegazzinine[3] isolated earlier from other Aspidosperma species. The ultraviolet absorption spectrum of aspidofiline is very similar to those of aspidospermine and spegazzinine, and characteristic of an *N*-acetyldihydroindole nucleus. The infrared spectrum shows an amide band at 6.14μ as in aspidospermine and spegazzinine. As in the case of other phenolic bases of the dihydroindole type, such as vomicine,[2] demethylaspidospermine,[2] and haplophytine,[4] aspidofiline shows no band in the OH or NH region, as a consequence of the strong hydrogen bonding of the phenolic hydroxyl with a carbonyl.

EXPERIMENTAL

The powdered leaves of A. pyrifolium (2/Kg.) were extracted with alcohol in a modified soxhlet. The extract was concentrated under reduced pressure and the viscous mass treated with 5% hydrochloric acid, the resinous part separated and the clear acid solution extracted with ether, basified with ammonia and again extracted with several portions of ether. The collected ether fractions were in turn extracted with dilute alkali.

The alkaline solution was acidified with hydrochloric acid and then treated with concentrated ammonia, and the precipitated base extracted with ether. In total, 2 g. of crystalline material was obtained.

After several crystallizations from ether, aspidofiline was obtained in well crystallized needles, m.p. 186°–187° (Kofler).

Anal. Calculated for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.47; H, 7.07; N, 8.62.

The ultraviolet absorption spectrum (in 95% ethanol) showed max at 258 mμ (log ϵ 3.85), a min at 242 mμ (log ϵ 3.67), inflection at 282 mμ. The infrared spectrum

(1) Fellow of the Brazilian Research Council.

(2) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **76**, 5603 (1954); B. Witkop, *J. Am. Chem. Soc.*, **70**, 3712 (1948).

(3) O. O. Orazi, R. A. Corral, J. S. E. Holker, and C. Djerassi, *J. Org. Chem.*, **21**, 979 (1956).

(4) H. R. Snyder, H. F. Strohmayer, and R. A. Mooney, *J. Am. Chem. Soc.*, **80**, 3708 (1958).

(mulled in Nujol) showed the following major bands: no bands in the OH or NH region; 6.35 (S), 6.27 (S), 6.14 (S).

Aspidofiline picrate. The picrate was prepared by treating an ethereal solution of aspidofiline with picric acid in ether; the crystalline picrate was separated and recrystallized several times from acetone, m.p. 146° (capillary, non-corrected).

Anal. Calcd. for $C_{26}H_{25}N_5O_9$: C, 56.62; H, 4.57; N, 12.70. Found: C, 56.83; H, 4.7; N, 12.49.

Acknowledgment. The author wishes to express his gratitude to Mr. R. Lauzon and Mr. H. Seguin (National Research Council of Canada) for the infrared measurements and for the analysis.

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Extractives from the Dipterocarpaceae

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The Dipterocarpaceae are an important family of trees which grow in southeast Asia and are characterized by an abundant secretion of resins such as dammar and gurjun which possess economic importance. References to early researches on dammar are given by Glimmann[1] and recently a comprehensive investigation of the constituents of dammar has been carried out by Mills[2,3] who determined the constitution of the neutral triterpenes present. Among those triterpenes was hydroxydammarenone-II first isolated by van Itallie[4] from the balsams of *D. hasseltii* and *D. trinervis*. King[5] *et al.* isolated this compound from three Dipterocarpus woods, "gurjun," "yang," and "keruing" and established the identity of hydroxydammarenone-II with dipterocarpol isolated by Ourisson[6,7] from the balsams of several Dipterocarpus species—*D. Dyeri*, *D. alatus*, *D. intricatus* and *D. atrocarpifolius*.

From the acidic fraction of gum dammar we have isolated asiatic acid and will report our findings in a future communication. From two woods of the *Dipterocarpus* species, *D. verrucosis* and *D. grandiflorus* we have isolated dipterocarpol in yields of 0.12% and 0.16% respectively.

EXPERIMENTAL

D. Verrucosis. The wood (4 lb.) in the form of shavings was extracted continuously with light petroleum for 24 hr. The extract was concentrated to give a resin (32.7 g.) which was hydrolyzed for 6 hr. with 10% methanolic potassium hydroxide (300 ml.). The hydrolysis liquor was filtered to remove a small amount of insoluble matter, diluted with much water, and extracted with ether to give a viscous oil (17.1 g.). Chromatographic analysis of the oil on alumina (500 g.) in light petroleum solution followed by elution with petrol (b.p. 60–80°) benzene mixtures, then by benzene gave eluates (2.5 g.) which did not contain triterpenoid material. Elution with benzene-ether, ether, and finally with ether containing methanol gave gums (12.5 g.) which when dissolved in methanol slowly deposited crystalline material, m.p. 118–123°. Repeated recrystallization from light petroleum (b.p. 60–80°) gave dipterocarpol, m.p. 132–134°, $[\alpha]_D^{20}$ +67° ($CHCl_3$; *c*, 1.09); infrared bands at 3500, 1695, 1440, 1370 and 815 cm.$^{-1}$ A mixed melting point with an authentic specimen of dipterocarpol kindly supplied by Dr. T. J. King of Nottingham University showed no depression and the infrared spectra of both specimens were identical.

D. grandiflorus. Wood shavings (4 lb.) of *D. grandiflorus* were extracted as above with light petroleum (b.p. 60–80°) and the extract (33.2 g.) when hydrolyzed with methanolic potassium hydroxide gave a non saponifiable fraction (20.2 g.) which was chromatographed as above. The eluates resulting from elution with benzene-ether and ether yielded gummy material which deposited dipterocarpol from methanol solution. Repeated recrystallization from light petroleum (b.p. 60–80°) gave dipterocarpol (2.9 g.), m.p. 132–134° identical with the material obtained above from *D. verrucosis; oxime*, m.p. 176–178° (Mills[8] gives m.p. 178–179°); *semicarbazone*, m.p. 203–205°. (Ourisson[7] gives m.p. 206–207°).

Dammarendiol-II. Reduction of dipterocarpol, isolated from *D. grandiflorus*, with lithium aluminium hydride followed by chromatography of the product on alumina gave dammarendiol-II, m.p. 130–133°, $[\alpha]_D^{20}$ +33° (c, 1.01). Mills[3] gives m.p. 131–133°, $[\alpha]_D^{20}$ +34°.

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9,11-Dihalosteroids

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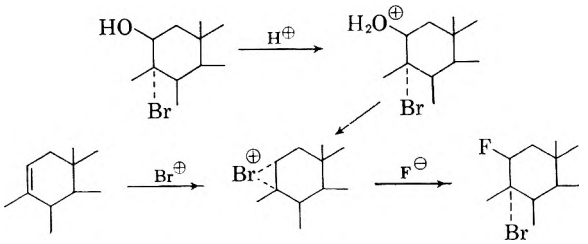
Exploratory experiments directed to the development of a program for the systematic investigation of dihalosteroids, in particular those with fluorine at C-11, were undertaken in these laboratories in 1957. The 11β-fluoro-9α-halosteroids were made either by the use of an *N*-haloamide in anhydrous hydrogen fluoride containing about 30% pyridine or by the reaction of an 11β-hydroxy-9α-bromosteroid with this same solvent pair.

The first of these methods is essentially the same as that reported by Robinson, Finckenor, Oliveto, and Gould[1] and by Bowers[2] and this method is the superior one from a preparative point of view. Both methods are presumed to proceed *via* a 9,11β-bromonium ion intermediate which is converted to the product by the nucleophilic attack of a fluoride ion on C-11.



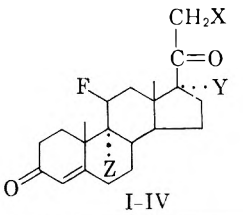
Satisfactory analyses of the dihalosteroids were difficult to obtain and in some cases chromatography followed by several crystallizations was required to obtain a pure sample. The reason for this is illuminated by the reaction of *N*-chlorosuccinimide with 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate in hydrogen fluoride–pyridine. In addition to the expected 9α-chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (I) there was obtained a compound $C_{23}H_{29}ClO_5$. It is apparent from the formula that chlorine has been substituted for hydrogen but the location of the chlorine has not been established. In no instance was a similar bromine compound isolated but its existence is suspected.

The reaction of hydrogen fluoride–pyridine with an 11β-hydroxy-9α-halosteroid suggested itself as a possible route to the 9α,11β-difluorosteroids. An attempt to prepare 9α,11β-difluoro-4-pregnene-3,20-dione by this method failed. It would appear that fluorine is too electronegative to enter into onium ion formation.

The oral progestational potency of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione (II), 9α-chloro-11β-fluoro-4-pregnene-3,20-dione (III), and 9α-bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (IV) are presented in Table I. In the 11β-fluoroprogesterone series activity is increased by the substitution of chlorine for bromine. This is contrary to the result obtained in the 11β-hydroxyprogesterone series.[3] The substitution of acetoxy for hydrogen at C-17 in progesterone produced the expected enhancement of activity.[4]

TABLE I

ORAL PROGESTATIONAL POTENCY



I–IV

	X	Y	Z	Oral Clauberg Assay[a] (Subcutaneous Progesterone = 1)
I	OAc	OH	Cl	
II	H	H	Br	<1
III	H	H	Cl	1
IV	H	OAc	Br	5

[a] See ref. 5a, b.

EXPERIMENTAL[6]

Hydrogen fluoride–pyridine reagent. When anhydrous hydrogen fluoride was added to pyridine cooled in an ice bath, pyridine hydrofluoride sometimes separated as a white crystalline solid and if the hydrogen fluoride addition were continued, ultimately a fuming, clear solution was obtained. A solution of about 70% hydrogen fluoride–30% pyridine was routinely used. This could be stored in polyethylene bottles at room temperature for many months although it was usually used immediately after preparation.

