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Hindered Diphenoquinones: Diradicals of Oxygen[1]

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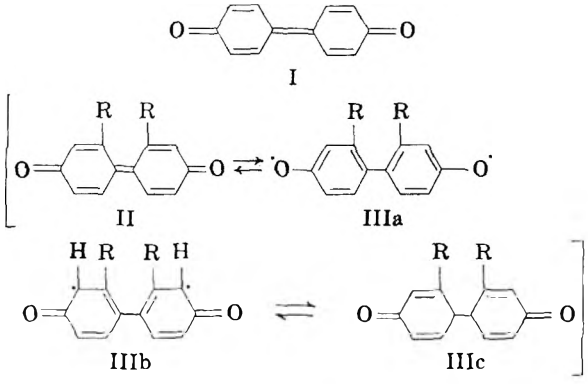
Attempts were made to prepare a diphenoquinone having substituents in 2,2′- positions in order to prevent the planarity of the molecule and get a diradical of oxygen. The 2,2′-dimethyl-5,5′-di-*t*-butyldiphenoquinone was prepared and was shown to be in equilibrium with a small amount of diradical. This compound slowly polymerizes.

It seems clear that the two rings of the diphenoquinone (I) are coplanar, the existence of the central double bond being responsible for this coplanarity. If this coplanarity is destroyed, the central double bond cannot exist and a diradical of oxygen might be expected. The coplanarity of the two benzene rings can be destroyed if one introduces in the 2,2′- positions any substituent which, by steric hindrance, obliges the rings to rotate from a common plane, thus allowing only the existence of a single bond between them.

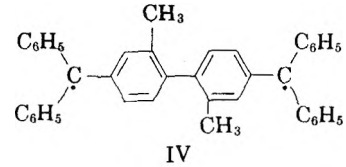


I

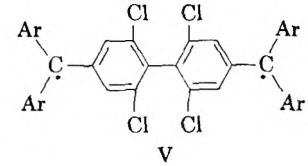
II ⇄ IIIa

IIIb ⇌ IIIc

The diradical III would be stabilized by resonance of the different limit forms IIIa, IIIb. In fact, such structures exist: the *p,p′*-diradical derived from Tchitchibabin's molecule in which are introduced in the 2,2′,6,6′- positions substituents such as methyl or chlorine, IV and V. These compounds isolated in the solid state by Theilacker[3] and Muller,[4] respectively, seem to be examples of diradicals resulting from noncoplanarity of the diphenyl skeleton. These products, almost colorless in the solid state, are deeply colored in solution (red, blue, or green).



IV



V

The existence of free radicals of oxygen has been definitely established in the mechanism of oxidation of phenols. The radicals VI, VII, VIII, IX,[5] and X have been proposed as intermediates in the oxidation of the corresponding phenols. The oxidation usually gives a dimer as the final product, for instance XI or XI′.[6]

Some of these free radicals (VII, VIII, IX, for

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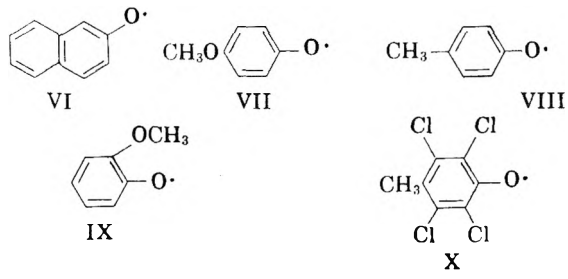
(3) W. Theilacker and W. Ozegowski, *Ber.*, **73**, 33, 898 (*1940*).

(4) E. Muller and H. Neuhoff, *Ber.*, **72B**, 2063 (1939); **74**, 807 (1941).

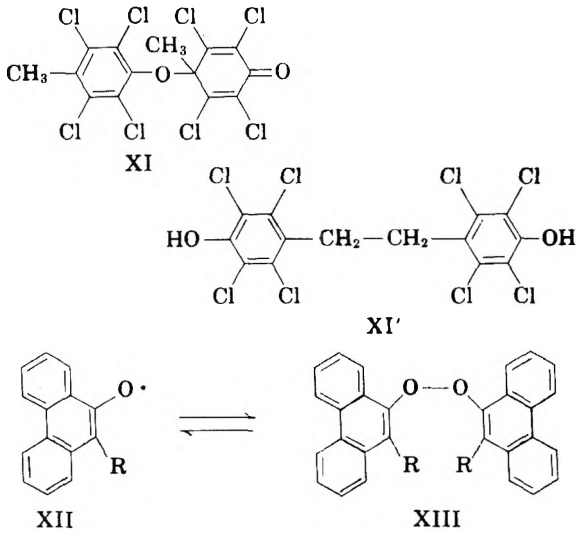
(5) S. Goldschmidt, *Ber.*, **55**, 3194 (1922).

(6) R. Pummerer, G. Schmidutz, and H. Seifert, *Ber.*, **85**, 535 (1952).



VI VII VIII IX X

example) made their appearance as a fugitive coloration during the reaction. Others exist in solution in a state of equilibrium with the dimer, for example the phenanthryl XII (R = OEt, Cl...) which exists in the solid state as a dimer XIII, dissociates partially in solution into a free radical (green).[5]

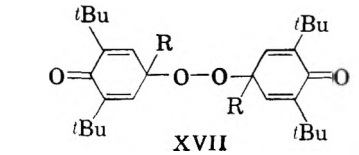


XI XI′ XII XIII

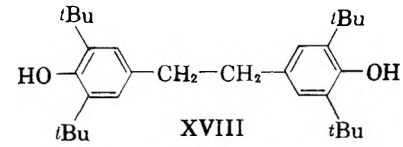
And recently, Muller[7] isolated a free radical of oxygen in the solid state. The tri-*t*-butylphenoxy (XVI) was obtained by oxidation of the corresponding phenol or by removal by silver of a halogen (chlorine or bromine) from the halogenated compound XV.

Muller explained the relative stability of this free radical by the steric hindrance introduced by the *t*-butyl groups which prevents the approach of reagents to the molecule. This free radical, deeply blue in the solid state, decolorized rapidly in the presence of air by formation of peroxide XVII.

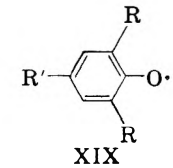
In the same way, Cook[8] prepared similar stable free radicals (XIX) and showed that these free radicals could exist when the *o*- and *p*- positions were substituted to prevent dimerization and when there was no hydrogen on the α-carbon. Thus, with α-hydrogen present, the 2,6-di-*t*-butyl-4-methyl-phenoxy gives the dimer XVIII.



XVII



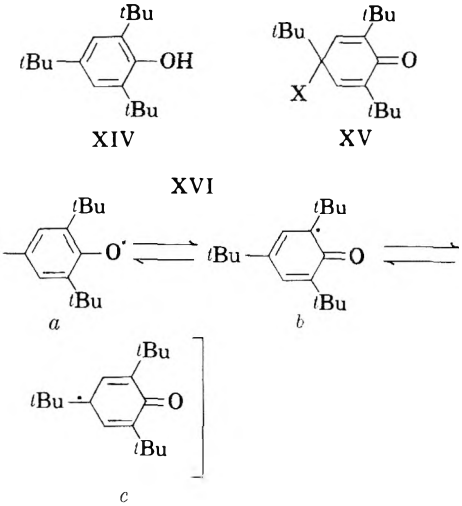
XVIII



XIX

R = *t*-amyl, R′ = *t*-amyl
R = *t*-butyl, R′ = methoxy
R = *t*-butyl, R′ = butoxy
R = *t*-butyl, R′ = ethoxy

All these facts encouraged the assumption that it should be possible to obtain a diradical such as III. As a matter of fact, the dianthrone XXa, which gives a yellow solution at room temperature, gives green solutions when heated to 265°. Some authors[9] explained this fact by the existence of the diradical form b, and LCAO-MO calculation[10] suggests that bianthrone would exist in a triplet state by rotation of one of the anthracene rings. On the other hand, some other compounds (XXI, XXII, XXIII, XXIV, XXV)[11] derived from 2,2′-disub-



XIV XV XVI a b c

(7) E. Muller and coworkers, *Ber.*, **87**, 922, 1605 (1954).

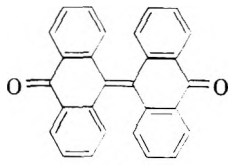
(8) C. D. Cook and coworkers, *J. Org. Chem.*, **18**, 261 (1953); *J. Am. Chem. Soc.*, **75**, 6242 (1953); *J. Am. Chem. Soc.*, **77**, 1783 (1955); *J. Am. Chem. Soc.*, **78**, 2002 (1956).

(9) W. T. Grubb and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **72**, 419 (1950); W. G. Nielsen and G. K. Fraenkel, *J. Chem. Phys.*, **21**, 1619 (1953); W. Theilacker, G. Kortum, and G. Friedheim, *Ber.*, **83**, 508 (1950).

(10) Matlow, *J. Chem. Phys.*, **23**, 152 (1955).

(11) N. A. Valyashko and M. M. Scherbak, *J. Gen. Chem. U.S.S.R.*, **8**, 1597 (1938); XXI: F. Henrich, *Ber.*, **71B**, 2049 (1938) [*Chem. Abstr.*, **33**, 165 (1939)]; F. Henrich, *Sitzber. physik. med. Sozietät Erlangen*, **71**, 199 (1939) XXII: C. V. Bordeianu, *Ann. sci. univ. Jassy*, **I, 23**, 240 (1937) [*Chem. Abstr.*, **32**, 5802 (1938)]. XXIII: G. Sanna and T. Zucca, *Rend. seminar. Fac. sci. univ. Cagliari*, **19**, 155 (1949) [*Chem. Abstr.*, **46**, 7087 (1952)]. XXIV: A. A. Levine, *J. Am. Chem. Soc.*, **48**, 797, 2719 (1926). XXV: F. D. Smith, U.S. Patent 2,449,088, Sept. 14, 1948 [*Chem. Abstr.*, **43**, 813c (1949)].

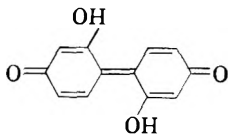
stituted diphenoquinone are claimed to have been obtained and are described as having a quinoid structure, but no real proofs of structure were given and no studies on the properties of these products have been reported.



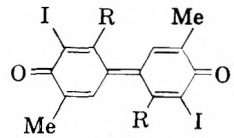
a

b

XX

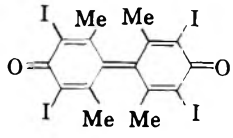


XXI

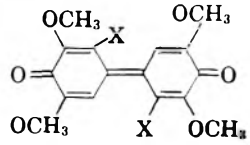


XXII

R = CH_3 or — $CH(CH_3)_2$

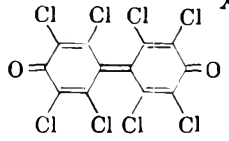


XXIII



XXIV

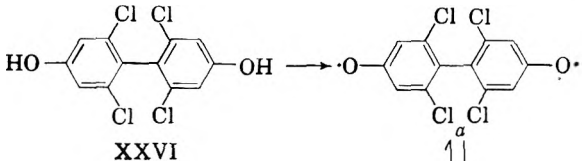
X = Br or Cl



XXV

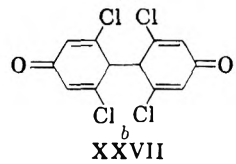
So we proceeded to the synthesis of a biphenol, 2,2′,6,6′-tetrasubstituted, without ambiguity in its constitution and potentially able to give by oxidation the expected diradical of oxygen.

Polychlorobiphenols and their oxidation. The diradical whose preparation was first attempted was the tetrachloro 2,2′,6,6′-diphenoxy XXVIIa which ought to result from the oxidation of the corresponding biphenol XXVI.



XXVI

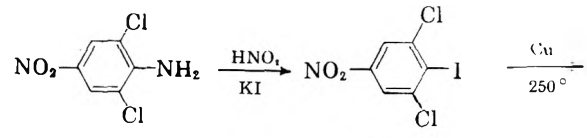
a



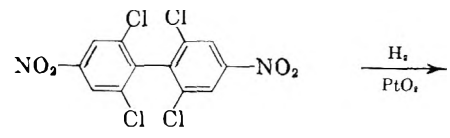
b

XXVII

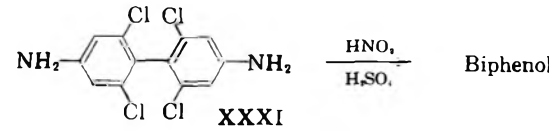
The method chosen for the synthesis of the biphenol is the following:



XXVIII XXIX



XXX

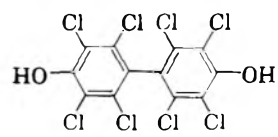


XXXI

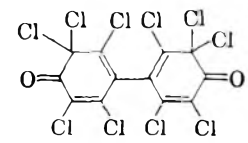
The compounds XXIX, XXX, and XXXI had been prepared by other authors using different methods, but the process used here gave better yields and the products obtained were much easier to purify than those obtained by the previous methods.

The structure of the biphenol was further confirmed by its spectrum (Fig. 1), similar to the spectrum of the pentachlorophenol and differing from the one of biphenol and 3,3′-dimethylbiphenol. The usual oxidizing agents were tried without success, the biphenol remaining unchanged. (Silver oxide[12] or lead dioxide in anhydrous ether or benzene, lead dioxide in moist ether,[5] ferric chloride in acetic acid, potassium permanganate in alkaline solution.) Potassium permanganate in acid solution completely destroyed the molecule, as was shown by U.V. examination.

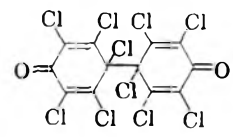
Then the action of chlorine was tried, expecting the formation of the octachlorobiphenol XXXII which, by further oxidation, might give the diradical XXXV. Chlorine in chloroform gave the expected octachlorobiphenol XXXII.



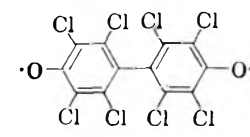
XXXII



XXXIII



XXXIV



XXXV

The structure of octachlorobiphenol XXXII was confirmed by its U.V. spectrum (Fig. 1), similar to the spectrum of the pentachlorophenol. Chlorination of either tetrachloro- or octachlorobiphenol in acetic acid solution gave a decachlorinated com-

(12) R. Willstätter and F. Müller, *Ber.*, **41**, 2580 (1908).

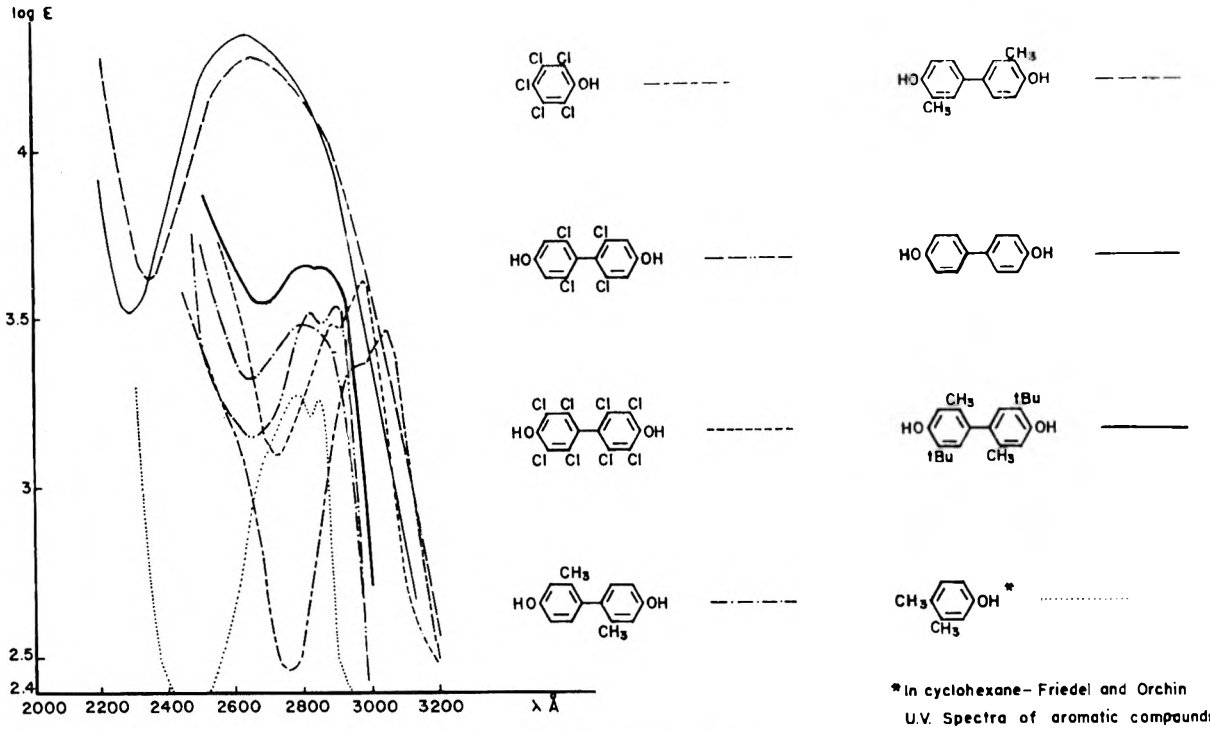


FIG. 1.—U.V. SPECTRA IN ALCOHOL

pound for which two structures were possible: XXXIII and XXXIV. Reaction with zinc and acid gave the octachlorobiphenol, showing that the diphenyl skeleton had been preserved.