9α-Chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (I). A mixture of 5.77 g. of 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate[7] and 2.00 g. (1 equiv.) of *N*-chlorosuccinimide in a polyethylene bottle was dissolved in 60 ml. of cold hydrogen fluoride–pyridine reagent. The solids dissolved rapidly, producing a very dark solution which was red by transmitted light. The reaction mixture was maintained at +2° for 1 hr. and then it was poured into a glass separatory funnel containing 0.50 l. of ethyl acetate and 0.25 l. of water. The ethyl acetate layer was washed with water and with saturated aqueous sodium bicarbonate solution. After drying with anhydrous sodium sulfate, the solvent was removed by distillation at reduced pressure. The crude product was chromatographed on silica gel. Elution with a 10% ethyl acetate solution in benzene gave a series of fractions which were crystallized from acetone or acetone–petroleum ether. Mixtures of prisms, m.p. *ca.* 210°, and rods, m.p. *ca.* 260°, were obtained from most fractions with the higher melting rod-like forms being concentrated at the end of the series. The crystals were purified by a combination of fractional crystallization and manual separation. After the final crystallization from acetone, the prismatic material weighed 495 mg., m.p. 210–213° dec.,

(1) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959).

(2) A. Bowers, *J. Am. Chem. Soc.*, **81**, 4107 (1959).

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(5) (a) C. W. Emmens, *Hormone Assay*, Academic Press, Inc., New York, N.Y., 1950, p. 422. (b) These values were determined by Dr. R. L. Elton, Division of Biological Research, G. D. Searle and Co.

(6) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Rotations were determined in chloroform at 25 ±2° and at a concentration of about 1%. Ultraviolet spectra were determined in methanol. Petroleum ether was the fraction boiling at 60–71°. Microanalyses, rotations, and spectral data were supplied by the Analytical Department, G. D. Searle and Company.

(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(8) E. L. Bennett, C. W. Gould, E. H. Swift, and C. Niemann, *Anal. Chem.*, **19**, 1035 (1947).

darkening above 198°, λ_{max} 240.5 mμ (16,000), $[\alpha]_D$ + 102°. A qualitative test for fluorine was negative.[8]

Anal. Calcd. for $C_{23}H_{29}ClO_5$: C, 65.65; H, 6.95; Cl, 8.43. Found: C, 65.99; H, 7.14; Cl, 8.38.

A final crystallization of the rod-like crystals from acetone gave 236 mg. of pure 9α-chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, m.p. 276–277.5° dec., λ_{max} 238 mμ (17,800), $[\alpha]_D$ +149°. A positive Beilstein test and a positive qualitative fluorine test were obtained.

Anal. Calcd. for $C_{23}H_{30}ClFO_5$: C, 62.65; H, 6.86. Found: C, 62.47; H, 6.65.

9α-Bromo-11β-fluoro-4-pregnene-3,20-dione (II). To a solution of 1.00 g. of 4,9(11)-pregnadiene-3,20-dione[9] in 15 ml. of hydrogen fluoride–pyridine reagent was added 0.66 g. (1.5 equiv.) of *N*-bromoacetamide. After 30 min. at room temperature the reaction mixture was partitioned between 0.20 l. of ethyl acetate and 0.10 l. of water. The organic phase was washed with water and with saturated aqueous sodium bicarbonate solution. After being dried with anhydrous sodium sulfate, the solvent was removed by distillation at reduced pressure. The residue was crystallized from acetone–petroleum ether to give 205 mg. of crude product, m.p. 148–152° dec. Successive crystallizations from acetone and acetone–petroleum ether failed to give a product of constant melting point. The highest melting point was 165.5–172° dec. and the melting point of the analytical sample was 161–165° dec., λ_{max} 240 mμ (15,700). A positive Beilstein test and a positive qualitative fluorine test were obtained.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86. Found: C, 59.59; H, 6.41.

An attempt was made to convert II to its bisethylene ketal using ethylene glycol, *p*-toluenesulfonic acid, and benzene in the usual way.[10] Chromatography of the product on silica gel failed to yield any product corresponding to the ketal, but a pure sample, m.p. 159–161° dec., of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione was obtained by crystallization from acetone–petroleum ether of those fractions eluted from the column with 5% and with 10% ethyl acetate in benzene solutions.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86. Found: C, 61.22; H, 6.49.

Preparation of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione from 9α-bromo-11β-hydroxy-4-pregnene-3,20-dione. A solution of 0.50 g. of 9α-bromo-11β-hydroxy-4-pregnene-3,20-dione[11] in 10 ml. of hydrogen fluoride–pyridine reagent was kept at room temperature for 2 hr. The reaction mixture was partitioned between 0.10 l. of benzene and 0.10 l. of water. The benzene solution was washed with water and with saturated aqueous sodium bicarbonate solution. After drying with anhydrous sodium sulfate the solvent was removed by distillation at reduced pressure. Crystallization from acetone–petroleum ether and from benzene–petroleum ether gave 38 mg. of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione, identical in melting point and infrared spectrum with II prepared from 4,9(11)-pregnadiene-3,20-dione. Admixture of the two samples did not depress the melting point.

9α-Chloro-11β-fluoro-4-pregnene-3,20-dione (III). Cold hydrogen fluoride–pyridine reagent (10 ml.) was added to a mixture of 1.00 g. of 4,9(11)-pregnadiene-3,20-dione and 426 mg. (1 equiv.) of *N*-chlorosuccinimide. After 1 hr. at 3° the crude product was isolated as described under the preparation of II. The crude product was triturated with ether and there was obtained 230 mg. of crystals, m.p. 135–165°. Repeated crystallization from ether–petroleum ether and from acetone–petroleum ether gave 60 mg. of pure 9α-chloro-11β-fluoro-4-pregnene-3,20-dione, m.p. 179–180°, λ_{max} 238 mμ (17,200). The analytical sample gave a positive Beilstein test and a positive qualitative fluorine test.

Anal. Calcd. for $C_{21}H_{28}ClFO_2$: C, 68.74; H, 7.69. Found: C, 68.77; H, 7.66.

9α-Bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (IV). A mixture of 336 mg. of 17α-hydroxy-4,9(11)-pregnadiene-3,20-dione 17-acetate[12] and 126 mg. (1 equiv.) of *N*-bromoacetamide was treated with 4 ml. of cold hydrogen fluoride–pyridine reagent. After 1 hr. at 2° the crude product was isolated as described under the preparation of II. Trituration with ether gave a first crop of crystals, 163 mg., m.p. 190–193° dec. and a second crop, 67 mg., m.p. 185–187° dec. The crops were combined and the mixture was crystallized from ether and from acetone–petroleum ether. The yield of pure 9α-bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate was 95 mg. The melting point was variable, being 185–188° dec. and 193–196° dec., λ_{max} 240 mμ (17,100), $[\alpha]_D$ +85°. The analytical sample gave a positive Beilstein test and a positive qualitative test for fluorine.

Anal. Calcd. for $C_{23}H_{30}BrFO_4$: C, 58.85; H, 6.44. Found: C, 58.68; H, 6.31.

The attempted preparation of 9α,11β-difluoro-4-pregnene-3,20-dione. A solution of 100 mg. of 9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione[11] in 10 ml. of hydrogen fluoride-pyridine reagent (77% hydrogen fluoride) was kept at room temperature overnight. The course of the reaction was followed by removing 2-ml. samples at 0.5, 1, 2, 4, and 18 hr. The samples were partitioned between ethyl acetate and water. The organic phase was washed with water, saturated aqueous sodium bicarbonate solution, and with water. After drying over anhydrous sodium sulfate the solvent was evaporated and the residue from each sample was submitted to infrared analysis. All of the samples gave a crystalline residue and all of the infrared spectra were identical with the spectrum of 9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione.

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N-Acylation of 2-Amino-2-deoxy-D-glucose with Mixed Carboxylic Acid Anhydrides

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The acylation of amino compounds such as hydroxylamine,[1] substituted amino acids,[2] and amino acids[3] with mixed carboxylic acid anhydrides has been reported by several authors, and the

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(2) T. Wieland and R. Sehring, *Ann.*, **569**, 122 (1950).

(3) J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952).

mechanism of the splitting of mixed acid anhydrides has also been well discussed.[3-5]

The solvent, steric, and induction effects were the main object of these investigations. Vaughan and Osato[3] prepared peptides by the reaction of mixed carboxylic acid anhydrides with aromatic amines and stated that under anhydrous conditions the combined action of an electronic and a steric effect was the cause of the preferential formation of the peptide bond, whereas under aqueous conditions a marked change of the ratio of the acylation products was observed. Emery and Gold[4] have also studied the solvent effect on the composition of the products obtained by interaction of mixed acid anhydrides and primary amines. The mechanism of the reaction of symmetrical anhydrides with amines has also been reported.[5,6]

Inouye, Onodera, Kitaoka, and Hirano[7] have reported the *N*-acylation of D-glucosamine (2-amino-2-deoxy-D-glucose) with symmetrical acid anhydrides in methanol, in which free D-glucosamine has been formed and treated with the anhydrides under supersaturation conditions. In the present paper the reaction of D-glucosamine in methanol with mixed carboxylic anhydrides to produce *N*-acylated D-glucosamine is reported.

Acetic benzoic anhydride was treated with D-glucosamine in methanol, from which *N*-acetyl-D-glucosamine was isolated in 69%. The reaction of acetic palmitic anhydride with D-glucosamine gave *N*-palmitoyl-D-glucosamine in 63% yield and that of caprylic palmitic anhydride also gave rise to *N*-palmitoyl-D-glucosamine in 79% yield. The reaction of benzoic myristic anhydride with D-glucosamine resulted in the isolation of *N*-myristoyl-D-glucosamine in 86% yield, and acetic butyric anhydride with D-glucosamine gave *N*-butyroyl-D-glucosamine in over 50% yield. The reaction of benzoic phthalylglycine anhydride with D-glucosamine gave rise to *N*-(phthalylglycyl)-D-glucosamine in 65% yield. The results are listed in Table I.

TABLE I

N-ACYLATED-D-GLUCOSAMINES

Mixed Anhydrides	Reaction Products	Yields (%)
Acetic benzoic	*N*-Acetyl-D-glucosamine	69
Acetic palmitic	*N*-Palmitoyl-D-glucosamine	63
Benzoic myristic	*N*-Myristoyl-D-glucosamine	86
Caprylic palmitic	*N*-Palmitoyl-D-glucosamine	79
Acetic butyric	*N*-Butyroyl-D-glucosamine	50
Benzoic phthalyl-glycine	*N*-(Phthalylglycyl)-D-glucosamine	65

It is reasonable to assume that in a polar solvent like methanol the ionization of a mixed anhydride, RCO—O—OCR′ will probably proceed according to $R'CO^+ + RCO_2^-$ provided that $R'CO_2H$ is a weaker acid than RCO_2H. Therefore, it is more probable to find in the solution $R'CO^+$ instead of RCO^+ ions. The theory has been predicted by Emery and Gold on the basis of acylium ion theory. Accordingly, it is clear that acetic benzoic anhydride will produce *N*-acetyl-D-glucosamine. The reaction in the present paper was not studied in a quantitative way but preparatively, and the mechanism is not discussed here. There is a report on the reaction of mixed anhydrides with aniline,[8] which resulted in the isolation of acetanilide in a larger amount and of benzanilide in a smaller amount from the reaction mixture of acetic benzoic anhydride with aniline. Acetic butyric anhydride with aniline produced *N*-butylaniline in a larger amount.

The tendency of the reaction is clearly the same as in these reports. The procedure developed here will constitute an alternate method for the preparation of *N*-acyl-D-glucosamine, and some examples described here show that this procedure could be applied in general to prepare *N*-(*N*′-substituted amino acid)-D-glucosamines.

EXPERIMENTAL[9]

Reaction of acetic benzoic anhydride with D-*glucosamine.* Acetic benzoic anhydride was prepared according to the procedure of Autenrieth[10] and Nef.[11]

Acetic benzoic anhydride (8 g.) was added to the methanolic solution of D-glucosamine, which had been prepared by treating D-glucosamine hydrochloride (10 g.) in methanol (70 ml.) with metallic sodium (1.0 g.). The reaction mixture was allowed to stand at room temperature for 1 hr. and then at ice-box temperature overnight, during which time crystals deposited; yield, 7.1 g. (69%). The crude crystals were recrystallized twice from water-methanol; yield, 6.5 g. (63%); m.p. 204°, $[\alpha]_D^{14}$ +41° (*c* 2, water); mixed melting point with the authentic sample of *N*-acetyl-D-glucosamine showed no depression.

The mother liquor from the crude *N*-acetyl-D-glucosamine was concentrated to yield 5.4 g. (94%) of benzoic acid.

Reaction of acetic palmitic, caprylic palmitic, benzoic myristic, and acetic butyric anhydrides with D-*glucosamine.* Acetic palmitic and caprylic palmitic anhydrides were prepared by the procedures of Ralston and Reck[12] and of Chiozza.[13]

A. *Acetic palmitic anhydride.* To anhydrous sodium acetate (1 mole) was added palmitoyl chloride (1.03 moles) and the reaction mixture was heated at 90° for 30 min. The product was recrystallized twice from petroleum ether (b.p. 40–60°), yield, 62%, m.p. 62–63°.

(4) A. R. Emery and V. Gold, *J. Chem. Soc.*, 1443, 1447, 1455 (1950); V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409, 1416 (1953); V. Gold, J. Hilton, and E. G. Jefferson, *J. Chem. Soc.*, 2756 (1954).

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(12) A. W. Ralston and R. A. K. Reck, *J. Org. Chem.*, **11**, 624 (1946).

(13) L. Chiozza, *Ann.*, **91**, 104 (1854).

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 72.96; H, 11.87.

B. *Caprylic palmitic anhydride.* To sodium palmitate (1 mole) which had been prepared from sodium methoxide and palmitic acid was added caproyl chloride (1.03 moles) and the reaction mixture was kept at 90° for 2 hr. The reaction product upon recrystallization twice from petroleum ether (b.p. 40–60°) gave caprylic palmitic anhydride in 85% yield, m.p. 58–59°.

Anal. Calcd. for $C_{24}H_{46}O_3$: C, 75.35; H, 12.12. Found: C, 75.71; H, 12.39.

C. *Benzoic myristic anhydride.* Benzoic myristic anhydride was prepared by the procedure reported by Ralston and Reck.[12]

D. *Acetic butyric anhydride.* Acetic butyric anhydride was obtained as a by-product in the preparation of the symmetrical anhydride,[13] b.p. 155–157°.

E. *The reactions with* D-*glucosamine.* To the methanolic solution of D-glucosamine was added an equivalent amount of the mixed acid anhydride, and the reaction mixtures were placed at ice-box temperature overnight. The crystals deposited were collected and recrystallized from ethanol. The reaction of acetic palmitic anhydride yielded *N*-palmitoyl-D-glucosamine (63%), m.p. 202–203°.

Anal. Calcd. for $C_{22}H_{43}O_6N$: C, 63.28; H, 10.38; N, 3.55. Found: C, 63.14; H, 10.42; N, 3.16.

The reaction of caprylic palmitic anhydride with D-glucosamine gave rise to *N*-palmitoyl-D-glucosamine in 79% yield, m.p. 201–202°.

Anal. Calcd. for $C_{22}H_{43}O_6N$: C, 63.28; H, 10.38; N, 3.55. Found: C, 63.24; H, 10.24; N, 3.40.

Benzoic myristic anhydride with D-glucosamine gave *N*-myristoyl-D-glucosamine in 86% yield, m.p. 208–209°, $[\alpha]_D^{16}$ +62° (c 1, water).

Anal. Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68; N, 5.61. Found: C, 47.87; H, 7.60; N, 5.60.

Acetic butyric anhydride with D-glucosamine gave *N*-butyroyl-D-glucosamine in yields over 50%, m.p. 208–209°, $[\alpha]_D^{16}$ +62° (*c* 1, water).

Anal. Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68; N, 5.61. Found: C, 47.87; H, 7.60; N, 5.60.

The reaction of benzoic phthalylglycine anhydride with D-*glucosamine.* Benzoic phthalylglycine anhydride was prepared by the procedure reported by Wieland, Kern, and Sehring.[14]

Benzoic phthalylglycine anhydride with D-glucosamine gave rise to *N*-(phthalylglycyl)-D-glucosamine in 65% yield, m.p. 218–219°, $[\alpha]_D^{18}$ +48° (*c* 1, water).

Anal. Calcd. for $C_{16}H_{18}O_8N_2 \cdot H_2O$: C, 50.00; H, 5.52; N, 7.29. Found: C, 49.83; H, 5.21; N, 7.36.

The water of crystallization was lost on drying for 1 hr. at 100° *in vacuo*.

Anal. Calcd. for $C_{16}H_{18}O_8N_2$: C, 52.46; H, 4.95; N, 7.65. Found: C, 51.91; H, 4.58; N, 7.83.

Refluxing phthalylglycine and acetic anhydride produced unstable acetyl phthalylglycine anhydride, which on reaction with D-glucosamine yielded *N*-(phthalylglycyl)-D-glucosamine.

*Tetra-O-acetyl-N-(phthalylglycyl)-*D-*glucosamine.* *N*-(Phthalylglycyl)-D-glucosamine (5 g.) was acetylated with the mixture of acetic anhydride (20 ml.) and pyridine (20 ml.). The acetylation product was treated in the usual manner. Recrystallization was effected from ethanol, yield, 4.0 g., m.p. 202–203°, $[\alpha]_D^{16}$ +29° (*c* 1, $CHCl_3$).

Anal. Calcd. for $C_{24}H_{26}O_{12}N_2$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.26; H, 5.19; N, 5.53.

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(14) T. Wieland, W. Kern, and R. Sehring, *Ann.*, **569**, 117 (1950).

Constituents of the Saguaro (*Carnegiea gigantea*). I. Proximate Analysis of the Woody Tissues

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This report describes the results of a proximate chemical analysis of the "woody" portions of the giant Saguaro cactus, *Carnegica gigantea, Br. and R.* This initial investigation is part of a larger study of the Saguaro, which has been undertaken in this laboratory to establish its relationship to other xerophytic plants with respect to identity and mode of formation of polysaccharides, lignin, suberin, and extractives.

The Saguaro, largest of the United States cacti, is endemic to the Sonoran desert. It thrives under conditions of high temperature, low rainfall, and loose rocky soil. Individual plants may attain a height of fifty feet, a weight of six tons and an age of 200 years. The ability of the cactus to accumulate and retain water enables it to flower and bloom during periods of prolonged drought. The cortex of the plant is unusually large, permitting a variety of studies not possible with the smaller cortex of other dicotyledons.

A unique feature of the plant is the inner framework of ligniferous ribs, the secondary xylem, which is its main structural member. The chemical composition of this woody rib material as related to the composition of typical heartwoods is of interest to organic chemists and taxonomists alike. Another interesting feature of this plant is its response to injury or bacterial infection following injury.[1] A hard callus tissue is formed in concentric layers around the injured part. This callus tisse may extend deep into the pulpy cortex, sometimes more than six inches and, like the ribs, it is highly ligniferous. The mechanism of callus formation, as well as the formation of related wound tissues and the mechanism of abscission, have been studied in other plants from an anatomical, physiological, and histochemical viewpoint.[3,4] Bonner[6,7] and

(1) Alice M. Boyle, *Phytopathology*, **39** (12), 1029–52, (1949).

(2) (a) B. L. Browning and I. H. Isenberg, "Wood Chemistry," L. E. Wise and E. C. John, eds., Reinhold Publishing Company, New York, 1952, Chapt. 34. (b) B. L. Browning, *Wood Chemistry*, L. E. Wise and E. C. John, eds., Reinhold Publishing Company, New York, 1952, Chapt. 32.