An *o*-quinoid structure (XXXIII) was suggested by the U.V. spectrum (Fig. 2). The spectrum of the decachloro- compound is very similar to the spectrum of *o*-benzoquinone and quite different from the spectra of hexachlorophenol XXXVII and *p*-benzoquinone. In fact, the *o*-quinoid structure is more probable for steric reasons than the *p*-quinoid structure XXXIV.

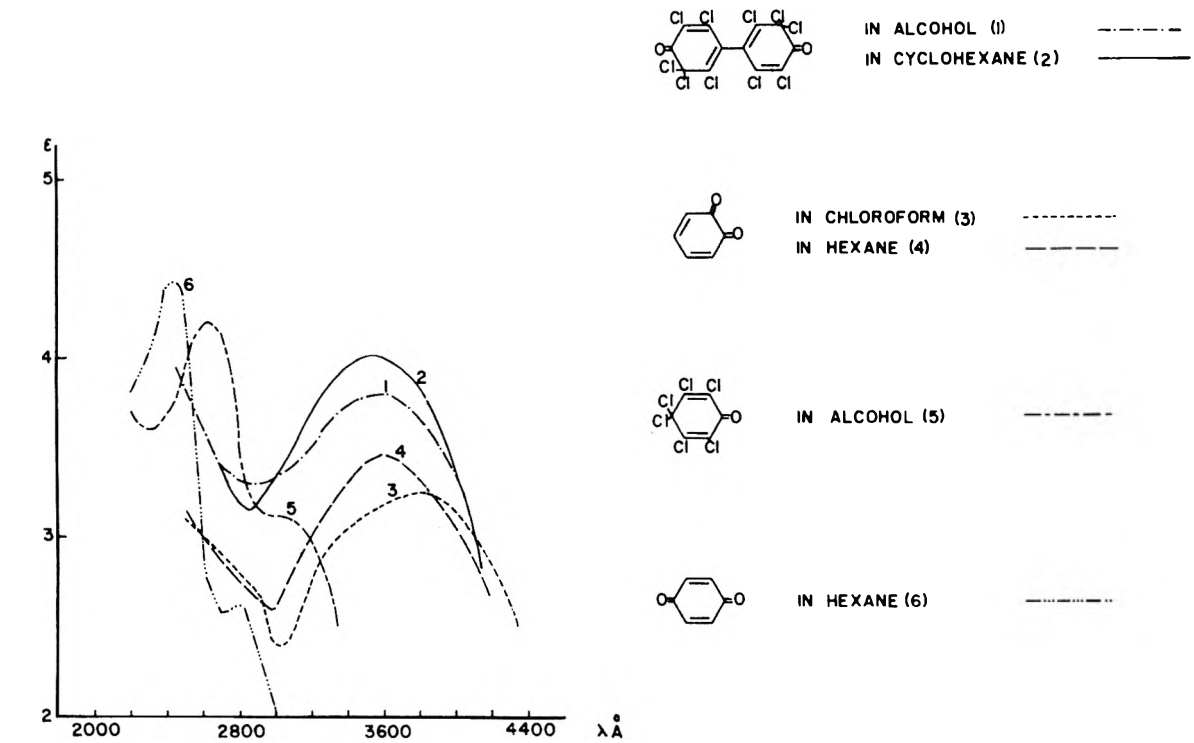
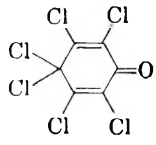


FIG. 2.—U.V. SPECTRA OF DECACHLORO COMPOUND AND ANALOGS. [See Friedel and Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, p. 77; Goldschmidt, *Ber.* **61**, 1868 (1928)]



XXXVII

It should be noted that the decachloro compound XXXIII is slowly reduced to octachlorobiphenol by alcohol at room temperature (complete reaction in approximately 24 hr.), showing the same behavior as the hexachlorophenol XXXVII toward this solvent. This reduction is approximately ten times faster with the diphenyl compound.

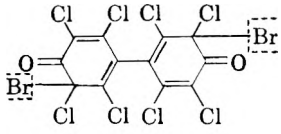
The 2,2′,3,3′,5,5′,6,6′-octachlorobiphenol seems even less sensitive toward oxidizing agents than the tetrachloro-compound.

None of the following reagents gave any color to the solution; that is to say, no formation of a radical: lead dioxide in moist ether or in benzene, alkaline potassium ferricyanide in benzene under nitrogen, potassium dichromate in boiling acetic acid with traces of sulfuric acid, potassium permanganate with sulfuric acid. In most cases, the biphenol was left unchanged. The action of aqua regia for one month at room temperature according to the method used by Smith,[11] reported to prepare the same product, was here completely unsuccessful; the starting material was recovered unchanged.

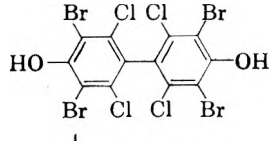
Thus, neither the diradical XXXV nor the diphenoquinone XXV could be obtained because of the strong resistance of this biphenol toward the oxidizing agents.

After these failures, another completely different method was tried. This method consisted in the removal of two extra atoms of chlorine from the decachloro-compound XXXIII by the action of silver in benzene solution. For this procedure we refer to the reaction used by Muller[7] to prepare the tri-*t*-butyl-phenoxy radical. In this case, however, after 18 hr. of agitation of the solution with active silver under pure nitrogen, the decachloro-compound XXXIII was recovered unchanged.

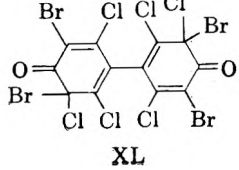
Since the two chlorine atoms seemed to be too tightly bound to the molecule, we tried to replace them by two bromine atoms, as in XXXVIII. This compound might be expected from bromination of the octachlorobiphenol, but the only product obtained by several procedures was a substance with the properties of a polymer. Next we tried bromination of the tetrachlorobiphenol to get XXXIX, followed by chlorination giving XL which possesses the desired chlorine and bromine on the same carbon atom.



XXXVIII



XXXIX



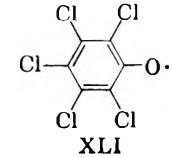
XL

The tetrabromo compound XXXIX was obtained by action of bromine on tetrachlorobiphenol. Then the chlorine was allowed to react in MeOH-AcOH[7] and even at −20° the bromine was replaced by the chlorine with production of the decachloro compound XXXIII previously described.

From all the foregoing observations the idea arises that perhaps the presence of the electronegative chlorine prevents the oxidation of the biphenol and the formation of the diradical.

A test of this notion was made by a study of pentachlorophenol and attempts to prepare the corresponding radical (XLI).

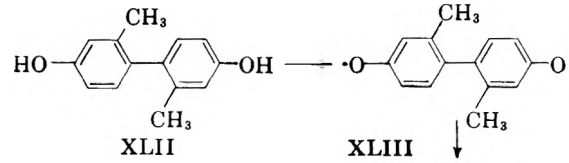
Most of the strong oxidizing agents[13] transform pentachlorophenol into chloranil by removal of *p*-chlorine. An analogous reaction is observed with *sym*-trichlorophenol.[14] Such results could not be expected for the octachlorobiphenol.



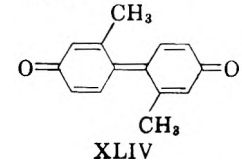
XLI

The lead dioxide in moist ether at 0° gave no color and neither did potassium ferricyanide in alkaline solution, differing in this way from tri-*t*-butylphenol. Pummerer reports that the dehydrotetrachloro-*p*-cresol, X-XI, a strong oxidizing agent, was without action on pentachlorophenol.[6]

2,2′-Dimethyl-p,p′-biphenol and its oxidation. So we tried to prepare a diradical free from chlorine and for this purpose the 2,2′-dimethyl-*p*-biphenol XLII was prepared. The angle between the two phenyl rings ought to be smaller than with four chlorine atoms and it may be expected that some stabilization of the diradical XLIII by the methyl groups should be apparent.



XLII XLIII

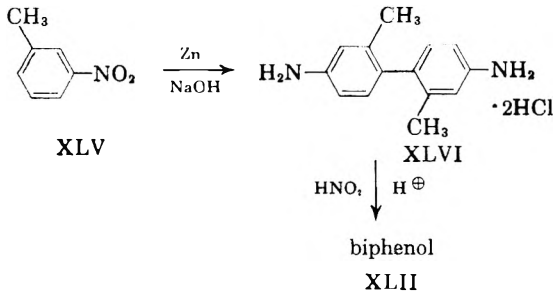


XLIV

The 2,2′-dimethylbiphenol was prepared in the following way:

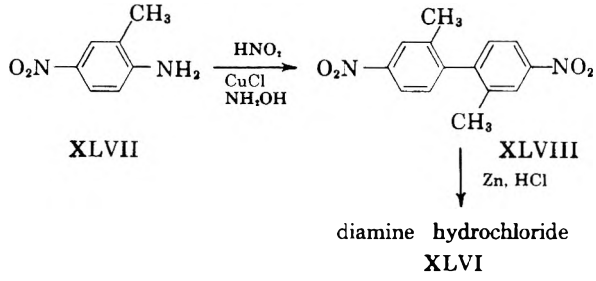
(13) Beilstein, VI, 194.

(14) W. H. Hunter and M. Morse, *J. Am. Chem. Soc.*, 48, 1615 (1926).



The alkaline reduction of *m*-nitrotoluene by zinc and alcohol gives, directly after acidification, a very good yield of the diamine which is transformed into biphenol in the usual way.

The diamine XLVI has been prepared in another way:



XLVI

In contrast with the other biphenols, an easy oxidation was possible, although it was not possible to see any color of a diradical. An insoluble brown polymer was formed by action of potassium ferricyanide. This polymer was mostly absorbed by lead dioxide when using this reagent. The same result was observed even at low temperature (−80°) under pure nitrogen.

From these facts we were led to believe that the biphenol XLII was oxidized, presumably with formation of the diradical, but that this reacted further to give dimers or polymers.

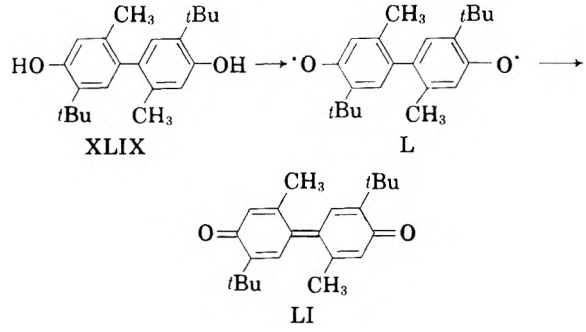
2,2′-Dimethyl-5,5′-di-t-butylbiphenol and its oxidation. As suggested by Muller,[7] two *t*-butyl groups in positions ortho to the hydroxyl increase the stability of the corresponding free radical by steric hindrance, in preventing the approach of the reagents to the molecule.

So, in order to stabilize the diradical (XLIII) we tried to introduce four *t*-butyl groups in the 3,5,3′,5′-positions of the 2,2′-dimethylbiphenol (XLII). According to the method of alkylation of phenol,[15] isobutylene was allowed to react with the dimethylbiphenol at 70° in benzene solution with a trace of sulfuric acid. Under these conditions, only two *t*-butyl groups could be introduced in the 5,5′-positions apparently because of the hindrance of the two methyl groups preventing the substitution on the 3,3′- positions.[16]

(15) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

(16) M. J. Schlatter and R. D. Clark, *J. Am. Chem. Soc.*, **75**, 361 (1953); E. E. Burgoyne, T. E. Close, and D. K. Watson, *J. Org. Chem.*, **20**, 1508 (1955).

The 2,2′-dimethyl-5,5′-di-*t*-butylbiphenol, in accordance with the observation by Stillson[15] for similar hindered phenols, is not soluble in dilute alkali and could be purified from other phenols by use of this property. Its spectrum (Fig. 1) is similar to the spectrum of the 2,2′-dimethylbiphenol, showing that the two benzene rings are not coplanar.



In contrast to the other biphenols prepared above, this one gives deeply colored solutions with oxidizing agents. Thus, with lead dioxide in moist ether or in benzene, we readily got a deep red solution stable several hours. The same result was obtained with alkaline potassium ferricyanide.

According to our hypothesis, these solutions could contain the diradical (L) or the quinone (LI) or a mixture of the two products in equilibrium L ⇌ LI, and/or products of polymerization.

In fact, studies of electronic paramagnetic spin resonance (ESR)[17] and optical spectra of these solu-

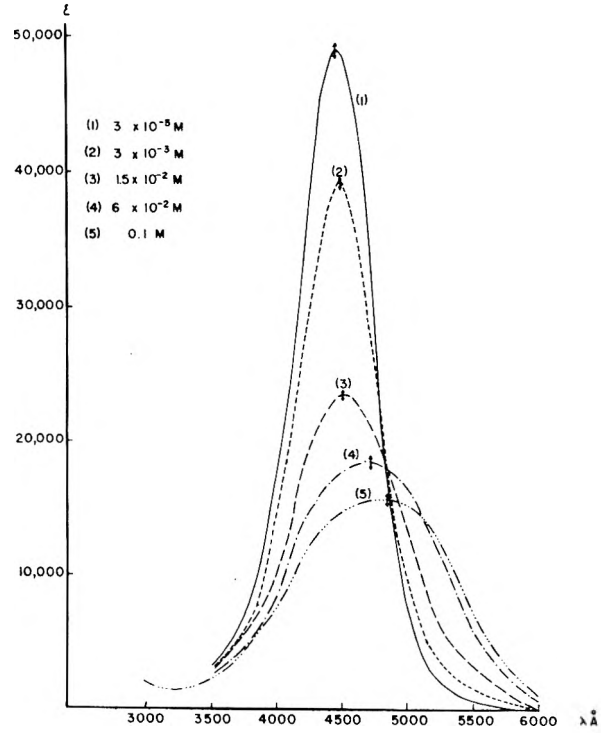


FIG. 3.—SPECTRA OBTAINED BY OXIDATION WITH LEAD DIOXIDE UNDER VACUUM AT DIFFERENT CONCENTRATIONS OF BIPHENOL IN BENZENE

(17) J. E. Werz. *Chem. Revs.*, **55**, 830 (1955).

tions showed that the reaction of oxidation was a complex phenomenon involving several steps. Most of this study was done in benzene solution with lead dioxide as oxidizing agent. The solutions obtained were somewhat more stable when free from oxygen; therefore, many experiments were carried out under nitrogen or under vacuum.

A solution of biphenol in benzene was shaken with lead dioxide until the reaction was complete. This was indicated when the principal absorption band of the spectrum reached an apparent maximum (about 15 min.). Results, shown in Fig. 3, demonstrate that the reaction follows a different course when it is done in dilute or in concentrated solution.

In dilute solutions (3×10^{-5} mol./l.) the absorption spectrum of the reaction product exhibits one band (Fig. 3: λ_{max} = 4440 Å, ϵ_{max} approximately 49,000), indicating that there is only one compound in the solution which is, as it will be shown later, the hindered diphenoquinone LI. When the concentration of the solution is increased (Figs. 3 and 4), λ_{max} of this band is shifted toward the longer wave length (4830 Å) and ϵ_{max} decreases considerably and settles for a saturated solution of the starting diphenol to a value of 16,000 (Fig. 4). A new maximum becomes apparent at 5000 Å producing a broadening of the entire absorption (Curve 5, Fig. 3). It is apparent that a polymerization of the hindered quinone LI occurred with the increase of the concentration.

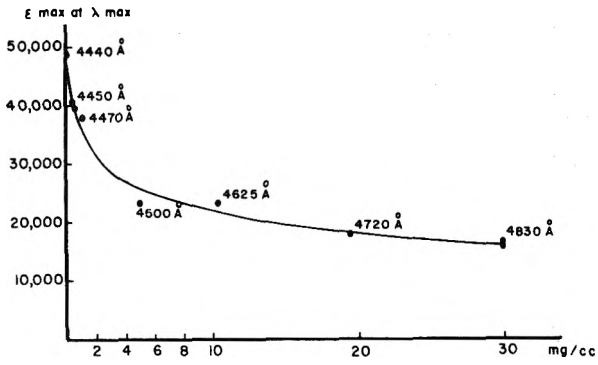


FIG. 4.—APPARENT ϵ_{max} AS A FUNCTION OF CONCENTRATION OF THE REACTION; VALUES CORRESPONDING TO CURVES OF FIG. 3.

This study will, therefore, be divided into two parts: (1) study of the hindered diphenoquinone (produced in dilute solution), and (2) study of the polymerization products (in concentrated solution).