(3) E. J. Butler and S. G. Jones, *Plant Pathology*, MacMillan Company, London, 1949.

(4) E. Gaumann, *Principles of Plant Infection*, Hafner Publishing Company, New York, 1950.

(5) L. E. Wise, M. Murphy, and A. A. D'Addieco, *Paper Trade J.*, **122**, #2, 35 (1946).

(6) J. Bonner, J. M. Henderson, and Mary E. Durrell, *Am. J. Botany*, **39**, 467–73 (1952).

(7) J. Bonner, *Plant Biochemistry*, Academic Press, New York, 1950.

TABLE I[a]

SAGUARO TISSUE ANALYSIS

Tissue	Extractives[b]								Lignin[c]	Holocellulose	Percent of Holocellulose		
	Pet. Ether	Ethyl Ether	Benzene	Ethanol	Cold H_2O	Hot H_2O	1% NaOH	Steam Volatile			Alpha	Beta	Gamma
Saguaro rib	0.16	0.11	0.05	2.85	3.41	1.68	11.7	0.08	21.90	68.56	49.35	14.36	36.31
Saguaro callus	3.16	2.20	1.02	4.24	2.92	1.46	13.5	0.08	30.40	53.30	52.95	15.00	32.00

TABLE II[d]

TYPICAL HEARTWOOD COMPOSITION

Hardwoods	0.5–2.0	1.8–4.0	1.5–7.0	14–21	19–24	71–78	62–73	
Conifers	0.4–5.6	1.4–8.0	0.4–5	9–15	25–29	60–74	66–75	
Conifer bark	4–34		1–33	5–41	20–44	27–55		

[a] All results in % of oven-dry (105°) unextracted samples. [b] Successive extractions with petroleum, ether, ether, benzene, 95% ethanol, cold H_2O, hot H_2O, and 1% NaOH. [c] TAPPI Standard T-13m Method. [d] These values represent a range from minimum to maximum percentages of ten species (see Ref. 2a).

others have investigated the effect of plant growth hormones on the rate of formation of these tissues. However, little is known concerning the chemical composition of these pathological excrescences or their co-occurring chemical precursors.

The Saguaro appeared to be ideally suited for a study of callus formation, lignification, and suberization because of its large cortex, its easy mechanical separation into distinct tissues, and its availability.

This preliminary investigation was concerned with a proximate chemical analysis of the ribs and callus tissue (the two ligniferous parts of the plant). In order to compare adequately these two tissues with one another and with other plants, we have determined the concentrations of lignin, polysaccharides, and extractives. Standard methods of heartwood analysis were used. The data obtained from Saguaro tissue are listed in Table I. To emphasize the relation of cactus wood to economic woods, data showing the composition ranges of some typical heartwoods are presented in Table II.

The above results may be summarized as follows:

1. The chemical composition of the ribs is quite similar to a number of representative hardwoods.

2. The extractive content of the callus tissue (particularly that portion which is soluble in organic solvents) is significantly greater than that for the rib tissue.

3. The lignin content of the callus tissue is approximately 50% greater than that for the rib tissue, whereas the holocellulose content is considerably lower.

The last two results are not entirely unexpected, since it is known[3,4] that the formation of plant callus tissue is accompanied by a large increase in cell-wall lignin, suberin, resinous substances, and compounds soluble in organic solvents.

Although most callus tissue is found deeply imbedded in the cortex of the Saguaro, no detectable concentration of lignin is present in the uninjured portion of the cortex. A clearer understanding of the mechanism of callus formation must await the determination of the nature of the callus lignin and the identities of some of the co-occurring extractives in the adjacent tissues. Work is now in progress in this laboratory to elucidate the structures of some of these constituents.

EXPERIMENTAL

Sampling. A 20-foot plant, which had been recently felled by wind, was cut 10 feet above the base. A 1-foot section was removed, the pulp stripped away from the ribs, and the latter dried at room temperature and finally ground in a Wiley mill to pass 40–60 mesh screen.

Lignin determination. Lignin in the callus and ribs was determined by the TAPPI Standard T-13m methods, as outlined by Browning (see Ref. 2b, p. 1218).

Holocellulose determination. The method of Wise[5] was used.

Alpha-, beta-, and gamma-cellulose determination. Alpha-cellulose content in the isolated holocellulose was determined by the TAPPI Standard T203m Method (Ref. 2b, p. 1240). Beta and gamma-cellulose were determined by the volumetric method outlined in Ref. 2b, p. 1242.

Extractives. A 30-g. sample of air-dried material, ground to pass a 40–60 mesh screen, was placed in an Soxhlet extractor and extracted continuously for 12 hr. with 500 ml. of appropriate solvent. Successive extractions were performed with petroleum ether (b.p. 60–75°), diethyl ether, benzene, and ethanol (95%). The residual meal was then triturated with cold water for 14 hr., after which it was extracted with boiling water in the Soxhlet apparatus. A final extraction was made with cold 1% sodium hydroxide. All fractions were evaporated to dryness (with the exception of the sodium hydroxide fraction which was neutralized and filtered) and the residues dried at 105°, after which they were weighed.

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Isolation of β-Sitosterol from Chufa (*Cyperus esculentus* L.) Tubers

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The chemical constitution of the tubers of *Cyperus esculentus* L., also known as chufa, tiger nut, edible cyperus, rushnut, and earth almond, has received sporadic attention through many years. The principal component is the oil, sometimes called sedge oil, which forms about 25% of the tubers and which was valued as a food and for lubrication purposes.[1] The detailed analysis of the oil and other constituents of the tubers cultivated in Egypt will be shortly reported elsewhere.[2]

An early publication by Baughman and Jamieson[3] dealing with the fatty acid constituents of the oil mentioned a phytosterol that was isolated by saponification of the unsaturated acid fraction. These authors reported for the crystalline product m.p. 134–135° and for its acetyl derivative m.p. 122–123°. As it appears that the product has not been examined by later workers, we wish now to report on its identity.

Saponification of the oil (about 25% of the tubers, by light petroleum extraction) with alcoholic potassium hydroxide gave a nonsaponifiable fraction as a bright yellow oil in 0.68% yield. By chromatographic fractionation of this material, there has been obtained β-sitosterol, m.p. 136–137°, $[\alpha]_D^{28}$ −34°. It afforded an acetate, m.p. 126–127°, $[\alpha]_D^{28}$ −41°, and a benzoate, m.p. 142–4°, $[\alpha]_D^{28}$ −15°. The properties of the compound, its acetate, and benzoate agree with those reported by Bernstein and Wallis[4] for β-sitosterol isolated from cottonseed oil; moreover, the melting points of the alcohol and the acetate were undepressed by the authentic samples. The infrared absorption spectrum[5] (Nujol) of the alcohol contained bands at 3400 cm.$^{-1}$ (OH), 840 and 803 (trisubstituted olefin), and was identical with that of authentic material. It is likely, therefore, that β-sitosterol is the material which has been isolated by Baughman and Jamieson.[3]

(1) J. Pieraerts, *L'Agronomie Coloniale*, 9, No. 67, 7 (1923); H. Winter, *Z. Lebensmittel-Unters. u.-Forsch.*, 105, 200 (1957); F. R. Earle *et al.*, *J. Am. Oil Chemists' Soc.*, 36, 304 (1959).

(2) A preliminary report, A. M. Gad and F. Osman, *Egypt. J. Chem.*, 2, No. 1, 123 (1959), will be followed by more details.

(3) W. F. Baughman and G. S. Jamieson, *J. Agric. Research*, 26, 77 (1923).

(4) S. Bernstein and E. S. Wallis, *J. Org. Chem.*, 2, 341 (1937–1938).

(5) We thank Professor F. G. Baddar, Ein-Shams University, for the infrared measurements.

EXPERIMENTAL[6]

β-Sitosterol. Exhaustive extraction of the finely ground tubers of *Cyperus esculentus* L. with light petroleum (b.p. 70–80°) removed about 25% as oil. Saponification of the oil with ethanolic potassium hydroxide followed by work-up in the usual manner gave 0.68% of a bright yellow thick oil. Percolation of a benzene solution of 0.683 g. of the nonsaponifiable matter through an alumina column and prolonged washing with the same solvent removed 0.368 g. of wax and oily unsaturated hydrocarbon material. Final stripping of the column with 3% methanol in benzene removed 0.268 g. of a colorless solid. Recrystallization from methanol gave β-sitosterol as colorless plates, m.p. and mixed m.p. 136–137°, $[\alpha]_D^{28}$ −34° ($CHCl_3$); ϵ_{max} = 3,200(204 mμ); in ethanol; (reported[4] m.p. 136–137°, $[\alpha]_D^{28}$ −36°). The infrared absorption spectrum (Nujol) was identical with that of an authentic sample.

β-Sitosteryl acetate was prepared by treating a pyridine solution of β-sitosterol with acetic anhydride at 100° for 1 hr. The product, isolated by the usual work-up, was crystallized from methanol to give colorless needles, m.p. and mixed m.p. 126–127°, $[\alpha]_D^{28}$ −41° ($CHCl_3$), ϵ_{max} = 3400 (204 mμ, ethanol); (reported[4] m.p. 125–126°).

β-Sitosteryl benzoate was prepared by heating a mixture of β-sitosterol, pyridine, and benzoyl chloride on the water bath for 1 hr. followed by isolation in the usual manner. Crystallization of the product from methanol gave needles, m.p. 142–144°, $[\alpha]_D^{28}$ −15° ($CHCl_3$); (reported[4] m.p. 145°).

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(6) Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord 137 spectrophotometer.