(*1*) *Hindered diphenoquinone* (*dilute solutions*). Several lines of evidence were used in establishing the structure of this compound.

In Fig. 5 optical spectra of this quinone LI, diphenoquinone I, 3,3′-dimethyldiphenoquinone, Tchitchibabin's hydrocarbon and hindered Tchitchibabin's hydrocarbon IV are compared. From the behavior of the spectra we can be confident that dilute solutions ($3 \times 10^{-5}M$) contain almost exclusively the quinone LI.

Such a hindered diphenoquinone should have a higher oxidation potential than diphenoquinone itself. This was established by the reaction of biphenol with the hindered quinone:

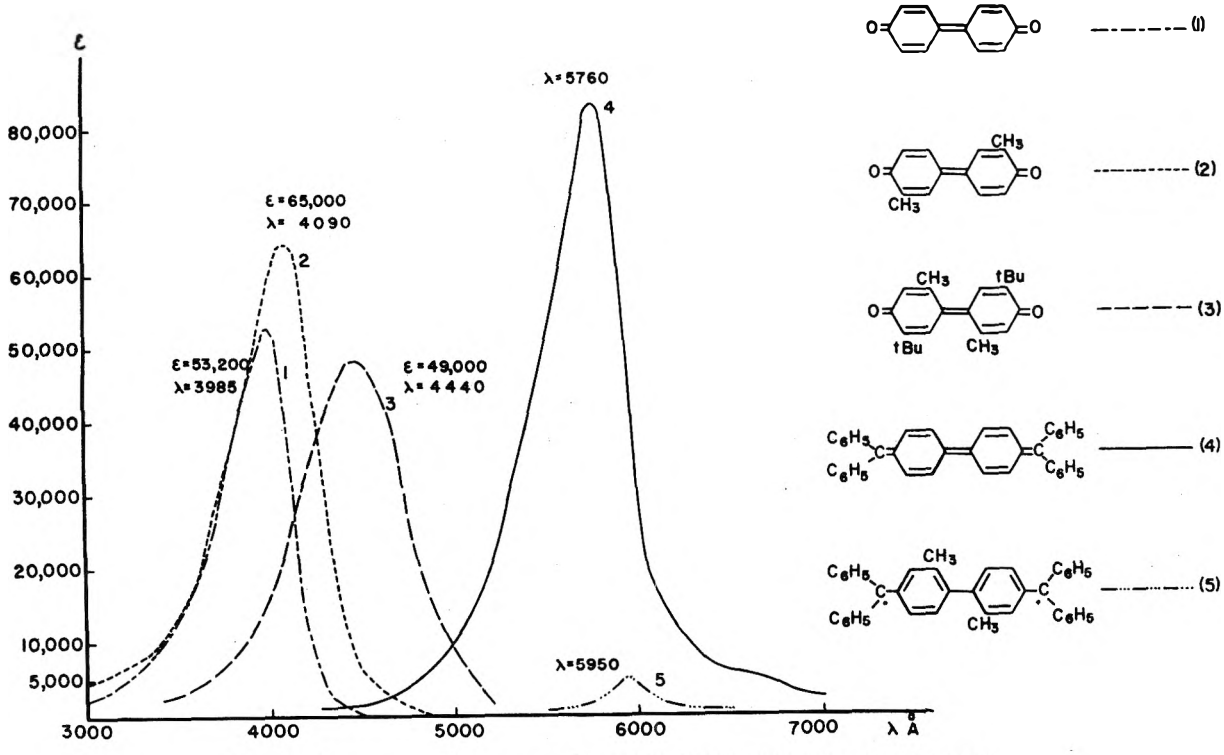
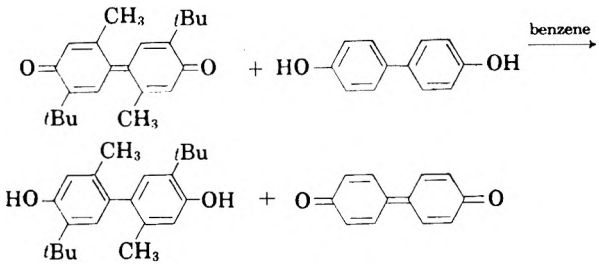


FIG. 5.—SPECTRA IN BENZENE OF HINDERED DIPHENOQUINONE AND ANALOGS



The exchange between the two compounds takes place in a few hours in benzene-ether solution with production (according to the spectrum, Fig. 6a) itself or with biphenol XLIX, giving dimers LIII and trimers LV, LVII with a quinoid structure. Several facts support this suggestion:

(a) The 390 Å shift of the absorption band toward the red and the decrease by two thirds of the corresponding ϵ_{max} value from their value in the dilute solution.

(b) The titration of oxidation equivalents by sodium iodide and thiosulfate gave a value of 0.24 to 0.52 per molecule of starting biphenol. The diphenoquinone LI would give 2 equivalents per molecule and the trimer LIV should give 0.66.

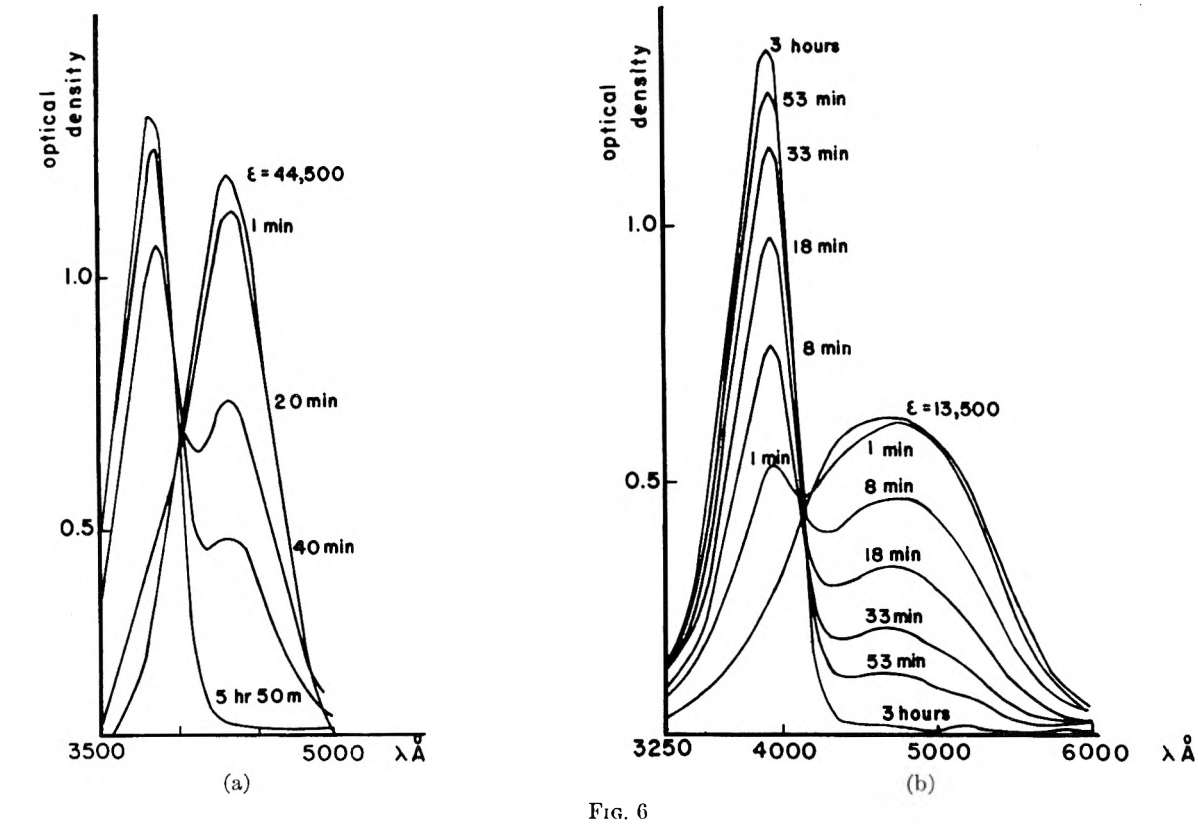


FIG. 6

(a) Action of biphenol (3 mol.) on the hindered diphenoquinone (1 mol.) in benzene. Quinone prepared in dilute solution.
(b) Action of biphenol (7 mol.) on the so-called trimer quinone (1 mol. monomeric unit) in benzene. Trimer prepared in concentrated solution.

of 0.86 molecule of diphenoquinone per molecule of oxidized hindered biphenol (or 0.95 per molecule of apparent hindered quinone formed).

The hindered diphenoquinone LI, according to our hypothesis, is supposed to be in equilibrium (LI $\rightleftharpoons$ L) with the diradical L. This radical could be observed directly only in a more concentrated solution (10^{-3} mol./l., Curve 2, Fig. 3. ϵ_{max} = 39,600) by ESR studies. A weak signal (G = 2) was obtained corresponding to a content of about 1 free electron for 1000 to 2000 molecules.

(2) *Polymerization products (concentrated solutions).* We have mentioned above the possibility of a polymerization in concentrated solutions. The molecule of diphenoquinone LI is able to react with

(c) The products of the iodide reduction are weakly colored, possess a spectrum very similar to the starting biphenol, have a very low solubility, and cannot be sublimed, thus differing from starting biphenol.

(d) The action of biphenol in benzene, as above for the diphenoquinone LI, gave a similar result (Fig. 6b), that is to say, reduction of the quinoid polymers with simultaneous formation of diphenoquinone. The reaction established the diphenoquinoid structure of these polymeric compounds; 0.32 to 0.53 molecules of diphenoquinone were formed per molecule of starting hindered biphenol (0.64 to 1.06 oxidation equivalent).

The discrepancy between these values and the

one found in experiment (b) can be explained by the presence of varying amounts of peroxides due to varying conditions in the two experiments.

(e) The successive polymerization reactions which occur during the oxidation of the hindered biphenol could be realized in several separated steps with production of some of the hypothesized intermediate compounds (Figs. 7, 8, and 9).

To a dilute solution of monomeric quinone LI (λ_{max} 4440, Σ_{max} 44,000, Curve 1, Fig. 8) was added a solution of hindered biphenol (1 mol. for 1 mol.). The solution was slowly decolorized at room temperature and after 6.30 hr. (Curve 2, Fig. 7) 85% of the quinone had disappeared. (The reaction could be accelerated by heating at 50–70°.) At the same time, a solution of quinone LI alone (at the same total molar concentration) decayed by only 22% (Curve 1, Fig. 7).

The resulting decolorized solution, supposed to contain the dimer LII, (Fig. 9) was shaken 2 min. with lead dioxide, resulting in formation of an orange solution (λ_{max} 4470, ϵ_{max} = 25,000, Curve 2, Fig. 8), corresponding to the dimer quinone LIII.

Then to this solution was added, once more, the hindered biphenol (1 mol. for 1 mol. of dimer), resulting in the fading of the solution. The reaction was slower (Curve 4, Fig. 7) than the first one (about one half) due to the hindrance of one of the functions of the diphenoquinone in the compound LIII.

Then this solution, supposed to contain the trimer LIV, was shaken 2 min. with lead dioxide and gave

---------- Decay of the hindered monomeric diphenoquinone (LI)

———————— Action of 1 mol. of hindered biphenol on 1 mol. of hindered biphenoquinone

-·-·-·-·-·- Decay of the so called dimer diphenoquinone (LIII)

—·—·—·—·— Action of 1 mol. of hindered biphenol on 1 mol. of dimer diphenoquinone

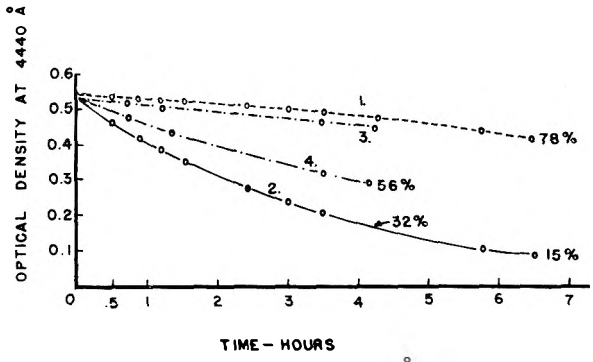


FIG. 7.—OPTICAL DENSITY AT λ = 4440 Å AS A FUNCTION OF TIME IN BENZENE AT ROOM TEMPERATURE

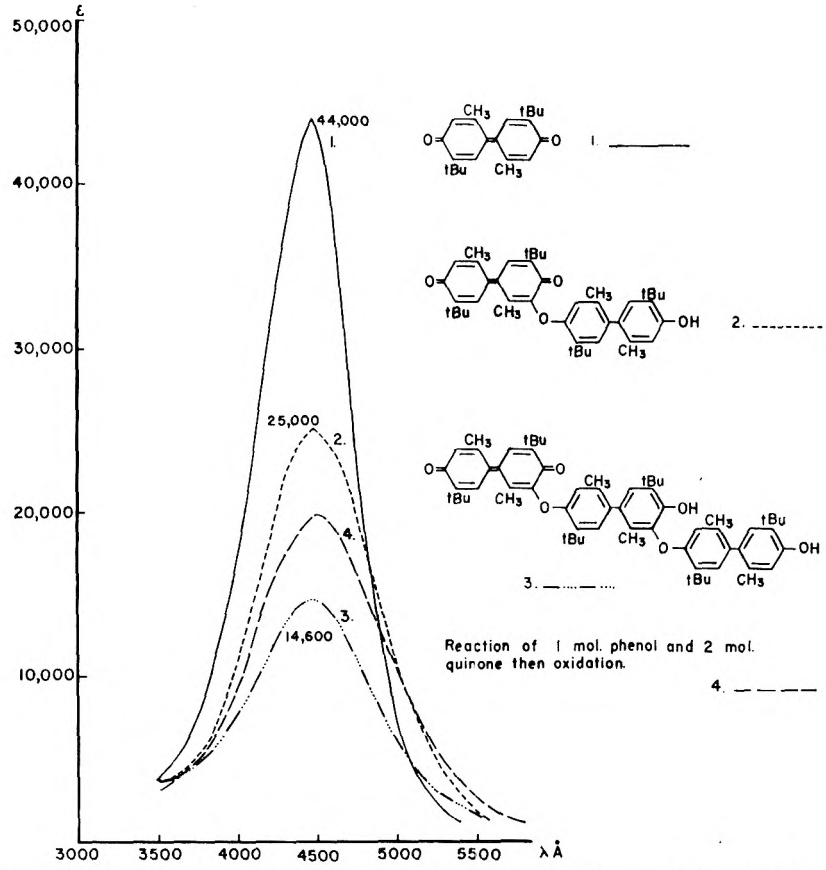


FIG 8.—SPECTRA IN BENZENE OF THE HINDERED QUINONES, CALCULATED WITH M = 326

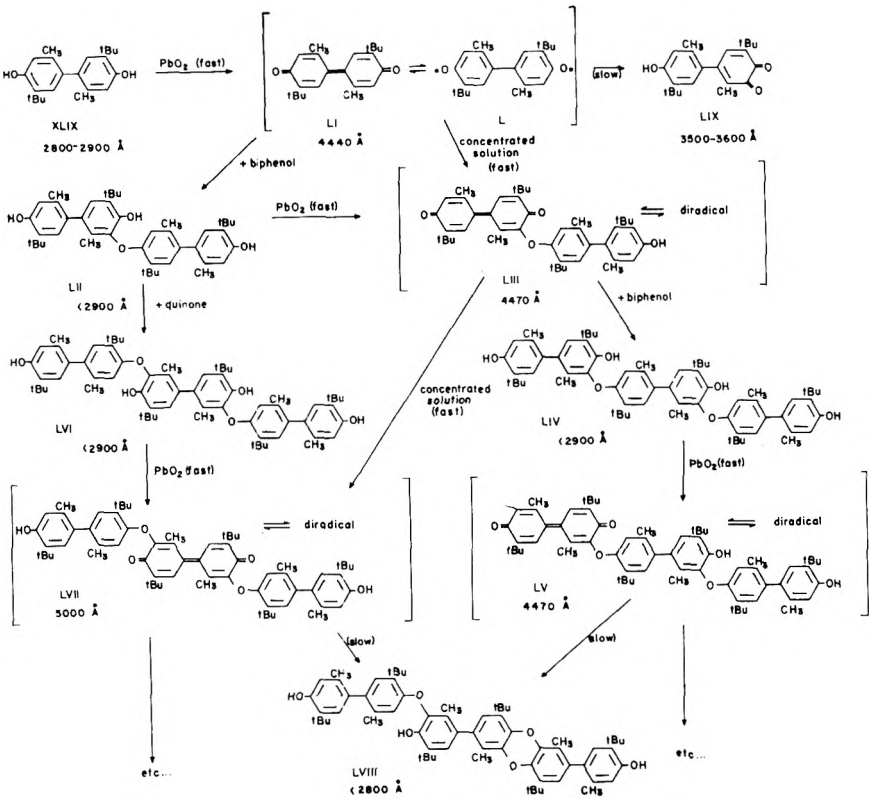


FIG. 9.—OXIDATION OF HINDERED PHENOL

an orange solution (λ_{max} 4470, ϵ_{max} = 14,600, Curve 3, Fig. 8). The three successive values of ϵ_{max} (44,000, 25,000 and 14,600) are in fairly good agreement with the formation of the monomer LI, dimer LIII, and trimer LV quinones.