The Orientation of the Isopropyl Group of Dihydroabietic γ-Lactone

Laurence J. Gough,[1a] Thomas F. Sanderson,[1b] Virgil I. Stenberg, and Ernest Wenkert

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Treatment of commercial, partially hydrogenated rosin or dihydroabietic acids with strong mineral acid has led to dihydroabietic α-lactone (the lactone of "hydroxytetrahydroabietic acid"[1c]).[2–7] The con-

(1a) Department of Chemistry and Food Technology, Borough Polytechnic, London S.E. 1, England; (1b) Present address: Experiment Station, Hercules Powder Co., Wilmington, Del. (1c) T. Hasselstrom and J. D. McPherson, *J. Am. Chem. Soc.*, 60, 2340 (1938).

(2) (a) L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, 5, 315 (1922); (b) L. Ruzicka, H. Waldmann, P. J. Meier, and H. Hosli, *Helv. Chim. Acta*, 16, 169 (1933).

(3) E. E. Fleck and S. Palkin, *J. Am. Chem. Soc.*, 61, 1230, 3197 (1939).

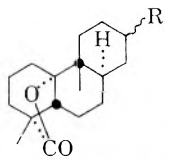
(4) R. Lombard and J. Ebelin, *Bull. soc. chim. France*, 930 (1953), and references contained therein.

(5) L. Velluz, G. Muller, A. Petit, and J. Mathieu, *Bull. soc. chim. France*, 401 (1954).

(6) Le-van-Thoi, *Bull. soc. chim. France*, 439 (1954).

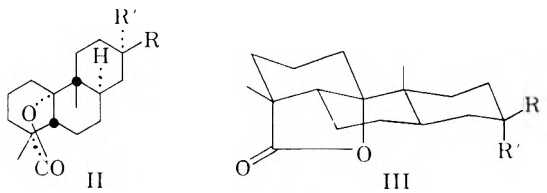
(7) R. F. B. Cox (assigned to Hercules Powder Co.), U. S. Patent 2,355,782.

figuration of all asymmetric centers of the lactone, except that to which the isopropyl side chain is attached, has been assigned (*cf.* Ia).[8] Recently oxidation experiments have been reported which affected exclusively this side chain of undetermined configuration.[9] In two of the three reaction products the isopropyl function had been converted into a hydroxyisopropyl group (cf. Ib) and into an acetyl group (cf. Ic), respectively. The structural relationship of these two oxidation products has been established by the conversion of the latter (Ic) into the former (Ib) with methyl magnesium iodide and hydrolysis.[9]



Ia. R = $CH(CH_3)_2$
b. R = $C(OH)(CH_3)_2$
c. R = $COCH_3$

In view of the small likelihood of the oxidation of the isopropyl group having affected its neighboring asymmetric carbon atom, the above data indicate the stereochemistry of Ia, b, and c to be identical. Hence the elucidation of the configuration of the side chain of any of these substances would determine the stereochemistry for all. This has now been accomplished. Equilibration of the ketone Ic in refluxing methanolic sodium methoxide solution left the starting material unchanged. This fact implies that the acetyl group possesses the equatorial β configuration. Furthermore, formula IIa, IIIa in conformational form, represents the stereostructure of dihydroabietic γ-lactone.

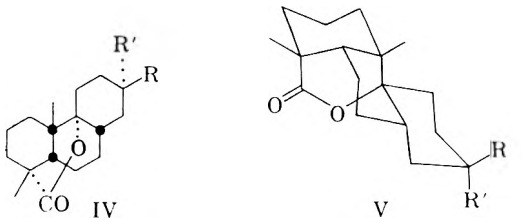


II III

a. R = $CH(CH_3)_2$, R′ = H
b. R = $C(OH)(CH_3)_2$, R′ = H
c. R = C_2H_5, R′ = CH_3
d. R = CH_3, R′ = C_2H_5

Strong acid treatments of pimaric and isopimaric acids have been shown to lead to a hydroxy γ-lactone among other products.[10,11] Comparison of its infrared spectrum, melting point, and mixed melting point with those of the hydroxylactone, obtained by the oxidation of dihydroabietic γ-lactone,[9] showed these substances to be identical. Hence, structure IIb, IIIb in conformational representation, can be assigned now to the hydration product of the pimaric acids.

It has been reported[12] that treatment of dihydroabietic γ-lactone with concentrated sulfuric acid yielded a δ-lactone. Its structure can be represented now by IVa, conformationally by Va. Were the conversion of the γ- into the δ-lactone assumed to be high-yielding, a configuration of the isopropyl group opposite to that depicted in IIa–Va might be deduced, since, among other changes, a bulky isopropyl group is inverted from an equatorial into an axial conformation.[13] However, a preliminary study of the acid-catalyzed equilibration of the lactones reveals an equilibrium mixture containing only 25–50% δ-lactone. Furthermore, the following simple theoretical calculation leads to a similar conclusion.



IV V

a. R = $CH(CH_3)_2$, R′ = H
b. R = C_2H_5, R′ = CH_3
c. R = CH_3, R′ = C_2H_5

A recent study of the equilibrium position between the five- and six-membered lactones derived from dihydropimaric and dihydroisopimaric acids has afforded these data[11]: IIIc⇌Vb: 95.0 ± 0.6% δ-lactone; IIId⇌Vc: 96.4 ± 0.8% δ-lactone. The average between these values, 95.7 ± 0.8% δ-lactone, corresponds to the equilibrium position of the lactones of a hypothetical system II–V, where R = R′, e.g. R = R′ = H. In this system the six-membered lactone would be favored by 1.8 ± 0.1 kcal. at equilibrium. Since the introduction of an axial isopropyl group into such a δ-lactone implies its de-stabilization by two more skew nonbonded interactions, *i.e.*, *ca.* 1.8 kcal.,[14] the resulting compound should have the same energy content as its γ-lactone counterpart. Hence, the equilibrium mixture of the dihydroabietic lactones should contain *ca.* 50% δ-lactone.

EXPERIMENTAL

Equilibration of ketolactone Ic. A solution of 7.6 mg. of ketolactone Ic, m.p. 135–136.8°, $[\alpha]_D$ −15.4° (chloroform), and sodium methoxide, from 0.76 mg. of sodium, in 0.5 ml. of methanol was refluxed under nitrogen for 1.5 hr. The mixture then was neutralized with 1% methanolic hydrogen chloride, the solvent evaporated, and the white residue ex-

(8) L. A. Subluskey and T. F. Sanderson, *J. Am. Chem. Soc.*, **76**, 3512 (1954).

(9) J. Minn, T. F. Sanderson, and L. A. Subluskey, *J. Am. Chem. Soc.*, **78**, 630 (1956).

(10) E. E. Fleck and S. Palkin, *J. Am. Chem. Soc.*, **62**, 2044 (1940).

(11) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959).

(12) Le-van-Thoi, *Bull. soc. chim.*, 761 (1955).

(13) Indeed, this type of assumption has led to an erroneous assignment of the configuration of the isopropyl group in the dihydroabietic acid precursor of IIa.[11]

(14) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947). •

tracted with ether. Removal of the solvent gave 6.6 mg. of colorless crystalline material. Crystallization of the latter from aqueous acetone and aqueous methanol yielded 4.4 mg. of colorless crystals, m.p. 136–137.2°, $[\alpha]_D$ −19.2° (chloroform), no depression of mixed melting point with starting material, infrared spectrum (chloroform) identical with that of starting ketone.

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Acenaphthene Arsenicals

RICHARD J. GARASCIA, GEORGE W. BATZIS, AND JOHN O. KROEGER

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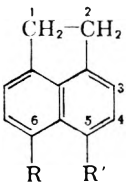
Several years ago, we gave some attention to the preparation of a number of acenaphthene arsenicals.[1] More recently,[2] we have repeated and extended this work. A search of *Chemical Abstracts* reveals no mention of acenaphthene arsenic compounds, a somewhat surprising situation, considering the number of acenaphthene compounds now in existence. Part of our interest in the series lies in the fact that the dimethylene bridge of acenaphthene can be oxidized into various forms some of which ought to prove of value as insecticidal or antifungal agents.

Since direct aromatic substitution of acenaphthenes produces, largely, 5-substituted compounds and disubstitution the 5,6- compounds, all of the compounds prepared by us belong to one of these structure types. The chemical literature describes satisfactorily the preparation of 5-nitroacenaphthene.[3] This compound was found to be reduced nicely in the laboratory to the corresponding amine either by low pressure hydrogenation using Raney nickel or palladium-charcoal, or by refluxing in hydrazine with the same catalysts. Other methods of reduction were found to be less satisfactory.

The 5-aminoacenaphthene was then converted into acenaphthene-5-arsonic acid, the first of the new compounds (I), *via* the Bart reaction on the diazotized amine. Application of the Scheller reaction (acetone solvent, arsenic trichloride, cuprous bromide catalyst) gave very poor yields even though conditions were varied extensively. The method of arsonation proceeding through the diazonium fluoborate (decomposition in aqueous as well as nonaqueous media) failed to give appreciable yields.

Acenaphthene-5-arsonic acid was then converted to the 5-dichloroarsine (II) and the 5-dibromoarsine (III) using the appropriate phosphorus trihalide



I. R = H, R′ = AsO_3H_2
II. R = H, R′ = $AsCl_2$
III. R = H, R′ = $AsBr_2$
IV. R = H, R′ = AsI_2
V. R = NO_2, R′ = AsO_3H_2

in organic media. Attempts to convert the arsonic acid into the diiodoarsine (IV) with hydriodic acid in glacial acetic acid gave a tan product melting at 95–96°, but having an analysis some five or more per cent high in iodine. There is some question of the method to be employed in the analysis for iodine in the presence of arsenic, but the compound was probably contaminated with elemental iodine or arsenic iodide.

The direct nitration of acenaphthene-5-arsonic acid was then attempted, leading to the supposed 6 - nitroacenaphthene - 5 - arsonic acid (V). After several exploratory runs, the correct conditions were established and a product giving the proper nitrogen content was obtained.

Several attempts to oxidize acenaphthene-5-arsonic acid into a naphthalic acid derivative with chromic anhydride failed to yield isolable material.