The absorption observed at 5000 Å in very concentrated solutions (Curve 5, Fig. 3) should be attributed to a trimer quinone such as LVII, which can be produced when an excess of quinone LI is present in the solution (Fig. 9, LI → LIII → LVII or LI → LII → LVI → LVII).

This was partially accomplished in dilute solution by allowing 1 molecule of hindered biphenol to react with 2 molecules of quinone LI. After almost complete bleaching of the solution corresponding to the formation of LVI and LIV, the oxidation as above gave an orange solution. This solution (λ_{max} 4500, ϵ_{max} = 19,800, Curve 4, Fig. 8) exhibits a definite increase of absorption at 5000 Å.

Free radical content. The presence of free radicals in solutions containing these quinoid compounds (LIII, LV, LVII) was shown, as for the monomeric quinone, by ESR studies. A signal (G = 2) was found, indicating a content of about 1 free electron for 800 monomeric units, a value somewhat higher than for the monomer. This would correspond to one electron for the approximately 270 molecules of trimer LVII.

Compounds with such a quinoid structure should be in equilibrium with the corresponding diradical and therefore the ESR signal should show a dependency on temperature, that is to say, an increase of diradical content by heating and a decrease in cooling (Nielsen and Fraenkel).[9] Such a reversible increase of ESR signal between 30° and 100° was found (Fig. 10) until the quinone was completely transformed by polymerization and cyclization (LVIII). This transformation takes place faster than at room temperature.

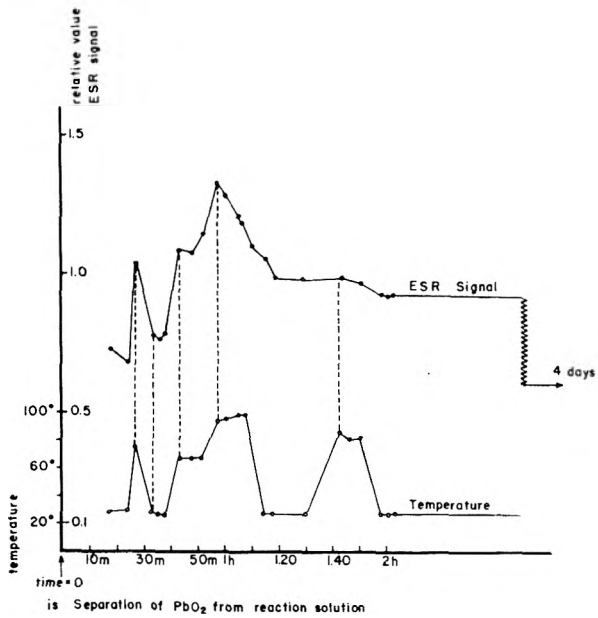


FIG. 10.—INFLUENCE OF TEMPERATURE ON THE INTENSITY OF THE ESR SIGNAL OF THE HINDERED QUINONE

Unfortunately, such an effect could be studied only on the polymers (LIII, LV, LVII) and not on the quinone (LI) in the very dilute solution, because of the weakness of the signal.

Decay of the compounds (Figs. 11 and 12). According to the ESR signal, the proportion of the free radical is higher in concentrated solution and reaches a value of about 1 free electron for 600 to 1000 monomeric units (average 800). When the concentrated solution is freshly oxidized, the signal is even higher (1 electron for 200 units), but decays in less than half an hour and drops to the rather stable value of 1 electron for 800. During the same time the ϵ_{max} of the optical spectrum is decreasing more slowly (Fig. 12). This discrepancy between the behavior as the function of time of the ESR signal and optical absorption would indicate the initial presence of some unstable free radical produced during the reaction (probably a monoradical). After decay, the signal of this radical can be regenerated by addition of lead dioxide.

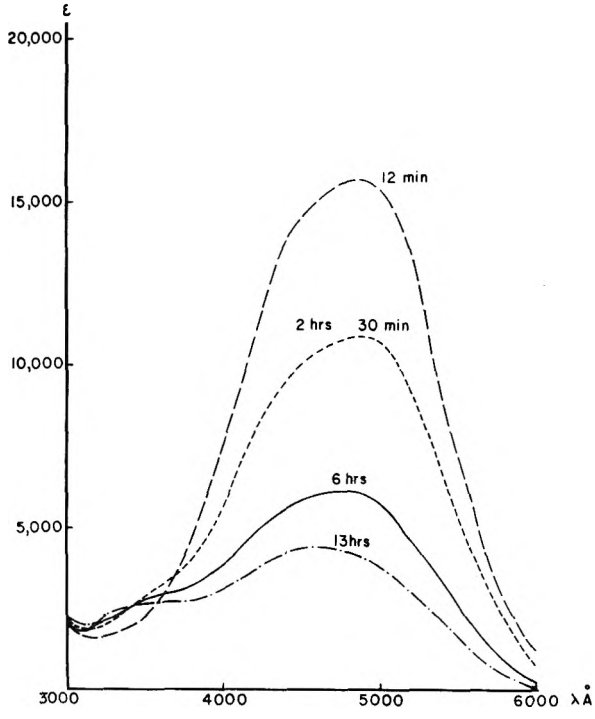


FIG. 11.—DECAY OF THE HINDERED QUINONE IN A CONCENTRATED BENZENE SOLUTION ($^1/_{10}$ MOL./L.) UNDER VACUUM AS A FUNCTION OF TIME (SPECTRA IN BENZENE)

All these solutions are decolorized after 1 or 2 days. This fading corresponds to the disappearance of the main band (4440–5000 Å, Fig. 11).

The spectra shown in Fig. 13 (Curves 3, 4, and 5) correspond to transformation products from various sources and show the absorption band of phenol (2800 to 2900) and a general increase of absorption below 2800 as compared to the absorption of the quinone (Curve 1) and of the biphenol (Curve 2). Sometimes a peak (Fig. 11 and 13) is found around 3400–3600 Å, which could indicate formation of an orthoquinone LIX by oxidation.

Attempts to isolate quinones as solids. All the above experiments were carried out in solutions. Some attempts were made to prepare a solid sample from 0.01*M* solution.

One obtains, in all cases, a red glass, giving, in chloroform, a spectrum similar to the one of Curve 5, Fig. 3, corresponding to the structure LVII. This red glass has a somewhat higher content of free radical ($^1/_{100}$, G = 2.0). It decays rapidly in the presence of air, more slowly in vacuum, giving a yellow powder. The ESR signal can still be observed, approximately $^1/_{300}$, in the almost completely transformed material (Curve 3, Fig. 13), indicating the trapping of free electrons in the polymer, which would have a structure derived from LVIII. The analysis of the red glass is in agreement with the theory.

Fig. 9 gives a proposal for the complete scheme of oxidation and polymerization. It is a hypothesis which fits quite satisfactorily all of our various observations. The results demonstrate that as few

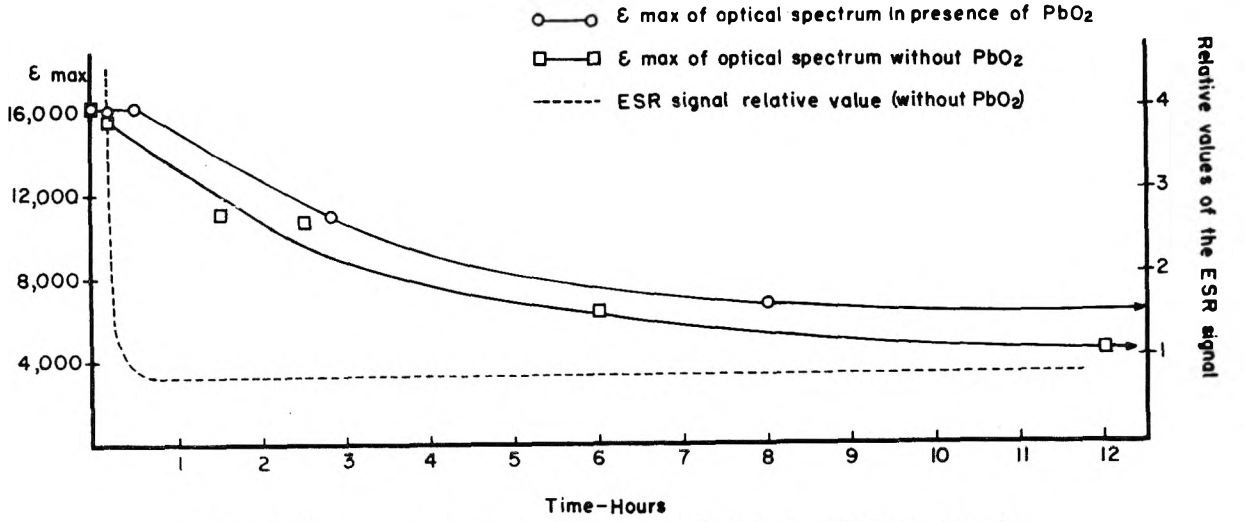


FIG. 12.—DECAY OF QUINONE AND RADICAL AS A FUNCTION OF TIME ($^1/_{10}$ MOL./L.)

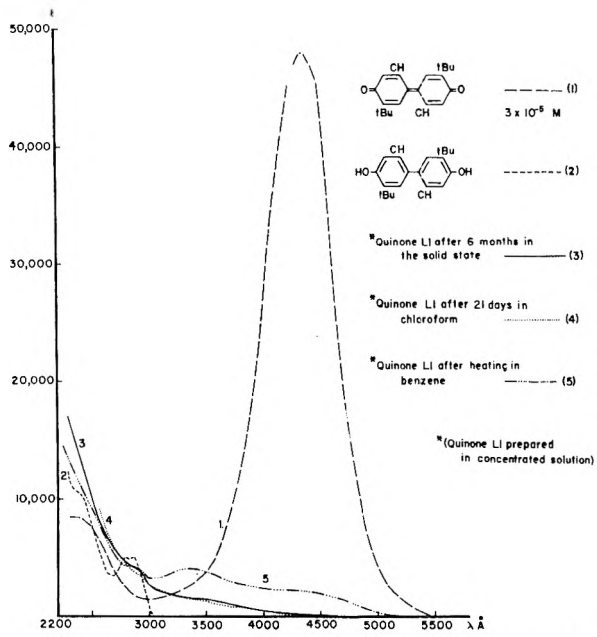


FIG. 13.—SPECTRA IN ETHER. Compounds of transformation of hindered quinone, compared to hindered quinone and hindered biphenol.

as two ortho-methyl groups in diphenoquinone provide sufficient steric hindrance to coplanarity to raise the energy of the quinone to the point where there is an appreciable amount of oxygen diradical in equilibrium with it at room temperature. Presumably if the reactivity of the oxygen diradical could be further reduced by two additional ortho-*t*-butyl groups it should be possible to obtain the diradical in appreciable amounts. In fact, such a diradical should exceed in stability the phenoxy monoradicals of Muller and Cook.

EXPERIMENTAL

Preparation of 3,5-dichloro-4-iodonitrobenzene.[18] A solution of 50 g. of 2,6-dichloro-4-nitroaniline (Kodak) in 165 cc. concentrated sulfuric acid was cooled to 0°C. To another 165 cc. of concentrated sulfuric acid were slowly added 17.5 g. $NaNO_2$, care being taken to keep the temperature below 40°, and the resulting solution of nitrosylsulfuric acid was cooled to 0°C. The two solutions were mixed and allowed to stand 0.5 hr. Then, 600 cc. of H_3PO_4 (85%) were added at such a rate as to keep the temperature below 5°C. (1.5 hr.). The yellow solution was allowed to stand 0.5 hr. at 0°, 1 g. of urea was added, and the solution was poured into one liter of ice water containing 42 g. of potassium iodide. The decomposition of the diazo compound produced much foam, and the iodo compound precipitated as a light brown product. After 1 hr. the precipitate was filtered, washed with water, and recrystallized from alcohol. Yield: 63 g. (82%), m.p. 151–153°.

2,2',6,6'-Tetrachloro-4,4'-dinitrodiphenyl. This compound had previously been prepared by Ridge[19] by deamination of 2,6-dichloro-4-nitroaniline, but with poor yields. A different procedure was used: 40 g. of 3,5-dichloro-4-iodonitrobenzene were melted in a large test tube at 240–250°, and 0.5 g. of bronze copper was added. The reaction caused the mixture to boil and it was sometimes necessary to cool it. The rest of the copper (15 g.) was slowly added over a period of 0.5 hr., the temperature being kept at 250–260°. The mixture was extracted, while still hot, with boiling benzene. The solution was chromatographed on alumina to eliminate the tars. The product obtained was contaminated with a yellow oil and was recrystallized from AcOH, yielding 9.5 g. of yellow crystals (37%), m.p. 181–182°.

2,2',6,6-Tetrachlorobenzidine. This compound had been previously prepared by benzidine rearrangement[20,21] of 3,3',5,5'-tetrachlorohydrazobenzene with H_2SO_4 in very poor yield. An attempt to prepare this compound by the reduction of the 2,2',6,6'-trichloro-4,4'-dinitrodiphenyl by zinc and acid (AcOH, HCl) in various solvents (AcOH, EtOH) gave a product which was impossible to crystallize. However, catalytic hydrogenation (PtO_2) of this product gave a pure crystalline benzidine in good yield. The hydrogenation was carried out using 390 mg. PtO_2, 600 mg. dry Na_2SO_4, 200 cc. cyclohexane, and 2 g. of the dinitro compound. The theoretical quantity of hydrogen was taken up in 2 hr., giving a light yellow solution. The catalyst was filtered off, washed several times with ether, and then the combined solutions were concentrated; 1.37 g. of tetrachlorobenzidine (light yellow needles) were obtained. Yield: 81%, m.p. *ca.* 207°. After purification, the melting point was raised to 212–213°. The benzidine gave a dihydrochloride and a diacetyl derivative (acetylation with acetic anhydride and pyridine on a steam bath, crystallization from AcOH), m.p. 314°. Titration of the diamine was done by acetylation.[22] Result: 1.98 amino groups.

Anal. Calcd. for $C_{12}H_8Cl_4N_2$: C, 44.75; H, 2.5; Cl, 44.04; N, 8.69. Found: C, 45.03; H, 2.74; Cl, 42.64; N, 8.97.

Diacetylated derivative. Calcd. for $C_{16}H_{12}Cl_4N_2$: C, 47.31; H, 2.97; Cl, 34.92; N, 6.89. Found: C, 47.52; H, 2.95; Cl, 34.70; N, 7.03.

2,2',6,6'-Tetrachloro-4,4'-biphenol. The diamine (1 g.) was dissolved in concentrated H_2SO_4 (20 cc.) and cooled to 0°C. $NaNO_2$ (450 mg.) was slowly dissolved in concentrated H_2SO_4 (20 cc.) at a temperature below 40°C. The two solutions were mixed at 0°C., 35 cc. H_3PO_4 (85%) were added slowly so that the temperature remained below 5°C. After 1 hr., this solution was poured into aqueous H_2SO_4 (110 cc. acid for 140 cc. water), and the acidic solution was boiled 12 min. and then poured onto ice. A precipitate was obtained and the product was extracted from the suspension with ether; the ether solution was then extracted several times with 5*N* NaOH, and the product was precipitated from the reddish alkaline solution by the addition of dilute HCl. The product obtained was extracted with ether, the resulting ether solution was washed with water, dried, and the ether was removed under vacuum. A yellow oil was obtained which crystallized slowly. The crude product was purified by sublimation (160°/1 mm.). Yield: 760 mg. (76%), m.p. 185–186°, after resublimation, 186°.

Anal. Calcd. for $C_{12}H_6Cl_4O_2$: C, 44.48, H, 1.86; Cl, 43.77. Found: C, 44.55; H, 2.01; Cl, 43.75. The titration of the tetrachlorophenol by alkali gave 1.98 phenolic hydroxyl groups.

Diacetyl derivative (pyridine, acetic anhydride, purification in acetic acid), m.p. 164–165°.

2,2',3,3',5,5',6,6'-Octachloro-4,4'-biphenol. This compound (XXV) has been described by Smith[11] (XXV) but it is believed to be a mixture of different octachlorobiphenols. Here, a different method of preparation was used. The tetrachlorobiphenol (0.5 g.) was dissolved in $CHCl_3$ (30 cc.). A rapid current of chlorine was passed through the solution

(18) H. A. J. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

(19) D. Ridge, *J. Chem. Soc.*, 734 (1947).

(20) F. L. W. van Roosmalen, *Rec. trav. chim.*, **53**, 375 (1934).

(21) R. B. Carlin and W. D. Forshey, *J. Am. Chem. Soc.*, **72**, 793 (1950).