Structure proof for the supposed 6-nitro-5-arsonic acid based on the known 6-nitro-5-amine[4] is planned for the near future.

EXPERIMENTAL

Melting points were obtained on a Fisher-Johns melting point apparatus calibrated against pure compounds of known melting points.

Acenaphthene. Technical grade material was purchased from the Reilly Tar and Chemical Corporation of Indianapolis, and was recrystallized from glacial acetic acid with a charcoal treatment; m.p. 92–93°.

5-Nitroacenaphthene. This was prepared in 66% yield by direct nitration of acenaphthene using essentially the method of Sachs and Mosebach,[3] m.p. 101–102°.

5-Aminoacenaphthene. I. *Palladium-hydrazine method.* Five grams (0.033 mole) of 5-nitroacenaphthene was dissolved in 60 ml. absolute ethanol and 5 ml. of 95% hydrazine was added. The solution was heated to near reflux temperature and 0.05 g. of 10% palladium on charcoal (Matheson Coleman & Bell) was added. The mixture was refluxed for 10 min., an additional 0.05-g. portion of catalyst was added and reflux was continued for 90 min. The material was then treated with charcoal, filtered hot, and poured slowly into 800 ml. of cold water. The white solid separating was filtered, washed with water, and dried to give a product (3.6 g., 84% yield) melting at 104–105°.

II. *Palladium or raney nickel with low-pressure hydrogen.* Five grams (0.033 mole) of acenaphthene was placed with 60 ml. of absolute alcohol in the pressure bottle (400 ml. capacity) of a low-pressure Parr hydrogenation apparatus and 0.1 g. of 10% palladium-on-charcoal or approximately 0.5 g. of Raney nickel[5] was added. Hydrogen gas at 35 p.s.i.g. was supplied and the suspension was shaked for 90 min. The

(1) G. W. Batzis, Master's Thesis, Xavier University, Cincinnati, Ohio, 1952.
(2) J. O. Kroeger, Master's Thesis, Xavier University, Cincinnati, Ohio, 1959.
(3) F. Sachs and G. Mosebach, *Ber.*, **43**, 2473 (1910).
(4) H. J. Richter, *J. Org. Chem.*, **21**, 619 (1956).
(5) R. Mozingo, *Org. Syntheses*, **21**, 15, (1941).

suspension was then transferred to an Erlenmeyer flask, treated with charcoal, and filtered hot. The filtrate was poured into 800 ml. of cold water to give yields varying from 80 to 90% (3.5–4 g.), melting at 104–105°.

Acenaphthene-5-arsonic acid. Seven grams (0.04 mole) of 5-aminoacenaphthene was suspended in 225 ml. of water and 25 ml. of 12*N* hydrochloric acid. The mixture was heated to 75° to dissolve the amine and the solution was then cooled rapidly in an ice–hydrochloric acid bath to 0°. A solution of 2.5 g. (0.036 mole) of sodium nitrite dissolved in 20 ml. of water was added slowly below the surface over the period of 30 min. with stirring, keeping the temperature below 5°. A dark green color appeared as the diazotization progressed as well as some dark insoluble matter. After an additional hour of stirring at this temperature, the diazonium solution was quickly filtered into a chilled flask and the solid residue was discarded.

The diazonium solution, kept cold with the aid of an ice bath, was added in small portions over a period of 30 min. to a mixture, at room temperature, of 7 g. (0.036 mole) of arsenic trioxide, 7 g. of sodium bicarbonate, 24 g. of potassium hydroxide, and 1.5 g. of hydrated copper sulfate in 200 ml. of water. From time to time, 8*N* sodium hydroxide was added to maintain alkalinity. The dark brown solution was allowed to stand overnight, treated on a hot water bath for 90 min., and was filtered hot. The filtrate was treated with charcoal, filtered again, and reduced by boiling to 400 ml. After cooling to 40°, the solution was acidified with 6*N* hydrochloric acid and chilled in the ice box. The crystals of the product were filtered by suction and extracted with a hot solution of 6 g. of sodium bicarbonate in 200 ml. of water. After charcoal treatment and filtration, the solution was acidified with 6*N* hydrochloric acid, chilled, and the product was filtered and dried. The white crystalline material (2.6 g., 22% yield) melted at 168–169°.

Anal. Calcd. for $C_{12}H_{11}O_3As$: As, 27.06. Found: As, 26.88.

Acenaphthene-5-dichloroarsine. One gram (0.0036 mole) of acenaphthene-5-arsonic acid was suspended in 13 ml. of chloroform and the temperature was raised to reflux. Heating was interrupted and 1.2 ml. (0.017 mole) of phosphorus trichloride was added dropwise. The chloroform was boiled away on the water bath and the residue refluxed with 8 ml. of petroleum ether (b.p. 60–90°). The solution was filtered and chilled overnight in the ice box. The crystalline material was separated and recrystallized again from 8 ml. of petroleum ether. The product, weighing 1.1 g. (55%), melted at 88–90°.

Anal. Calcd. for $C_{12}H_9Cl_2AS$: Cl, 23.7. Found: Cl, 24.2.

Acenaphthene-5-dibromoarsine. The method described above for the preparation of the dichloroarsine was employed, using phosphorus tribromide. The yield of purified dibromoarsine was 56% and the compound melted at 72–73°.

Anal. Calcd. for $C_{12}H_9Br_2As$: As, 19.4. Found: As, 19.7.

Acenaphthene-5-diiodoarsine. One gram (0.0036 mole) of acenaphthene-5-arsonic acid was suspended in 20 ml. of glacial acetic acid and 8 ml. of 43% hydriodic acid was added with shaking. The suspended arsonic acid dissolved and a heavier precipitate appeared. The mixture was refluxed gently for a few minutes to dissolve the product, and the clear solution was placed in the ice box. After standing overnight, the crystals were separated by filtration and recrystallized from glacial acetic acid. The yield of yellow-tan product was 0.4 g. (30%) melting at 95–96°. Analysis for iodine gave values 5–6% too high (theoretical value: 52.7%).

6(?)-Nitroacenaphthene-5-arsonic acid. Into a 200-ml. 3-neck flask, equipped with stirrer, thermometer, and dropping funnel, was placed 2 g. (0.0072 mole) of acenaphthene-5-arsonic acid suspended in 23 ml. of glacial acetic acid. The contents were heated to dissolve the arsonic acid, then cooled to 15° with an ice bath. To the stirred solution was added 20 ml. of fuming nitric acid (*d* 1.5) dropwise over a period of 30 min. The temperature dropped to 5° and stirring was maintained at this temperature for an additional 3 hr. The mixture was then brought to room temperature and slowly added to 100 ml. of ice water with vigorous stirring. A yellow precipitate appeared, changing to light brown on standing. The solid material was filtered, washed with water until the filtrate showed no color, and dissolved in a solution of 6 g. of sodium bicarbonate in 200 ml. of water. The solution was treated with charcoal, filtered, and neutralized with 6*N* hydrochloric acid. The yield of nitroarsonic acid was 1.0 g. (43.5%); the compound did not melt below 300°.

Anal. Calcd. for $C_{12}H_{10}AsO_5N$: N, 4.33. Found: N, 4.36.

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Structure and Partition Coefficient. Synthesis and Properties of the Dodecyl Methyl Pentaerythrityl Ethers

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Relatively few attempts have been made to relate structure to distribution coefficients in a systematic manner. Collander[1] has developed several useful semiquantitative generalizations for a number of systems. Alders[2] has shown that K_0, the distribution coefficient at infinite dilution, can be related to the hydrophobic chain length n by the expression

$$\mathrm{Log_{10}}K_0 = A - B_n$$

for several series of homologous compounds in a variety of solvent pairs. The constants A and B are dependent on the solvent pair and the nature of the solute.

This paper reports on some results encountered in the preparation and isolation of dodecyl pentaerythrityl ether, I, and its methylation products, II, III, and IV. Partition coefficient data from the

$C_{12}H_{25}OCH_2C(CH_2OH)_3$ I

$C_{12}H_{25}OCH_2C(CH_2OH)_2CH_2OCH_3$ II

$C_{12}H_{25}OCH_2C(CH_2OH)(CH_2OCH_3)_2$ III

$C_{12}H_{25}OCH_2C(CH_2OCH_3)_3$ IV

Craig separation of these compounds indicated that in the solvent system used the number of unmethylated hydroxyl groups was linearly related to the logarithm of the partition coefficient, similarly to Alders' equation relating chain length to distribution. These results have been expressed as standard free energy terms since they are more

(1) R. Collander, *Acta Chem. Scand.*, **3**, 717 (1949); **4**, 1085 (1950); **5**, 774 (1951).

(2) L. Alders, *Appl. Sci. Research*, **4A**, 171 (1954).