(22) S. Siggia, *Quantitative Organic Analysis Via Functional Groups*, John Wiley and Sons, Inc., New York, 1949, p. 5.

for 10 min. The excess chlorine and chloroform were removed under vacuum. The crystalline residue was purified by sublimation (200°/1 mm.), to give 660 mg. (95%), m.p. 237–237.5°; pure product, m.p. 238°.

Anal. Calcd. for $C_{12}H_2Cl_8O_2$: C, 31.2; H, 0.43; Cl, 61.4. Found: C, 31.07; H, 0.69; Cl, 61.42.

The diacetyl derivative was prepared with hot acetic anhydride and a drop of H_2SO_4 and recrystallized from acetic acid, m.p. 195°.

Anal. Calcd. for $C_{16}H_6Cl_8O_4$: C, 35.2; H, 1.1; Cl, 51.96. Found: C, 35.36; H, 1.27; Cl, 51.84.

2,2',3,3,3',3',5,5',6,6'-Decachloro-3,3',4,4'-tetrahydro-4,4'-diketodiphenyl.—The tetrachlorobiphenol (250 mg.) was dissolved in acetic acid (25 cc.) and a rapid current of chlorine was passed through the hot solution until it was saturated (0.5 hr.). Then 7 cc. of water were added and a crystalline product precipitated on cooling. The product was washed with water and dried. Yield: 390 mg. (96%), m.p. 190–191°. It was recrystallized from boiling acetic acid–water, m.p. 191.5–192°. It is soluble in AcOH, ether, $CHCl_3$, less soluble in alcohol.

Anal. Calcd. for $C_{12}Cl_{10}O_2$: C, 27.15; H, 0; Cl, 66.81. Found: C, 27.27; H, 0.45; Cl, 66.46.

This product could be obtained also by action of the same reagent (chlorine in AcOH) on the octachlorobiphenol with a yield of 92%.

Reduction of the decachloro compound (XXXIII). (1) By Zn and AcOH: 24 mg. of the compound were dissolved in 1 cc. acetic acid. The solution was decolorized by boiling for 2 min. in the presence of zinc powder. Two cc. of water were added to precipitate the product. Yield: 91%, m.p. 234°. *(2) By alcohol:* This reaction has been studied by U.V. as a function of time. The decachloro compound (4.8 mg.) was dissolved in 50 cc. of alcohol and the U.V. spectrum was taken from time to time. The reaction was complete after 24 hr. The same behavior toward alcohol has been observed with the hexachlorophenol, but the reaction was much slower (about 280 hr.).

Action of silver on the decachloro compound (XXXIII). The active silver was prepared by reduction of AgCl in alkaline solution of hydroxylamine.[7] The reaction was carried out under nitrogen free from oxygen in anhydrous benzene, which had been dried by distillation from metal cetyl of benzophenone. The nitrogen was purified by passing through Fieser's solution, through an aqueous solution of lead acetate, through concentrated H_2SO_4, and finally through a solution of metal cetyl of benzophenone in ether. The blue color of the ether solution indicated the absence of oxygen and water.

In a two-armed flask was placed a solution of 50 mg. of the decachloro compound in 25 cc. of benzene and 500 mg. of active silver. Nitrogen was bubbled through the suspension for 0.5 hr. Then the flask was cooled at −80°C., the two arms were sealed, and the flask was shaken for 16 hr. at room temperature. No reaction seemed to have occurred. The silver was filtered off, washed with ether, and the solvents were removed to give a yellow crystalline substance. The U.V. spectrum showed that this compound was the unchanged starting material. Heating a mixture of the decachloro compound with active silver under vacuum (200°/1 mm.) resulted only in sublimation of the starting material.

Attempts to prepare the 3,3'-dibromo-2,2',3,3',5,5',6,6'-octachloro-4,4'-diketo-3,3'-4,4'-tetrahydrodiphenyl. (1) The addition of bromine to a boiling methanol solution left the octachlorobiphenol unchanged. (2) The addition of bromine to a cold or boiling acetic acid solution of biphenol gave no reaction. (3) The addition of bromine to an acetic acid solution of biphenol in the presence of a 15% excess of sodium acetate at 10° for 12 hr. gave no crystalline products. (4) Reaction (3) was carried out with twice the quantity of sodium acetate for 8 days. A yellow precipitate, insoluble in alcohol, chloroform, benzene, boiling acetic acid, and water, was slowly formed. This product did not melt at 310° and could not be sublimed. It was probably polymeric.

2,2',6,6'-Tetrachloro-3,3',5,5'-tetrabromo-4,4'-biphenol. Fifty mg. of tetrachlorobiphenol were dissolved in 5 cc. *N* NaOH. To this solution 100 mg. of bromine in 10 cc. *N* NaOH were added. The yellow solution was rapidly decolorized. After 0.5 hr. it was neutralized and extracted with ether. After removal of the ether, the residual oil crystallized slowly and was sublimed at 200°/1 mm., m.p. 251–252°. The product was recrystallized from aqueous alcohol (50%), m.p. 257–258° with decomposition.

Anal. Calcd. for $C_{12}H_2Br_4Cl_4O_2$: C, 22.4; H, 0.32; Br, 49.80; Cl, 22.18. Found: C, 22.75; H, 0.49; Br, 48.2; Cl, 21.5.

(Bromine was calculated assuming that the molecule contained four chlorines.)

Attempts to prepare the 3,3',5,5'-tetrabromo-2,2',3,3',6,6'-hexachloro-4,4'-diketo-3,3',4,4'-tetrahydrodiphenyl. (1) Action of an excess of chlorine on the biphenol in an acetic acid solution at room temperature gave the decachloro compound previously described. (2) The technique of Muller,[7] *i.e.*, action of chlorine in a solution of biphenol in MeOH, AcOH at −20°C. yielded 99% of the decachloro compound.

2,2'-Dimethyl-4,4'-dinitrodiphenyl. This compound was prepared according to the procedure of Sherwood and Calvin.[23] The product was recrystallized from ethanol in the presence of charcoal. Yield: 30%, m.p. 170°.

2,2'-Dimethylbenzidine hydrochloride. This product was prepared by two methods: (1) By reduction of 2,2'-dimethyl-4,4'-dinitrodiphenyl. Nine hundred mg. of dinitro compound were dissolved in 25 cc. ethanol. Then HCl and Zn were added to the boiling solution until the reduction was complete (1.5 hr.). The solution was neutralized with Na_2CO_3 and extracted with ether which was evaporated to dryness. The residue from the ether extract was dissolved in dilute HCl and the hydrochloride was precipitated by the addition of concentrated HCl. Yield: 60%. (2) Preparation according to the method of Schultz and Rohde[24] and purification as above. Yield: 80%.

Anal. Calcd. for $C_{14}H_{16}Cl_2N_2$: C, 58.95; H, 6.36; Cl, 24.86; N, 9.82. Found: C, 59.11; H, 6.27; Cl, 24.66; N, 9.75.

2,2'-Dimethyl-4,4'-biphenol. This compound was prepared according to the method of Brockmann and Dolars[25] and recrystallized from benzene. Yield: 90%, m.p. 116°.

2,2'-Dimethyl-5,5'-di-t-butylbiphenol.[15] Two g. of dimethyl-2,2'-biphenol were dissolved in 70 cc. benzene at 60–70°, then 0.1 cc. of concentrated sulfuric acid was added and isobutylene passed through the solution by means of a sintered glass bubbler for 6 hr.

The solution was washed three times with 2*N* NaOH, dried and concentrated. The resulting crystalline colorless product was contaminated with an oil which was absorbed by pressing the product between filter paper. The white crystals (1.75 g.) obtained were sublimed at 170–200° under 1 mm. Yield: 1.3 g. (41%), m.p. 213–214°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.9; H, 9.26. Found: C, 81.05, 81.09; H, 9.65, 9.04.

This biphenol is soluble in benzene, ether, and insoluble in 2*N* NaOH.

Oxidation of biphenols. Solvents used: Benzene, purified as indicated above; ether, anhydrous Merck, dried over sodium, then distilled and kept over sodium; water, distilled; acetic acid, analytical reagent. Nitrogen was free from oxygen (see above).

(1) Oxidation by active lead dioxide in moist ether at 0°.[5] The lead dioxide used here and in the following experiments was prepared according to the technique of Kuhn and Hammer[26] by hydrolysis of lead tetraacetate.

Technique of oxidation and results: 10–15 mg. of phenol were dissolved in 25 cc. of moist ether, cooled at 0°, then

(23) D. W. Sherwood and M. Calvin, *J. Am. Chem. Soc.*, 64, 1350 (1942).

(24) G. Schultz and G. Rohde, *Chem. Zeit., II*, 1447 (1902).

(25) H. Brockmann and A. Dorlars, *Ber.*, 85, 1180 (1952).

(26) R. Kuhn and I. Hammer, *Ber.*, 83, 413 (1950).

shaken at 0° with 1 g. lead dioxide for 5 min. The following results were obtained:

p-Cresol	Weak violet coloration, disappearing in a few minutes
p-Methoxyphenol	Strong blue coloration, disappearing in 20–25 min.
XLII	No coloration, but polymers
XXVI	No coloration
XXXII	No coloration
Pentachlorophenol	No coloration
XLIX	Deep red coloration, stable several hours

(*2*) *Oxidation by silver oxide*, prepared according to Willstatter[12] in anhydrous ether with dry sodium sulfate.

(*3*) *Oxidation by lead dioxide*, prepared as above, in anhydrous ether or benzene, in air or under nitrogen.

(*4*) *Oxidation with potassium ferricyanide in alkaline solution.*[7] The reaction was carried out in a 100 cc. two-necked flask with 100 mg. biphenol in 15 cc. benzene. The flask was cooled to −80° and then a solution of 1 g. potassium ferricyanide in 5 cc. 2*N* KOH was added under nitrogen. Nitrogen was passed through the flask for 15 min., then the flask was sealed and shaken at room temperature. Results of the reaction were observed by U.V. spectroscopy.

Oxidation of 2,2'-dimethyl-5,5'-di-t-butylbiphenol. In all the experiments a large excess of lead dioxide (5 to 10 times) was used.

Spectral and ESR studies on solutions. (1) $c = 3 \times 10^{-5}$ mol./l.: A solution of biphenol in benzene or ether (Curve 1, Fig. 3 and Curve 1, Fig. 13) was shaken with lead dioxide directly in the quartz cell of the spectrophotometer for 2 to 30 min. Then the cell was centrifuged for a few minutes and the optical spectrum was taken immediately. The reaction was complete after 2 min. The same results were obtained when the experiment was carried out in an atmosphere of nitrogen.

(2) $c = 10^{-3}$ mol./l. (Curve 2, Fig. 3): A special apparatus (Fig. 14a) was designed which made it possible to use the same sample of solution for optical and ESR spectra. The solution was free from lead dioxide and oxygen. The thickness of the borosilicate optical cell was 0.25 mm. After introducing the solution of biphenol into the flask, the apparatus was sealed at *a* under high vacuum and the solution was frozen in liquid nitrogen. Then the apparatus was tilted in such a way as to allow the iron weight, *d*, to break the thin wall, *c*. The liberated lead dioxide was poured onto the frozen solution, the flask was sealed at *b* and the solution was heated up to room temperature. After shaking the solution 2 min., the lead dioxide was centrifuged and by turning the apparatus upside down the solution filled the optical cell, *e*, and the side arm, *f*, making it possible to take the optical spectrum through *e* and the magnetic signal on *f*. Result: λ_{max} = 4450 Å, ϵ_{max} = 39,600. ESR signal: 1 electron for 1000–2000 molecules. By shaking a longer time (5, 10, 30 min.) a decrease of ϵ_{max} was observed, but there was no appreciable change in the ESR signal, indicating that the reaction was complete in less than 2 min.

(3) $c > 10^{-3}$ mol./l.: Reactions were carried out under vacuum in the apparatus shown in Fig. 14b. After shaking 15 min. (enough time to insure a complete reaction in all cases) the apparatus was centrifuged at 1000 rpm for 1 min. and the red solution decanted into the side arm where the ESR measurement could be taken directly. To take the optical spectrum the apparatus was opened at *a* and an aliquot of the solution was rapidly diluted with the adequate amount of benzene previously placed in the cell of the spectrophotometer (Curves 3, 4, 5, Fig. 3, Fig. 4, Fig. 11, Fig. 12).

(4) Titration of the solution (10^{-2}–10^{-3} mol./l.): The oxidation was carried out by shaking the benzene solution with potassium ferricyanide and 2*N* sodium hydroxide for 15–30 min. The solution was washed with water and an aliquot was added to sodium iodide in acetic acid, whereupon the color of the solution changed from red to orange. This solution was titrated with 0.10*N* sodium thiosulfate. Results: 0.24, 0.4, 0.44, 0.42 oxidation equivalents per molecule. The first measurement was made under pure nitrogen. Theory for the quinone LI, 2 equivalents; for the dimer, 1 equivalent; for the trimer, 0.66 equivalents.

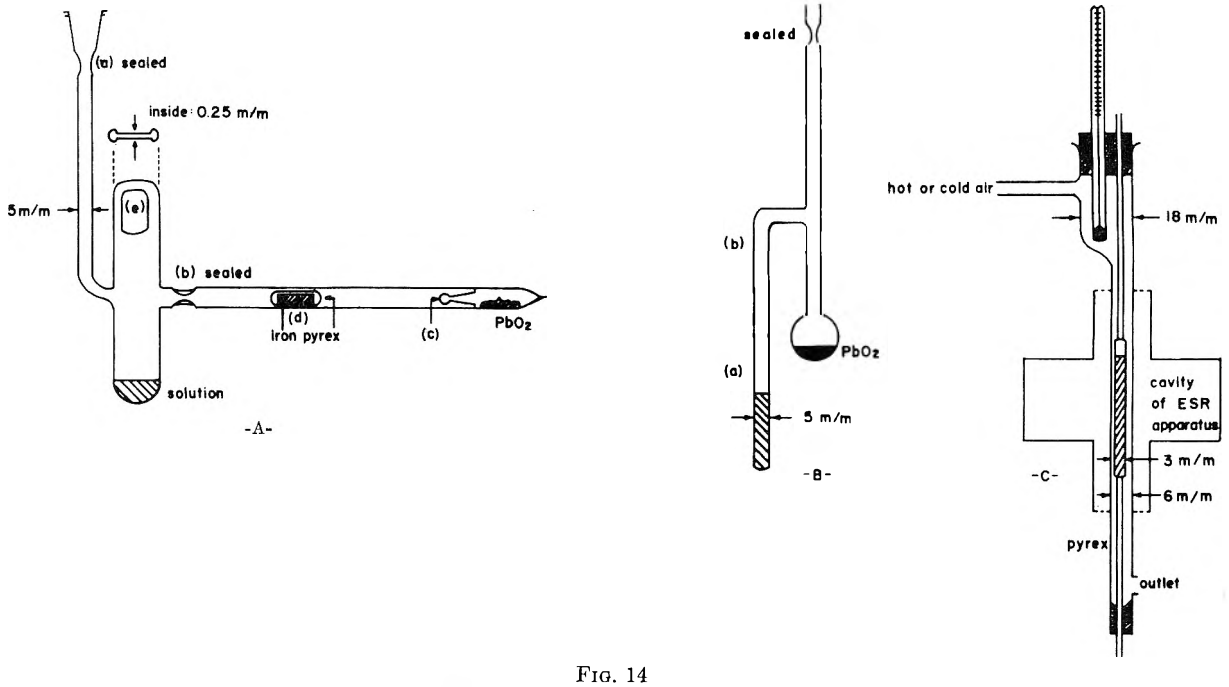


FIG. 14

(A) Apparatus to study ESR signal and optical spectrum of the quinone LI in dilute solution under vacuum. (B) Apparatus to study ESR signal of quinone LI in concentrated solution. (C) Equipment for temperature dependency study of the hindered polymeric quinones

Action of p,p'-biphenol on the hindered diphenoquinone LI (Fig. 6a). The diphenoquinone LI was prepared by shaking a benzene solution of the hindered biphenol (3×10^{-5} *M*) with lead dioxide for 4 min. The orange solution (Σ_{max} = 44,500) was added to an ether solution of biphenol (3 mol. for 1 mol.). The spectrum of the resulting solution was taken from time to time until the completion of the reaction.

The concentration of quinone LI was calculated from the initial amounts of hindered biphenol. The amount of the diphenoquinone produced was calculated from the Σ of the absorption band.

Action of p,p'-biphenol on the polymeric diphenoquinones. The quinones were prepared by shaking under vacuum for 15 min. a benzene solution of hindered biphenol (0.01*M*) with lead dioxide (Fig. 6b). An aliquot of the resulting solution was diluted 1000 times and added to the same volume of an ether solution of biphenol (7 mol. per mol. of initial hindered biphenol). The reaction was followed by U.V. spectrum as above. Calculations were made on the same basis.