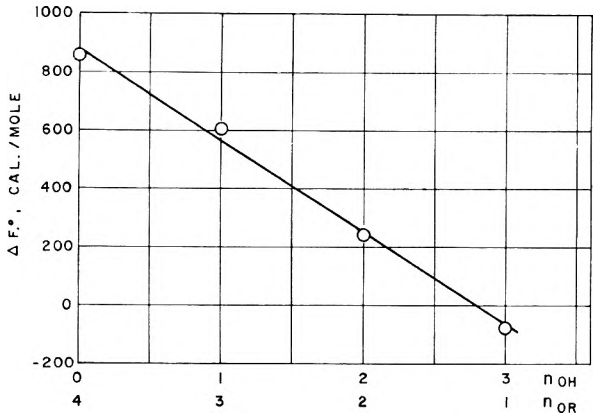

Fig. 1. Standard free energy *vs.* hydrophilic group content. Solvent: hexane—7 pts., chloroform—3 pts., ethanol—8 pts., water—2 pts.

directly related to the solvational energy changes accompanying the transfer of solute from one solvent phase to the other.[3] The data for the series of compounds are tabulated in Table I. Standard free energies are expressed as the energy change accompanying the transfer of solute from the upper, less-polar phase to the lower; *i.e.*, $\Delta F^\circ = -nRT\ln 1/K$ where K is used in the conventional sense. Fig. 1 shows the plot of number of hydrophilic groups *vs.* the standard free energy. The least squares equation best expressing this relationship[4] is

$$\Delta F^\circ = 882\text{-}347\ N_{OH}$$
$$\text{or, alternatively } \Delta F^\circ = -386\text{-}317\ N_{OR} \qquad (1)$$

The partition coefficient of *n*-hexadecane in the same solvent system (Table I) has been used as a reference point for comparing the relative contributions of the two functional groups in increasing polar character. While *n*-hexadecane is not an ideal choice for reference, the difference in molecular geometry should affect the partition coefficient of the hydrocarbon in this system only to a minor extent compared to the effects produced by introduction of ether or hydroxyl groups. The values of ΔF° for compounds I and IV computed from (1) can be used to calculate the contribution of each group to the free energy decrease accompanying the transfer of solute from upper to lower phase using (2) and (3).

$$\Delta F^\circ_{OR} = 1/4\ (\Delta F^\circ_{IV} - \Delta F^\circ \text{ hexadecane}) \qquad (2)$$

$$\Delta F^\circ_{OH} = 1/3\ (\Delta F^\circ_{I} - \Delta F^\circ_{OR} - \Delta F^\circ \text{ hexadecane}) \qquad (3)$$

The values of −242 and −559 cal./group respectively for ether and hydroxyl indicate the much greater effect of the hydroxyl group contribution in this system. Equation (2) assumes equivalence of methyl and dodecyl ether oxygens. The validity of this assumption can be justified by using the values of ΔF°_{OH} and ΔF°_{OR} obtained to calculate ΔF°_{II} and ΔF°_{III}. The values 248 and 565 cal./mole calculated respectively for II and III correspond to the measured values, 240 and 605 cal./mole, within the limits of reproducibility of the partition coefficients.

TABLE I

PARTITION COEFFICIENTS AND FREE ENERGY DATA OF ETHERS

Compound	Solvent: hexane-chloroform/ethanol-water (7-3/8-2)	
	K	ΔF° cal./mole
Dodecyl pentaerythrityl ether, I	0.88	−77
Dodecyl methyl pentaerythrityl ether, II	1.50	240
Dodecyl dimethyl pentaerythrityl ether, III	2.77	605
Dodecyl trimethyl pentaerythrityl ether, IV	4.26	858
n-Hexadecane	22.7	1851

The regularity of the pentaerythrityl ether series in this case is probably due to the stereochemical equivalence of oxygens attached to the neopentyl moiety. Results obtained with the isomeric 1- and 2-monoglycerides[5] indicate that this may well be the case, as the two position isomers, identical in functional group content, show different partition coefficients. It is possible that systematic study of selected series of compounds using methods similar to those used here could afford much valuable quantitative information about some of the effects which operate in the solvation of organic compounds.

EXPERIMENTAL

Dodecyl pentaerythrityl ether (I). To a well-stirred mixture of *n*-dodecyl alcohol (435 g., 2.33 moles) and 40 drops of concd. sulfuric acid was added 14.0 g. (0.118 mole) of 3,3-*bis*(hydroxymethyl)oxacyclobutane[6] dissolved in 1400 ml. chloroform. The chloroform solution was added over a 2-hr. period to the reaction mixture heated on the steam bath. After 1 hr. additional reflux the chloroform was removed *in vacuo* until the chloroform odor was very faint. Hexane (2 l.) was added to the residue and the solution chilled to 0° and filtered. The solid filter cake was redissolved in hot chloroform and filtered. Chloroform was removed from the filtrate and the residue recrystallized from hexane to give 12.9 g. (36% yield) crude dodecyl pentaerythrityl ether, I, m.p. 53.5–55.0° (uncorr.).

The crude product was contaminated at this stage by small amounts of dipentaerythritol and dodecyl alcohol. Purification was effected by solvent partition in a 200 stage Craig apparatus using a hexane-chloroform/ethanol-water mixture (7-3/8-2 parts by volume). The principal peak, K = 0.88, was the desired product I, m.p. 60–61°.

(3) A. Frumkin, *Z. physik. Chem.*, **116**, 501 (1925).

(4) Ideally, distribution coefficients at infinite dilution should be employed in arriving at this equation; however, the maximum concentrations involved in the isolation (0.2%) are small enough to involve little error in using the values directly as determined.

(5) E. S. Perry and G. Y. Brokaw, *J. Am. Oil Chemists Soc.*, **32**, 191 (1955).

(6) C. H. Issorides and A. I. Matar, *J. Am. Chem. Soc.*, **77**, 6382 (1955).

Anal. Calcd. for $C_{17}H_{36}O_4$: C, 67.18; H, 11.91; H.V., 553. Found: C, 66.77; H, 11.74; H.V., 547.

Dodecyl methyl pentaerythrityl ethers (II, III, and IV). To a mixture of 10 g. (0.033 mole) of crude I was added 3.95 g. (0.099 mole) of sodium hydroxide and 2.8 ml. water. The mixture was heated to 75° and 14.0 g. (0.099 mole) of methyl iodide was added over a 2-hr. period. After a 6-hr. period of heating at 70–75°, with stirring, the mixture was cooled and extracted with ether four times. The combined ether extracts were washed with water, dried over sodium sulfate, and the ether removed by evaporation. After repetition of the same methylation procedure, the mixture of ethers was separated on the Craig apparatus. The chloroform-hexane/ethanol-water system gave incomplete separation of III and IV. Dodecyl methyl pentaerythrityl ether, II, K = 1.50, could be cleanly separated from III and IV. For separation of the latter, the better solvent system isooctane-methanol (1:1) was used. Partition coefficients in this solvent system were 0.75 and 2.36 for III and IV, respectively. The dodecyl methyl pentaerythrityl ethers were all liquids.

Anal. Calcd. for $C_{18}H_{38}O_4$, II: C, 67.72; H, 12.03; H.V., 352. Found: C, 67.58; H, 11.90; H.V., 344. Calcd. for $C_{19}H_{40}O_4$, III: C, 68.63; H, 12.13; H.V., 169. Found: C, 69.15; H, 12.01; H.V., 161. Calcd. for $C_{20}H_{40}O_4$, IV: C, 69.31; H, 12.22; H.V., O. Found: C, 70.28; H, 12.36; H.V., O.

n-Hexadecane. The partition coefficient for *n*-hexadecane (Matheson) was obtained by partitioning the hydrocarbon between the equilibrated solvent phases at 0.5% total concentration. It was essential to remove solvents by efficient fractionation to avoid evaporation losses. Recoveries averaged 97%.

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Communications TO THE EDITOR

Electrophilic Substitution of 1,3-Dichloroazulene

Sir:

The electrophilic substitution of azulene in the 1-position and disubstitution in the 3-position were shown to occur several years ago[1] and are now well-known. Further substitution of 1,3-disubstituted azulenes has, however, not been reported.

The ground state electron density calculations by Julg[2] (Fig. 1) using the self-consistent field method show the 5-position to have the next highest value after the 1- and 3-positions.[3] The localization energies[4] (Fig. 1, β-values) show essential equivalence of the 2- and 5-positions in regard to ease of electrophilic substitution.[5]

We have now achieved the acetylation of 1,3-dichloroazulene (I) by means of acetyl chloride in carbon tetrachloride with stannic chloride as the catalyst. The principal product was isolated as green needles in 16% actual (36% net) yield. The major part of these needles melted at 92–95°, with

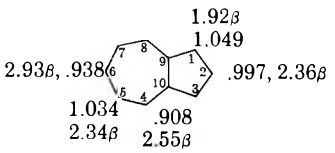
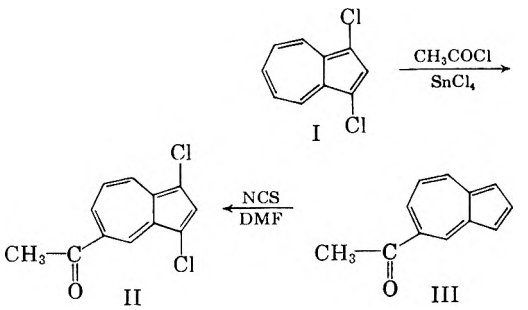


Fig. 1. Theoretical localization energies (in β) and ground state electron densities

the remainder melting at 101–103°. The resolidified sample then melted at 101–103°. An analytical sample partially melted and underwent a transition at *ca.* 95°, resolidified, and then melted at 103–104°.

Anal. Calcd. for $C_{12}H_8OCl_2$: C, 60.28%; H, 3.37%. Found: C, 60.55%; H, 3.29%. The infrared spectrum showed a carbonyl band at 5.97μ. A cyclohexane solution exhibited maxima in mμ ($\epsilon \times 10^{-4}$) in the ultraviolet at 227 (1.55), 242 (1.82), 296 (3.17), 306 (3.40), 322 (1.11), 379 (0.94), and 400 (1.62) and in the visible (ϵ) with a shoulder at 578 (323), shoulder at 606 (410), 627 (467), 655 (410), 664 (415), 687 (428), shoulder at 738 (183) and 769 (165).

The position (627 mμ) of the principal maximum in the visible suggested that the compound was 5-acetyl-1,3-dichloroazulene (II) on the basis of assumed additivity of the spectral shifts due to the substituents[6] (638 mμ for 1,3-dichloroazulene and -12 mμ for a 5-acetyl group[7] gives a calculated λ_{max} = 626 mμ). Proof of this structure was provided by the dichlorination of 5-acetylazulene (III)[7] in 40% yield with *N*-chlorosuccinimide in dimethylformamide. The products obtained *via* the two routes were identical (melting point; ultraviolet, visible and infrared spectra).



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(1) A. G. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953). A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957).

(2) A. Julg, *J. Chim. phys.*, **52**, 377 (1955).