Action of hindered biphenol XLIX on the hindered quinone LI (Figs. 7 and 8). The quinone LI was prepared in dilute solution as above (Curve 1, Fig. 8). Its decay in benzene (Curve 1, Fig. 7) was followed by the decrease of the ϵ_{max} at 4440 Å (Curve 4, Fig. 8): 20 cc. of a solution of diphenoquinone LI ($c = 3.07 \times 10^{-5}$) was mixed with 10 cc. of a solution of the hindered biphenol (same concentration). By heating the reaction mixture at about 60° for 40 min. there was a 90% decrease in the absorption band, then the solution was shaken for 2 min. with lead dioxide and the spectrum was taken again.

Temperature dependency study (Fig. 10). The reaction was performed in an apparatus similar to *B* (Fig. 14) having a side arm of 3 mm. diameter. The side arm was sealed off and placed in the apparatus, *C*, as is shown in Fig. 14. The apparatus was previously standardized with a thermocouple. The heating system consisted of a hot stream of air at various temperatures. The intensity of the ESR signal and the corresponding temperatures were recorded.

Red glass. (1) Oxidation with lead dioxide: 100 mg. of biphenol were dissolved in 30 cc. of benzene and the mixture was shaken in the presence of 2 g. of lead dioxide for 15 to 30 min. After centrifugation the solvent was removed under vacuum at room temperature (10–20°), giving a red glass which was left 2 hr. under 1 mm. pressure before analysis.

Oxidation under nitrogen: The apparatus was composed of two flasks connected by a piece of sintered glass to filter the lead dioxide (Fig. 15). After the apparatus had been

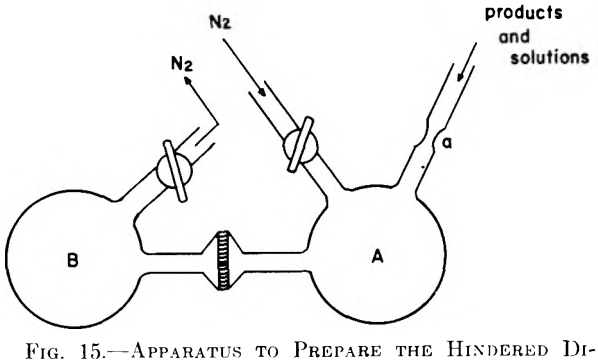


FIG. 15.—APPARATUS TO PREPARE THE HINDERED DIPHENOQUINONE IN THE SOLID STATE BY OXIDATION WITH LEAD DIOXIDE

filled with pure nitrogen and sealed at *a*, the reaction was performed in flask *A*, the solvent was filtered into flask *B* by pressure of the nitrogen; keeping *B* at 10° and freezing *A* at −80°, under vacuum, the benzene was distilled in *A*. A red glass was obtained in *B* and dried under 1 mm. pressure.

(2) Oxidation with potassium ferricyanide: The same solutions of biphenol were used. The oxidant was a solution of 2 g. of potassium ferricyanide in 20 cc. of 2*N* sodium hydroxide. The two solutions were shaken together for 15 to 30 min. and the layers were separated. The benzene layer was washed with water, dried over sodium sulfate, and evaporated at room temperature under vacuum, giving a red glass.

Oxidation under nitrogen (pure nitrogen was bubbled through all solutions and solvents before using them): The reaction was carried out in a special separatory funnel (Fig. 16) filled with nitrogen and kept at 10°. After shaking

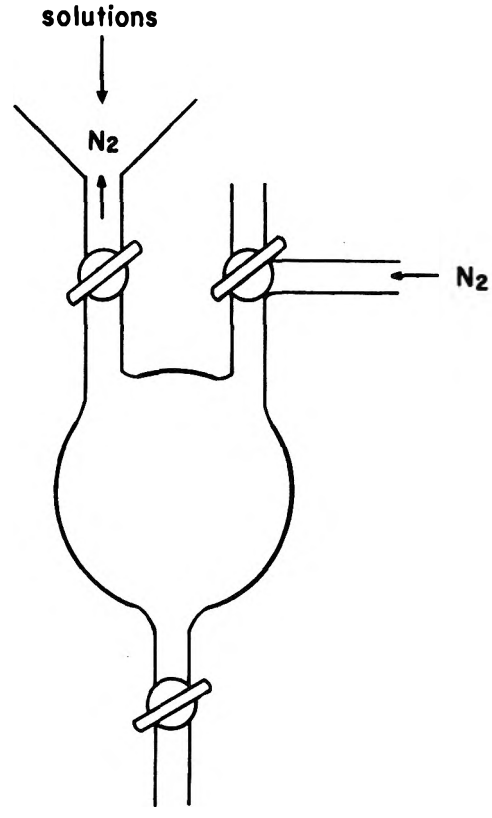


FIG. 16.—APPARATUS TO PREPARE THE HINDERED DIPHENOQUINONE IN THE SOLID STATE BY OXIDATION WITH FERRICYANIDE

in the separatory funnel for 30 min. the layers were separated; the red benzene layer was washed with boiled water, then dried over sodium sulfate in an apparatus (Fig. 15) filled with nitrogen; it was then filtered and evaporated as indicated above, giving the same red glass.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.43; H, 8.69. Found: (A) C, 80.05; H, 8.67. (B) C, 81.67; H, 8.72. (C) C, 80.20; H, 8.93. (D) C, 80.39; H, 8.93.

(A) was prepared by oxidation with lead dioxide in the presence of air and dried at room temperature. (B) was prepared by oxidation with potassium ferricyanide under nitrogen and dried at 35°. (C) was prepared by oxidation with potassium ferricyanide under nitrogen and dried at room temperature. (D) was prepared by oxidation with lead dioxide under nitrogen and dried at room temperature.

3,3'-Dimethyldiphenoquinone. This compound was prepared by boiling a solution of 3,3'-dimethylbiphenol (34 mg.) in 2 cc. of benzene with lead dioxide (700 mg.) for 5 min. The lead dioxide was separated and extracted several times with boiling benzene. The resulting orange solution was concentrated to 5 cc., yielding 15 mg. of quinone (dark red needles); λ_{max} = 4090 Å; ϵ_{max} = 65,000 (benzene).

Diphenoquinone. This compound was prepared from *p,p'-*

biphenol using the procedure described above. Dark orange needles resulted; λ_{max} = 3985 Å; ϵ_{max} = 53,200 (benzene).

Acknowledgment. All spectra were taken with a Cary recording spectrophotometer (Model 11 or 14) at a concentration of approximately $10^{-4}M$. Electronic spin resonance absorption measurements (ESR) were performed with equipment built by Dr. Power B. Sogo of the Radiation Laboratory. Analyses were performed by Dr. Charles Koch of the Microanalytical Laboratory of the Department of Chemistry.

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

Steric Considerations in Base Catalyzed Condensation; The Darzens Reaction[1]

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The Darzens condensation of benzaldehyde and choloroacetone has been carried out in good yield. The exclusive glycidic ketone product of this reaction has been shown by a synthetic procedure to have the *trans* arrangement of substituents on the oxide ring. The significance of this observation for the mechanism of the Darzens reaction in particular and aldol condensations in general is discussed. Circumstances are considered under which it is possible to obtain the *cis* isomer.

Ballester[2] has very recently reviewed the evidence that strongly points to a mechanism involving an alpha halogenohydrin anion as intermediate in the Darzens condensation[3] and indicates that the course of oxirane ring formation from this intermediate requires Walden inversion at the halogen bearing carbon atom. Further, the rate determining step in the over-all reaction has been deduced[4] to be the slow formation of this intermediate. The self-condensation[5] and cross-condensation[6] of phenacyl halides have afforded both *cis* and *trans* (substituted) benzalacetophenone oxides depending on the conditions of reaction. The respective structures of these isomers have been assigned on the basis of spectral characteristics and stereospecific chemical reactions.

The mechanism discussed by Ballester[2,7] has not considered the possibility of two diastereomerically related (*cis* and *trans*) intermediate anions; nor has the possibility been suggested that the occurrence of the two isomers in a given Darzens reaction may correspond to the possible formation of two discrete intermediates. In the present investigation we have shown that with simple Darzens reagents the condensation produces only one of the two possible oxiranes. We have determined the configuration of this product and attempted to generalize the significance of its exclusive formation.

RESULTS AND DISCUSSION

The Darzens condensation of benzaldehyde and monochloroacetone, using sodium methoxide in absolute methanol solution as the base, gave only one epoxyketone product. The composition of the product did not vary with the time and temperature of reaction though the yield of undistillable residue was increased beyond a certain optimum adjustment of these variables. The sharp melting, crystalline product was shown to possess the *trans* relationship of the substituents on the oxide ring by synthesis through an established procedure.

Benzalacetone, prepared by cross-aldol of acetone and benzaldehyde, was identified to have the *trans* configuration, (characteristic of the products of base catalyzed condensation reactions),[8] by its facile conversion through sodium hypochlorite oxidation to the known *trans* cinnamic acid. Additional proof of its configuration was afforded by the presence of a strong band in the region 10.2–10.6 microns.[9] Reduction with lithium aluminum hydride

(1) Part of this work is obtained from the Thesis of Lewis G. Kirk, presented in partial fulfillment of the degree of Master of Science at the University of Delaware.

(2) M. Ballester, *Chem. Rev.*, **55**, 283 (1955).

(3) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949).

(4) M. Ballester, *Anales real soc. espan. fis. y quim. (Madrid)*, **50B**, 759 (1954).

(5) (a) H. H. Wasserman and J. B. Brous, *J. Org. Chem.*, **19**, 515 (1954). (b) C. L. Stevens and V. J. Traynelis, *J. Org. Chem.*, **19**, 533 (1954). (c) C. L. Stevens, R. J. Church and V. J. Traynelis, *J. Org. Chem.*, **19**, 522 (1954). (d) H. H. Wasserman, N. E. Aubrey, H. E. Zimmerman, *J. Am. Chem. Soc.*, **75**, 96 (1953).

(6) N. H. Cromwell and R. A. Setterquist, *J. Am. Chem. Soc.*, **76**, 5752 (1954).

(7) M. Ballester and P. D. Bartlett, *J. Am. Chem. Soc.*, **75**, 2042 (1953).

(8) (a) S. E. Boxer and R. P. Linstead, *J. Chem. Soc.*, 740 (1931). (b) R. P. Linstead, E. G. Noble and E. J. Boorman, *J. Chem. Soc.*, 557 (1933).

(9) This absorption has been ascribed to out-of-plane deformation of the two hydrogens attached to the *trans* double bond, a corresponding mode being absent in the *cis*. See particularly R. S. Rasmussen, R. R. Brattain and P. S. Zucco, *J. Chem. Phys.*, **15**, 135 (1947); N. Sheppard and G. B. B. M. Sutherland, *Proc. Roy. Soc.*, **A196**, 195 (1949). The correlation has previously proven valid for a large variety of substituted olefins and has been accepted

TABLE I

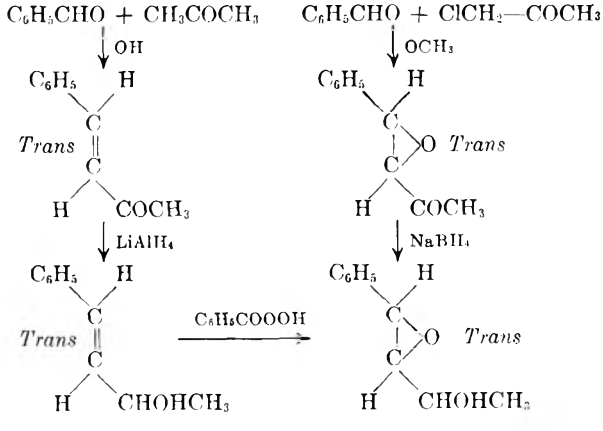
INFRARED SPECTRAL DATA

λ_{max} in microns; S—sharp; B—broad; SC—Sample cell thickness; NM—Nujol Mull; RC—Reference cell-50% Transmission

Strong	Intermediate	Weak
	trans C_6H_5—CH=CH—$COCH_3$; RC, NM	
3.5 B, 6.0 S 6.3 B, 6.9 B 7.3 S, 7.4 S 10.2 B, 13.4 B 14.5 B	8.0 S, 8.5 B	6.7 S, 7.1 B 7.5 S, 7.7 S 8.4 S, 9.3 S 11.0 S
	trans C_6H_5—CH(O)—CH—$COCH_3$; RC, NM	
3.4 B, 5.9 S 6.8 S, 7.4 S 8.0 B, 11.3 S 12.0 B, 12.6 S 13.3 B, 14.4 B	7.1 S, 9.2 S, 12.2 B	5.1 B, 5.35, 6.7 S 8.4 S, 8.6 S, 8.9 B
	trans C_6H_5CH=CH—CHOH—CH_3—0.025 mm. SC	
3.0 B, 3.4 S, 6.7 S 6.9 S, 7.3 S, 8.8 B 9.3 S, 9.5 B, 10.3 B 10.6 B, 14.5 B	3.3 S, 3.45 S, 3.5 S 6.2 S, 7.1 B, 7.5 S 7.7 B, 9.7 B, 11.4 S 11.7 B, 12.1 S	5.1 S, 5.3 S, 5.5 S 5.7 B, 6.0 S, 6.3 S 8.3 B, 8.5 S, 11.0 B
	trans C_6H_5CH—CH(O)—CHOH—CH_3—0.03 mm. SC	
2.9 B, 3.35 S 6.9 S, 8.7 B 9.0 B, 9.3 B, 9.7 B 11.3 B, 13.3 B 14.3 B	3.4 S, 3.45 S, 5.9 S, 6.7 S, 7.0 S 7.3 S, 7.45 S, 7.8 S, 8.3 S, 10.0 B, 10.55 S 11.8 B	5.1 B, 5.3 B, 5.5 B 6.25 S, 6.3 B 10.9 B, 12.7 B
	trans C_6H_5CH(O)—CH—CH—O—CO—NH—$C_{10}H_7(\alpha)$—RC, NM	
3.3 S, 3.45 S, 3.5 S 6.1 S, 6.25 S, 6.45 B 6.7 S, 6.9 S, 13.2 B 14.3 B	3.1 S, 7.3 B, 7.45 S, 8.0 S 8.3 B, 9.7 B, 11.0 S	5.1 S, 5.3 B 5.55 B, 5.8 B 8.6 B, 10.4 B 11.9 B

did not disturb the configuration about the double bond as has also been established in analogous cases.[10] This product, again, was confirmed as the *trans* alcohol by virtue of the strong infrared absorption near 10.3 and 10.6 microns. Epoxidation with perbenzoic acid gave a glycidic alcohol to which was assigned the *trans* configuration on the (well founded)[11] assumption of a *cis*-addition mechanism of the epoxidation reaction. This substance was characterized by its infrared spectrum (see table) and *alpha* naphthylurethan derivative.

The identical substance (confirmed by infrared spectrum and *alpha* naphthylurethan derivative) was obtained upon reduction with sodium borohydride of the Darzens condensation product, as outlined in the flow diagram.



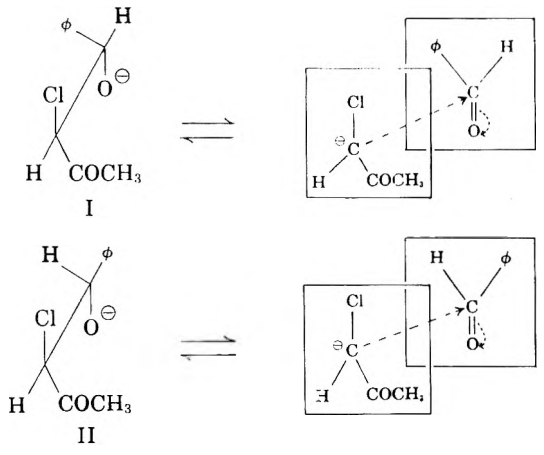
SIGNIFICANCE OF RESULTS

Ignoring rotational isomers, the two possible intermediates, I and II, may be visualized as being formed from two alternative collision orientations of the respective (planar) carbonyl and enolate anion

to be of diagnostic importance. See P. C. Rao and B. F. Daubert, *J. Am. Chem. Soc.*, **70**, 1102 (1948); O. S. Shreve, M. R. Heather, H. B. Knight and D. Swern, *Anal. Chem.*, **22**, 1261 (1950); L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707, 1714 (1950); *J. Chem. Soc.*, 869 (1952); R. N. Jones, *J. Am. Chem. Soc.*, **72**, 5322 (1950).

(10) L. F. Hatch and S. S. Nesbitt, *J. Am. Chem. Soc.*, **72**, 727 (1950).

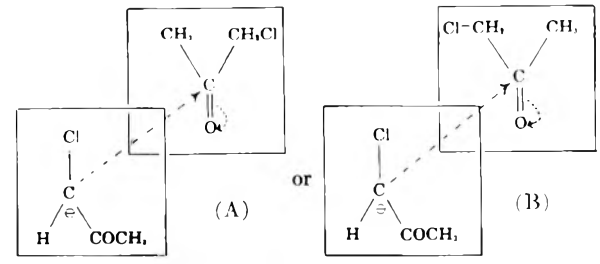
(11) For a fuller discussion of the basis for this statement see D. Swern, *Chem. Rev.*, **45**, 1 (1949).



I

II

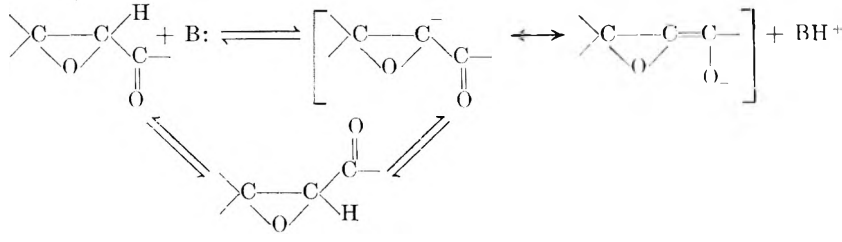
reagents. These possibilities are represented above in the *trans* coplanar arrangement required for effecting the Walden inversion[12] leading to epoxide. If, as Ballester has claimed,[2] the Darzens intermediate commonly is formed in the rate determining step, the exclusive formation of the *trans* product may be attributed to steric inhibition in the formation of II. One might suppose the formation of the



(A) or (B)

the (steric) environment of the interacting (planes of) components A and B are involved. The aldol condensation of acetone, where the enolic equilibrium is set up much more rapidly than the condensation equilibrium[15] is a most obvious case in point. Where the enolization is the rate controlling step in the Darzens[4] the formation of the *trans* product must obtain since here such steric factors are minimized.

Finally, one can anticipate the formation of both *alpha* and *beta* glycidates in the Darzens only under very special circumstances, namely where *cis* and *trans* can exist in equilibrium through base catalyzed enolization involving the alpha hydrogen, as in



product-forming intermediate I to occur only as a result of a very restricted orientation of colliding planes. Here, the transition state for bond formation between the reactive centers of these planes must strongly resemble the intermediate.[13] The steric strains between the adjacent tetrahedra developing at the bond-forming carbon atoms in the transition state tend to be minimized in the staggered conformation (in which the smallest group on the one carbon is accommodated between the two largest groups on the other.) The fact that no significant self-condensation of chloroacetone is observed (under these reaction conditions) suggests that the possible transition states for such reaction formed by collision orientations such as (A) or (B) engender relatively unfavorable steric factors, similar to those that prevent formation of intermediate II.

These deductions about the Darzens reaction are also applicable to the aldol. Enolization, normally the rate determining stop,[14] will be seen to be non-rate determining where factors pertaining to

The argument we have advanced above that a *cis* intermediate anion II is formed with the greater difficulty dismisses the possibility that a *trans-cis* interconversion of epoxyketones is established through reversion of the Darzens product to the halohydrin. We were able, in fact, to test this possibility by means of several experiments with the *cis* and *trans* pair of oxides of *o*-nitrobenzalacetophenone.[6,16]

Each of the isomers was treated with a large excess of chloride ion in alcohol solution for a longer period of time than the original Darzens preparation required. In each case almost pure starting material was recovered on addition of water to the reaction mixture and no isomerization was detectable.[17] Clearly, a *cis* halohydrin anion like II is not the intermediate in the formation of *cis* product in

(12) For a discussion of this conformational requirement for reaction see, for example, D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953) and other references cited therein.

(13) For a complete discussion on this point see G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(14) R. P. Bell, *J. Chem. Soc.*, 1637 (1937).

(15) W. D. Walters and K. F. Bonhoeffer, *Z. Physik. Chem.*, **B182**, 265 (1938).

(16) S. Bodforss, *Ber.*, **51**, 192 (1918).

(17) This failure to revert to halohydrin anion occurs despite the fact that chloride ion appears to have a specific effect in opening of oxide ring, (L. P. Hammett, Physical Organic Chemistry, McGraw-Hill and Co., p. 302 et. seq.), and despite the expectation that the benzoyl and o-nitrophenyl substituents on the oxide would increase the rate of displacement.

the (direct) Darzens reaction.[18] Rather, the only possible way in which *cis* can be obtained in the Darzens is through formation of the *trans* product followed by base catalyzed isomerization. The existence of a very large effect (in both the rates and equilibrium of ring-forming reactions) opposing the formation of *cis* substituents on small rings constitutes a further basis for assigning greater thermodynamic stability to a *trans* versus a *cis* oxide.[19] It is very possible, therefore, that when a significant yield of *cis* is obtained it is the result of the peculiar circumstances where the interlocking *enolization equilibria* outlined above are displaced in the direction of separating a *cis* product where it precipitates from solution as the least soluble component of the system, and that these circumstances are not an essential but rather a secondary aspect of the mechanism of the Darzens condensation. This conclusion is only tentative, however, and is receiving further investigation in this laboratory.

EXPERIMENTAL

Preparation of benzalacetone oxide. The best yields were obtained using conditions similar to those suggested in the general method for Darzens condensation by Newman and Magerlein.[3] In an atmosphere of dry nitrogen 86.2 g. (1.6 moles) of sodium methoxide dissolved in 300 ml. of absolute methanol was dropped into a stirred solution containing 102 ml. (1 mole) of benzaldehyde, 128 ml. (1.6 moles) of monochloroacetone and 100 ml. of absolute methanol at a rate such that the temperature did not rise above zero. Agitation was continued for six hours at 0° after which the temperature was raised to 25° for an additional three hours of stirring. The reaction mixture was then poured onto chipped ice-hydrochloric acid and sufficient additional hydrochloric acid added to turn litmus. After two extractions of the aqueous layer with ether the combined extracts were neutralized with saturated sodium bicarbonate solution, followed by washing with saturated sodium chloride before drying over magnesium sulfate. The ether was removed and the residual yellow oil distilled (with a dry nitrogen stream) under high vacuum. The pure epoxyketone fraction was obtained ($b_{0.4}$ 69.0–69.5°) in 74% yield. The liquid (n_D^{20} 1.5347) crystallized on standing. After two recrystallizations from pet. ether the product melted sharply at 56°. The infrared spectrum is summarized in the accompanying table. Other properties were identical with those reported by Temnikova and Martynov[20] who employed much shorter reaction times and excess benzaldehyde and obtained product in 50% yield. No differences, other than in yield, in the nature of the product were observed over a wide range of conditions (temperature, molar ratios, base catalyst) investigated.

Reduction of benzalacetone oxide. To a stirred solution of 200 ml. of absolute methanol and 40 g. (0.25 moles) of epoxyketone (above) was slowly added 150 ml. of absolute methanol containing 9.45 g. of sodium borohydride (Metal Hydrides Corp., Beverly, Mass.). After stirring for half an hour (beyond complete addition), small amounts of ice and hydrochloric acid were dropped into the reaction flask at intervals until hydrogen evolution ceased. The solution, made acid to litmus with additional hydrochloric acid, was saturated with sodium sulfate and extracted with four 100-ml. portions of ether. The combined extracts were washed with sodium bicarbonate solution, saturated salt solution and dried over magnesium sulfate. Removal of the solvent and distillation of the residual oil under high vacuum gave the epoxyalcohol ($b_{0.18}$ = 77–79°) in 87% yield. This product was characterized by its infrared spectrum and that of its *alpha* naphthyl urethan derivative (m. = 240–241° dec.). See accompanying table for infrared data.

Preparation of benzalacetone. A procedure similar to that used in Organic Synthesis[21] was used. The doubly distilled product had the following properties; $b_{16.5}$ 137°, m.p. 42°. See accompanying table for infrared data.

Reduction of benzalacetone. To a stirred solution of 150 ml. of anhydrous ether and 40 g. (0.27 mole) of benzaldehyde was slowly added 200 ml. of an ether solution containing 6 g. of lithium aluminum hydride (Metal Hydrides Corp., Beverly, Mass.). One hr. after the addition was completed the excess lithium aluminum hydride was decomposed with dilute hydrochloric acid. The combined ether extracts of the aqueous layer were neutralized with sodium bicarbonate solution, washed with saturated sodium chloride and dried over magnesium sulfate. Evaporation of the ether and distillation of the residual oil under vacuum gave the unsaturated (see infrared data) alcohol in 90% yield; b_{12} 126°. All properties compared favorably with literature values reported[22] for 4-phenyl-3-butene-2-ol prepared by another method.

Epoxidation of trans 4-phenyl-3-butene-2-ol. To a solution of 23 g. (0.15 mole) of the unsaturated alcohol (above) in anhydrous ether was added in fifteen minutes at room temperature 22 g. (0.16 mole) of perbenzoic acid[23] in 300 ml. of ether. After twenty-four hours a negative test obtained with sodium iodide indicated the reaction was complete. After neutralization with dilute sodium hydroxide the combined ether extracts were washed with water and dried over magnesium sulfate. Removal of solvent and distillation of the residual oil afforded a 60% yield of product, $b_{0.16}$ 76–77°. The properties of this product compared very well both in infrared spectrum and mixed melting point of the *alpha* naphthylurethan derivative with these corresponding properties of the sodium borohydride reduction product of the Darzens reaction described above. (See accompanying table of infrared data.)

Trans-o-nitrobenzalacetophenone oxide. This preparation was carried out according to the directions given by Cromwell and Setterquist[6]; m.p. 112–112.5° (literature[6] m.p. 111–113°) after recrystallizations from absolute ethanol.

Cis-o-nitrobenzalacetophenone oxide. The directions given in reference 6 were again used. After two recrystallizations from absolute ethanol the product melted sharply at 175° (literature[6] 174–175°).

Attempted isomerization of Darzens product with chloride ion. (a). A 2.0 g. sample of *trans* epoxyketone was dissolved in 75 ml. of absolute ethanol containing 1.9 grams of lithium

(18) J. A. Berson [*J. Am. Chem. Soc.*, **74**, 5177 (1952)] has interpreted the formation of both alpha and beta isomers in the Darzens as a situation in which the kinetically favored product (*trans*) is thermodynamically unstable with respect to a more slowly formed *cis* isomer. (See also reference 6, p. 5752). We have attempted to demonstrate here that this conclusion is neither required nor warranted by the evidence. Indeed, the contrary may be correct in accord with similar observations discussed by D. Y. Curtin in reference (19).

(19) D. Y. Curtin, Thirteenth National Organic Symposium Abstracts, p. 40–49, June 15–18 (1953), Ann Arbor, Michigan.

(20) T. I. Temnikova and V. F. Martynov, *J. Gen. Chem. (U.S.S.R.)*, **15**, 499 (1945); *C. A.*, **40**, 4694 (1946).

(21) N. L. Drake and P. Allen, Jr., *Org. Synthesis*, Coll. Vol. I, 77 (1941).

(22) (a) A. Klages, *Ber.*, **35**, 2649 (1902). (b) J. Sand and F. Singer, *Ber.*, **35**, 3186 (1902).

(23) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co., New York, 1948, p. 767.

chloride (AR). This corresponded to about a 6 to 1 molar ratio of chloride to epoxide. The solution was permitted to remain at 30° for three hours before drowning in water. The precipitate was identical with starting material on comparison of m.p. and infrared spectrum. (b) The *cis* epoxyketone was far less soluble and the reaction had to be carried out at the boiling point of ethanol. However, after three hours of refluxing, the product recovered was very pure *cis* starting material, as shown by m.p. and infrared spectrum.

NEWARK, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE NEWARK COLLEGE OF ARTS AND SCIENCES OF RUTGERS UNIVERSITY]

Peroxide Induced Reduction of 9,10-Anthraquinone by Sodium Borohydride in Diglyme[1]

GILBERT S. PANSON AND C. EDWIN WEILL

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9,10-anthraquinone is not reduced at room temperature by sodium borohydride in pure diglyme (dimethyl ether of diethylene glycol). In the presence of peroxides, 9,10-anthraquinone is reduced to 9,10-anthradiol in diglyme. A possible mechanism for the peroxide promoted reduction may be the cleavage of the solvent to aldehydes by a peroxide-induced reaction followed by the conversion of the aldehydes so produced to alkoxyborohydrides which are the effective reducing agent.

It has been reported that quinones may be quantitatively reduced to the hydroquinone by aqueous solutions of sodium borohydride at room temperature.[2] It has been found in this laboratory that although such quinones as 1,4-naphthoquinone and 9,10-phenanthrenequinone are readily reduced, 9,10-anthraquinone is not reduced under these conditions.

When 9,10-anthraquinone was treated under an argon atmosphere at room temperature with sodium borohydride in freshly purified diglyme (dimethyl ether of diethylene glycol), no visible evidence of a reaction was observed after 5 hr. Upon acidification of the reaction mixture, the volume of hydrogen evolved was equivalent to the amount of sodium borohydride initially present.

However, when 9,10-anthraquinone was treated with sodium borohydride in diglyme which had been exposed to air for as short a time as one day, a rapid reaction took place. The red color of the 9,10-anthradiol salt appeared within 3 min. A gasometric analysis at the end of 5 hr. showed a loss of borohydride equivalent to 100% reduction of the anthraquinone.

The positive reaction in the aged solvent suggested that peroxides, which form readily in the polyethers, might be involved in the reaction. To determine whether this positive reaction is due to the formation of peroxides in the diglyme, small amounts of various peroxides were added to the solution of anthraquinone and sodium borohydride in freshly purified diglyme under anaerobic conditions. In the case of benzoyl peroxide, lauroyl peroxide and *tert*-butyl hydroperoxide, the anthraquinone was reduced after an induction period of approximately 5 min. In a series of experiments with benzoyl peroxide it was shown that as little as 0.005 mole of the peroxide was sufficient to promote the reduction of a mole of anthraquinone. In a control experiment without added peroxide no reduction took place even after 5 hr. at room temperature.

To determine the role of the benzoyl peroxide in promoting the reduction, combinations of two of the reagents were mixed and allowed to stand for 10 min. before the addition of the other two. In only one case was the induction period for the reaction reduced from the normal value of 5 min. for the quantities used. This was when the benzoyl peroxide and the diglyme were allowed to age together before the addition of the anthraquinone and sodium borohydride. That the reduction was promoted by a product of the reaction between peroxide and the solvent was further proven by experiments with di-*t*-butyl peroxide. This peroxide did not cause a positive reaction under the conditions which were successful with the three mentioned previously. However, when the diglyme was first heated with di-*t*-butyl peroxide, and then cooled to room temperature, the reaction took place upon the addition of the sodium borohydride and anthraquinone.

There remained the possibility that the effect of the peroxide on the diglyme involved the formation of aldehydes by a free radical cleavage of the polyether. Thomas has reported that the peroxide-catalyzed thermal decomposition of a polyether yields aldehydes among other products.[3] While freshly prepared diglyme gave a negative Schiff test, it was found that the addition of a small

(1) This work was conducted under a research grant provided by Metal Hydrides, Inc., of Beverly, Mass.

(2) B. Lindberg and J. Paju, *Svensk Kem. Tidskr.*, 65, 9-10 (1953).

(3) J. R. Thomas, *J. Am. Chem. Soc.*, 77, 6107-9 (1955).

amount of benzoyl peroxide to the solvent caused the development of a pronounced positive test for aldehyde. Similarly, the aged diglyme preparations gave a positive Schiff test.

Small amounts of a wide variety of freshly distilled aldehydes were added to a solution of anthraquinone and sodium borohydride in diglyme. In each case the reduction of anthraquinone took place. In a series of experiments with isobutyraldehyde it was proved that as little as 0.01 mole of the aldehyde was sufficient to promote the reduction of one mole of anthraquinone. Alcohols were without effect in promoting the reduction even when used in rather large amounts.

Since the aldehyde in the presence of $NaBH_4$ was probably reduced to an alkoxy borohydride very rapidly, it is possible that this is the compound which was active in reducing the 9,10-anthraquinone. Brown, Mead, and Subba Rao[4] have recently found that acetone is reduced in diglyme much more readily by sodium triisopropoxyborohydride than by sodium borohydride. To verify this in the case of the reduction of 9,10-anthraquinone, a sample of the anthraquinone in freshly purified diglyme was treated with sodium trimethoxyborohydride under an argon atmosphere. The reduction was rapid and complete. No induction period was observed.

Amines were found to exert a catalytic effect on the reduction of 9,10-anthraquinone by sodium borohydride in diglyme. This is in agreement with a similar effect noted for the reduction of acetone in diglyme with sodium borohydride.[4] As little as 0.1 mole of *n*-butylamine per mole of 9,10-anthraquinone was found to promote the reduction.