(3) These values differ from other calculated electron densities which show the 2-position to have the next highest electron density. (*cf.* E. Heilbronner, Non-Benzenoid Aromatic Compounds, D. Ginsburg, ed., Interscience Publishers, Inc., New York, 1959, p. 196).

(4) R. D. Brown, private communication to D. Peters, *J. Chem. Soc.*, 1028 (1958).

(5) These considerations do not include any possible effect of substituents in the 1,3-positions.

(6) A. G. Anderson, Jr., C. G. Fritz and R. Scotoni, Jr., *J. Am. Chem. Soc.*, **79**, 6511 (1957); E. J. Cowles, **79**, 1093 (1957); A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957).

(7) W. Treibs and M. Quarg, *Ann.*, **598**, 38 (1955).

(8) National Science Foundation Predoctoral Fellow, 1959–1960.

Oxidative Coupling of Acetylenes

Sir:

The oxidative coupling of acetylenes has generally been effected with air or oxygen in an ammonia-

cal solution of copper(I) chloride.[1] Excellent yields are generally obtained. Recently Eglinton and Galbraith[2] found that copper(II) acetate in methanolic pyridine was a superior oxidant since reactions can be carried out in homogeneous media. Sondheimer and co-workers[3] have utilized this procedure for the preparation of some unusual large ring polyacetylenes.

We have found that acetylenes can be coupled in a matter of minutes at room temperature with oxygen or air using a catalytic amount of an amine complex of a copper(I) salt in an organic solvent. Pyridine can serve as both ligand and solvent. The copper(II) carboxylates are the only copper(II) salts that are catalysts for the reaction but they are far inferior in catalytic activity to copper(I) salts.

As an example: To a 500-ml. Erlenmeyer flask there was added 250 ml. of pyridine, 2 g. of copper(I) chloride, and 50 g. (0.49 mole) of phenylacetylene. Oxygen was bubbled through the vigorously stirred reaction mixture (Fisher "Vibromixer") which was kept in a bath at 30°. A vigorous reaction ensued and the temperature rapidly rose to 40°. After 40 min. the reaction had subsided and there was isolated 42.7 g. (0.21 mole, 86% yield) of diphenyldiacetylene, colorless needles, m.p. 88° (lit., m.p. 88°).

When *m*-diethynylbenzene[4,5] is oxidized in the same manner a pale yellow polymer separates out at the end of the reaction in essentially quantitative yield. *Anal.* for $C_{16}H_4$: C, 96.8; H, 3.2. Found C, 96.4; H, 3.5. The polymer is soluble in solvents such as chlorobenzene and nitrobenzene above 100°. Evaporation of a nitrobenzene solution at 170° yields transparent, flexible films. Infrared analysis of end groups (≡CH stretching, 3290 cm.$^{-1}$) indicates a molecular weight of at least 7000[6] and intrinsic viscosities (nitrobenzene, 150°) as high as 0.25 decil./g.[6] have been obtained. This material appears to be quite stable at room temperature. When rapidly heated *in vacuo* it abruptly decomposes at about 180°, evolving hydrogen and a small amount of methane[6] and leaving a residue of carbon. When ignited at room temperature in air an explosive reaction takes place; however, the net result is the loss of most of the hydrogen and some carbon, presumably as carbon dioxide, for a total weight loss of only 5–6%.

Oxidation of *p*-diethynylbenzene[5] gives a bright yellow product that is completely insoluble in all solvents we have tried and decomposes rapidly at about 100°.

Aliphatic ethynyl compounds are also oxidized with catalysts of this type. Further work will be reported in the near future.

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Received April 12, 1960

(1) R. A. Raphael, *Acetylene Compounds in Organic Synthesis*, Academic Press Inc., New York, 1955, p. 127.
(2) G. Eglinton and A. R. Galbraith, *Chem. & Ind. (London)*, 737 (1956).
(3) F. Sondheimer, R. Wolovsky, and Y. Gaoni, *J. Am. Chem. Soc.*, **82**, 755 (1960) and previous papers.
(4) R. Delucbat, *Ann. chim.* [11], **1**, 181 (1934).
(5) A. S. Hay, *J. Org. Chem.*, **25**, 637 (1960).
(6) We are indebted to Dr. P. D. Zemany for mass spectrometric analyses, to Drs. R. S. McDonald and A. E. Newkirk for infrared analyses, and to Mr. J. W. Eustance for determination of intrinsic viscosities.

Volatile Methyl Ketone Formed in Rubber Oxidation

Sir:

Tobolsky and Mercurio[1] have suggested that the volatile methyl ketone produced in high yield during the oxidation of rubber is 2,5-hexanedione rather than levulinaldehyde; no experimental support for this suggestion was offered.

The original identification of levulinaldehyde as an oxidation product was made by Whitby,[2] who gave no details in his report. We wish to report the following observations in confirmation of Whitby's identification. Treatment of the liquid condensed[3] from the reaction of 200 ml. of oxygen and 2-3 g. of rubber at 120° and 1 atm. with 2,4-dinitrophenylhydrazine reagent[4] yields a crude bis-dinitrophenylhydrazone whose X-ray diffraction pattern is indistinguishable from that of authentic levulinaldehyde bis-2,4-dinitrophenylhydrazone,[5]

(1) A. V. Tobolsky and A. Mercurio, *J. Am. Chem. Soc.*, **81**, 5535 (1959).
(2) G. S. Whitby, *India Rubber J.*, **63**, 742 (1922).
(3) E. M. Bevilacqua, *J. Am. Chem. Soc.*, **79**, 2915 (1957); **80**, 5364 (1958).
(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 4 ed., 1956, p. 111.
(5) C. L. Wilson, *J. Am. Chem. Soc.*, **70**, 1313 (1958).

and differs from that of the 2,5-hexanedione derivative. (Infrared spectra will not distinguish unequivocally between these two alternatives.)

Fractionation of a similar condensate on silica, without pretreatment, by the method of Bulen, Varner, and Burrell[6] yields a chromatogram with two major peaks (acetic and formic acids) and three minor peaks (two unidentified, one occurring at the position expected for levulinic acid). After passage of the crude reaction product over a silver oxide column[7] before fractionation, a new major peak appears at the position expected for levulinic acid. Its identification has been confirmed by comparison of the X-ray diffraction patterns of the silver salt and of the dinitrophenylhydrazone with those from authentic material.

Efforts to find 2,5-hexanedione in the neutral fraction after silver oxide treatment have not been successful. Control experiments showed that hexanedione was not oxidized to an acid by silver oxide at room temperature following the procedures used for oxidation of levulinaldehyde, or acid fractionation.

Gas-liquid chromatography on cyanoethylated glycerol, Apiezon L, or dioctyl sebacate–sebacic acid yields a large peak corresponding to levulinaldehyde. It gives evidence of only traces of material boiling higher. Hexanedione is readily separated from the aldehyde; if present at all as an oxidation product, it is formed in less than 5% of the yield of levulinaldehyde.[8]

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Received February 26, 1960

(6) W. A. Bulen, J. E. Varner, and R. C. Burrell, *Anal. Chem.*, **24**, 187 (1952).

(7) H. C. Bailey and J. H. Knox, *J. Chem. Soc.* (*London*), 2741 (1951).

(8) We are indebted to H. N. Campbell for X-ray diffraction comparisons and to R. R. Hampton and R. G. Kiley for gas chromatographic analyses. This is communication No. 190 from the Research Center of the United States Rubber Company.

Solvolysis of *S*-Benzoyl-8-mercaptoquinoline and the Spectrum of 8-Mercaptoquinoline

Sir:

The preparation 8-mercaptoquinoline *via* Edinger's method[1] involves the isolation of its *S*-benzoate. Although the ester when recrystallized from ethanol appears to be a reddish crystalline solid, the use of chloroform for recrystallization results in the formation of colorless crystals. The pure, colorless ester will slowly solvolyze in hydroxylic solvents as Banfield surmised.[2] We have found the solvolysis to follow pseudo first order kinetics in anhydrous methanol and ethanol. The specific reaction rate constant of the ester methanolysis at 20° is approximately 1.4×10^{-5} sec^{-1} whereas the rate of the corresponding ethanolysis is at least one order of magnitude slower. We are now engaged in a detailed study of the kinetics of the *S*-benzoate solvolysis in various hydroxylic solvents and in the presence of various metal cations to probe the effect of chelate formation on the reaction rate.

In connection with the reactions of 8-mercaptoquinoline and its derivatives it is interesting to note the dramatic solvent effect upon the long wave-length absorption of 8-mercaptoquinoline itself. Pure anhydrous 8-mercaptoquinoline is a mobile hygroscopic blue liquid which takes on a purplish hue as it becomes wet. The completely hydrated compound ($+2H_2O$) is a red crystalline solid. The color of the anhydrous material varies from red violet in *t*-butyl alcohol to orange in aqueous solutions. In acidic or basic aqueous media the solutions appear yellow. Measurements of the visible absorption spectra yield the following results:

Solvent	λ_{max}, mμ	ε (l./mole cm.)
H_2O	448	2032
CH_3OH	490	133
C_2H_5OH	503	43
n-C_4H_9OH	509	27
$(CH_3)_3COH$	528	17

The dramatic increase of the molar extinction with dielectric constant and the disappearance of the band in both acidic and basic aqueous solutions indicate that the species responsible is the dipolar ion (Ib). The dipolar ion would be formed in increasing concentration as a result of the shift of the equilibrium to the right with dielectric constant. The blue shift of the absorption band would seem to indicate an n-π transition of the dipolar form. If so, the unusually large molar extinction

Ia Ib

(1) A. Edinger, *Ber*, **41**, 937 (1908).

(2) J. E. Banfield, *J. Org. Chem.*, **25**, 300 (1960).

might reflect the greater degree of orbital overlap of the larger sulfur atom. An investigation on n-π transitions in other sulfur-containing compounds would be most interesting.

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