Repeated quantitative experiments in which 9,10-anthraquinone was reduced with sodium borohydride in diglyme and then the excess $NaBH_4$ was determined gasometrically indicated that each mole of 9,10-anthraquinone consumed 2 gram atoms of hydrogen. This would correspond to a reduction to 9,10-anthradiol. The dark red color of the reduced solutions is also characteristic of the salts of 9,10-anthradiol. In order to isolate the product a run was made using larger quantities. The reduction product upon isolation in the acid form was found to be the yellow-green crystalline 9,10-anthradiol. This material dissolved in alkali to give the characteristic red color of the salt. It was soluble in alcohol with a characteristic green fluorescence. However, since it rapidly decomposes in air, no attempt was made to purify it and determine a melting point. Instead a second run was made in which the reduced 9,10-anthraquinone was converted to the diacetate without attempting to isolate the 9,10-anthradiol from the reaction mixture. The diacetate obtained dissolved in glacial acetic acid to give a solution which displayed a blue fluorescence. When the diacetate was vigorously refluxed with aqueous sodium hydroxide it slowly dissolved to give the red color of the leuco sodium salt of anthraquinone.

EXPERIMENTAL

Purification of the solvent. The diglyme as supplied by Ansul Chemical Co. (E-141) was dried by storage over NaOH pellets. It was then refluxed over $NaBH_4$ and distilled. These operations were perfofmed in an atmosphere of deoxygenated nitrogen.

The experiments with peroxides, aldehydes, and amines were conducted on a small scale. In each case the reactions were carried out in an atmosphere of argon. All transfers were made under anaerboic conditions. In a typical experiment 10 mg. of sodium borohydride in diglyme was added to a homogeneous solution of 20 mg. of anthraquinone in diglyme. The peroxide or aldehyde was added to the anthraquinonediglyme solution either directly or as a dilution in diglyme. These reagents were added before the sodium borohydride in all experiments except those used to determine the nature of the peroxide effect.

Preparation of crude 9,10-anthradiol. One gram of 9,10-anthraquinone was dissolved in 20 ml. of diglyme which had been purified as in the preceding paragraph, but then had been allowed to stand exposed to air for several weeks. Upon the addition of 0.25 g. sodium borohydride (98+% pure, as supplied by Metal Hydrides, Inc.) a vigorous exothermic reaction started and the solution turned deep red. The reaction mixture was stirred under argon without heating for 45 min. At the end of this time, the reaction mixture was poured into 500 ml. of cold 1*N* HCl to decompose the excess $NaBH_4$ and precipitate the product. A yellow-green precipitate was obtained. This was filtered and washed with water. The precipitate (0.9 g.) was soluble in alcohol to give a green fluorescence. It dissolved in aqueous NaOH to give the red color of the sodium salt. The melting point of the crude 9,10-anthradiol was 157–180°. An attempt to recrystallize the crude material from alcohol yielded 9,10-anthraquinone (m.p. 285°).

Isolation of 9,10-anthradiol diacetate. The reaction was performed as in the preceding paragraph up to the point where the reaction mixture was added to dilute HCl. Instead of this, 5 cc. of acetic anhydride and 3 g. of fused sodium acetate were added to the dark red reaction mixture. The mixture immediately turned yellow-green. The reaction mixture, still under an atmosphere of argon, was warmed at 70° for 0.5 hr. It was then poured into ice water and the pale yellow precipitate was filtered, washed and dried. The yield was 0.8 gram. Colorless needles (0.6 g.) were obtained upon crystallization from glacial acetic acid. The melting point of the 9,10-anthradiol diacetate was found to be 268–271°, dec. This is in reasonably good agreement with the value reported by Fieser and Putnam[5] of 262–267° for 9,10-anthradiol diacetate prepared by the interaction of $Pb(OAc)_4$ and 9-acetoxyanthracene.

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(4) H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209–13 (1955).

(5) L. F. Fieser and S. T. Putnam, *J. Am. Chem. Soc.*, 69, 1038–41 (1947).

[Contribution from the Department of Chemistry, University of Toronto, and the Department of Chemistry, The Ohio State University]

Synthesis of 3,4-Dimethyl Spirobipyrrolidinium Salts by Cyclization of Pyrrolidinealkanols

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(1,1′)-Spirobipyrrolidinium bromide and its 3,4-dimethyl or 3,4,3′,4′-tetramethyl derivatives are readily prepared by cyclization of appropriate derivatives of 1-bromo-4-(1-pyrrolidinyl)-butane prepared from the corresponding pyrrolidinealkanols. The pyrrolidinealkanols are prepared in turn by reduction of the corresponding 4-oxo-4-(1-pyrrolidinyl)-butyric acid esters, derived from appropriately methylated pyrrolidine and succinic anhydride starting materials. Stereoisomerism of the products and intermediates is discussed.

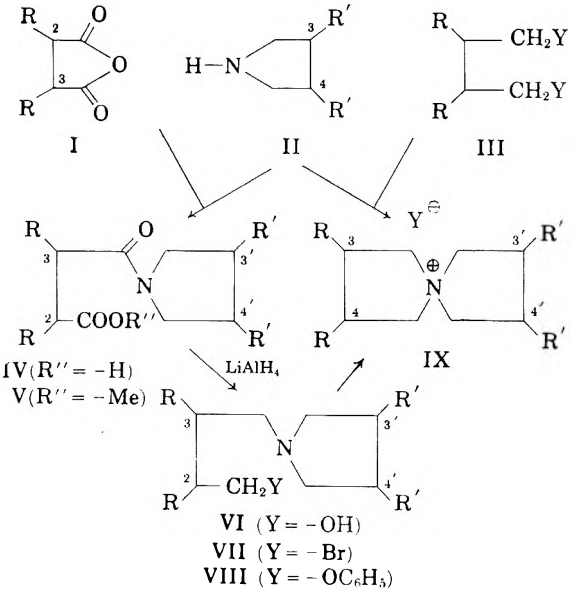
In recent communications[3] we have reported the synthesis of the four diastereomers of the tetramethylspirobipyrrolidinium *p*-toluenesulfonate, IX (R = R′ = Me). This set of diastereomers was of unusual interest because the molecule of one of them is superposable on its mirror image but possesses no plane or center of symmetry. The synthetic route utilized for the preparation of these spiranes was based on the cyclization of a suitable difunctional intermediate, III (Y = —Br or —$OSO_2C_6H_4CH_3$), caused by reaction with a suitable pyrrolidine derivative, II (R′ = Me).

During the course of these investigations we also explored an alternative route for the synthesis of such spiroquaternary salts, namely, the cyclization of a suitable *N*-alkylpyrrolidine derivative, VII, through the interaction of a side chain terminal functional group with the tertiary nitrogen atom.

The needed bromoalkyl pyrrolidine, VII, was prepared from the corresponding pyrrolidine alkanol, VI. The use of intermediates such as VII for spirane preparations has been known for many years,[4,5] but it is only recently that the convenient lithium aluminum hydride reduction procedure for preparing an alkanol VI from an amidic acid, IV (or ester V), has been available. The needed amidic acid is easily obtained by reaction of a heterocyclic secondary amine with a dicarboxylic acid anhydride.[6]

Nonmethylated spiranes. The reaction of pyrrolidine with succinic anhydride gave the amidic acid (IV, R = R′ = H). The crude liquid methyl ester of this amidic acid was reduced to give the known[7] liquid pyrrolidinebutanol (VI, R = R′ = H).

Chart I. Synthetic Routes for the Preparation of Spirobipyrrolidinium Salts (R,R′ = —H or —Me)



The pyrrolidinebutanol was converted by hydrobromic acid to the bromobutyl hydrobromide (VII. HBr, R = R′ = H). This bromobutyl hydrobromide had been previously prepared by von Braun[4] in 1924 from the corresponding phenyl ether (VIII) derived from 4-phenoxybutyronitrile. The free bromobutylpyrrolidine liberated from its hydrobromide rapidly cyclized to give the hygroscopic[8] spirane bromide.[4]

cis- and trans-Dimethyl spiranes. When two methyl groups are introduced at positions 3 and 4 in one of the spirane rings (formula IX), the sub-

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(2) Taken in part from a Ph. D. Thesis submitted by Stephen Proskow to the Graduate School, University of Toronto, 1956. Fellow of the National Research Council, 1954–1955. Present address: Department of Chemistry, University of Illinois, Urbana, Ill.

(3) G. E. McCasland and Stephen Proskow, *J. Am. Chem. Soc.*, (a) **77**, 4688 (1955); (b) **78**, 5646 (1956); (c) **76**, 6087 (1954); (d) **76**, 3486 (1954).

(4) J. von Braun *et al.*, *Ber.* **57**, 187 (1924); **56**, 1994 (1923); **49**, 970 (1916).

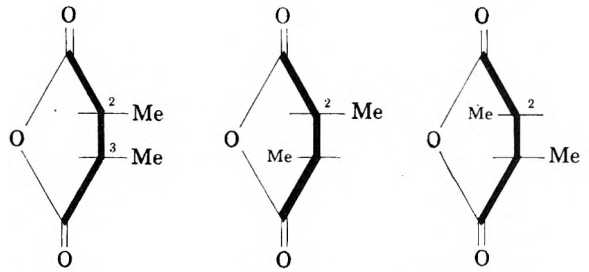
(5) A. Albert, *Ber.* **41**, 545 (1909).

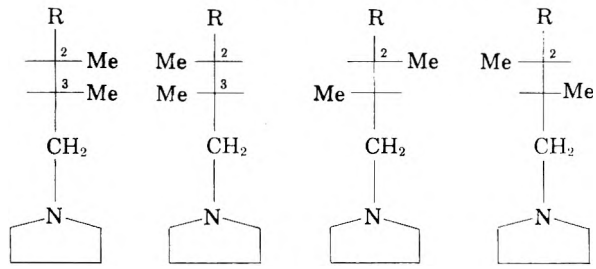
(6) D. Pressman, J. H. Bryden, and L. Pauling, *J. Am. Chem. Soc.*, **70**, 1352 (1948), carried out a similar reaction with piperidine in place of pyrrolidine.

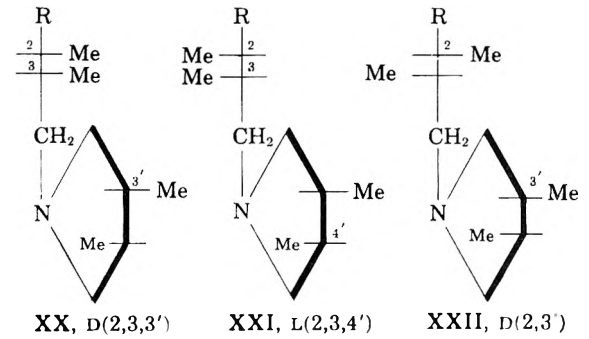
(7) R. B. Moffet, *J. Org. Chem.*, **14**, 862 (1949) prepared this pyrrolidinebutanol from pyrrolidine and 4-chlorobutanol-1.

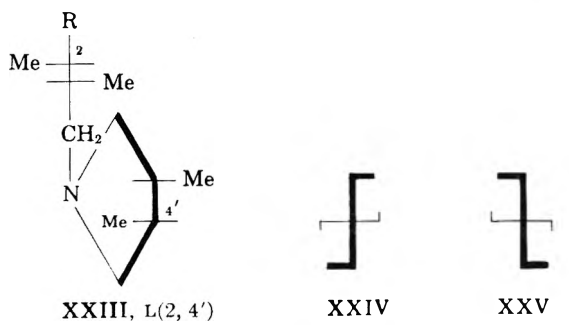
(8) It is of interest that the tetramethyl spirane shows no hygroscopic properties, perhaps because it lacks the extreme water-solubility of its dimethyl and unmethylated homologs.

CHART II. CONFIGURATIONAL FORMULAS OF INTERMEDIATES AND PRODUCTS.[9,11-14] (R = —COOH, —COOMe, —CH_2OH, —OR —CH_2Br. FOR PYRROLIDINE DERIVATIVES REPLACE THREE O ATOMS IN FORMULAS X, XI, XII WITH —NH— AND H, H)









stituted spirane can exist in two diastereomeric forms. The *meso-cis* diastereomer is conveniently depicted by the swastika-type projection formula,[9] XVII (Chart II), and the DL-*trans* diastereomer by the pair of formulas (XVIII, XIX). In order to prepare the *meso-cis* spirane, pyrrolidine was treated with *meso*-2,3-dimethylsuccinic anhydride,[10] X (Chart I). The preparation of the DL-*trans* spirane followed a parallel course.

In the first synthesis each of the monocyclic intermediates IV, V, VI, and VII had the DL-*erythro* configuration[11-13] (XIII, XIV). In the second synthesis each had the diastereomeric DL-*threo* configuration (XV, XVI).

The structure of the *trans* dimethylspirane bromide was confirmed by an independent preparation from pyrrolidine and DL-1,4-dibromo-2,3-dimethylbutane,[3d] and that of the *cis* isomer by a preparation from pyrrolidine and *meso*-1,4-dibromo-2,3-dimethylbutane.[3d]

trans/trans Tetramethyl spirane. The tetramethylspirane, IX (R = R′ = Me), can exist in four diastereomeric forms. All four have previously[3a,3b] been prepared. We have now demonstrated that the alternative synthesis described in our present article can be applied at least to preparation of the DL-*trans/trans* diastereomer[3a,3b,9] (XXIV, XXV).

By reaction of the racemic form of 3,4-dimethylpyrrolidine,[3c] (XI, XII) and of 2,3-dimethylsuccinic anhydride, we obtained an amidic acid, IV (R = R′ = Me), which is presumably a mixture of the

(9) For an explanation of the swastika-type projection formulas for spiranes, and of the double configurational prefixes such as "*trans/trans*." See Ref. 3b.

(10) (a) W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 839 (1899). For correction, see Ref. 3(b), footnotes 18 and 19. (b) P. E. Verkade and H. Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

(11) The side chains in formulas XIII–XVI and XX–XXIII are depicted by the usual projection-formula conventions, *i. e.*, lateral groups in front of plane of depiction, and lower-numbered end of chain at top. The rings in formulas XX–XXIII are twisted so that they can be depicted by vertical perspective-formulas, with ring regarded as perpendicular to paper, and shaded edge to front. (*Note:* To produce formulas XX–XXIII, each ring may be twisted *either* clockwise or counterclockwise. Formulas for *cis*-ring stereoisomers would require additional orientation conventions, which need not be considered here, but are proposed in Ref. 13.)

(12) Each of the monocyclic dimethyl intermediates in this article can exist in four stereoisomeric forms (2 racemic pairs), as shown in formulas XIII–XVI. Although no official rules for naming such stereoisomers are available, they can conveniently be designated by systematic configurational prefixes, as indicated in Chart II. For example, the prefix "D(2,3)" for stereoisomer XIII signifies that the methyl groups at positions 2 and 3 are both to the *right* of the properly oriented projection-formula. The corresponding racemic form (XIII, XIV) would be "DL(2,3)". For further explanation, see Ref. 13. However, when only racemic forms need be considered, the more familiar *erythro, threo* terminology is adequate, and it has been employed for the dimethyl intermediates in the present article.

(13) For an explanation of systematic configurational prefixes, see "A New General System for the Naming of Stereoisomers", 1953, a pamphlet available from Chemical Abstracts Service, Ohio State University, Columbus 10, Ohio. The capital letter "A" when included in a systematic configurational prefix signifies *absolute* configuration.

two *threo/trans* diastereomers,[14] DL-XXII and DL-XXIII. This diastereomeric mixture without separation was carried through the methyl ester (V) and alkanol (VI) stages. The picrate of the alkanol appears to consist of a single pure diastereomer, DL-XXII.

The pure alkanol (regenerated from picrate) was converted in the usual manner to the bromobutyl hydrobromide (VII. HBr). This product on cyclization gave a single diastereomerically pure spirane bromide. This product was found to be identical with the previously reported[3a,3b] DL-*trans/trans* tetramethylspirane derivative (XXIV, XXV). The corresponding picrates were also identical.

In a partially completed attempt to prepare the optically active (+)-*trans/trans* spirane,[3a,3b] XXIV, the above synthesis was repeated using dextrorotatory dimethylpyrrolidine,[15] XI, in place of racemic. After several steps, the apparently homogeneous picrate of a dextrorotatory pyrrolidinealkanol (XXII or XXIII) was obtained.

Using *meso* dimethylsuccinic anhydride and racemic dimethylpyrrolidine, we have also prepared an *erythro/trans* diastereomer (presumably a mixture of DL-XX and DL-XXI) of the above *threo/trans* amidic acid, but have not examined the further reactions of this intermediate.

EXPERIMENTAL

All melting and boiling points have been corrected. Melting points were taken on the Köfler micro hot-stage unless otherwise noted. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill., and by Mr. Charles K. Cross, Toronto.

NONMETHYLATED SERIES

4-Oxo-4-(1-pyrrolidinyl)-butyric acid. To a vigorously stirred solution of 25.0 g. of succinic anhydride in 200 ml. of absolute ether was gradually added a solution of 17.8 g. of pyrrolidine in 50 ml. of ether. After addition, the mixture was boiled for 1 hr.

The ethereal solution was decanted and the oily solid residue was dried, and recrystallized from ethyl acetate (charcoal), giving 29.2 g. of product, m.p. 105–108°. A second crop (2.3 g.) of the same m.p. was obtained. The combined product was again recrystallized, giving 25.8 g. (60%) of the nearly pure amidic acid, m.p. 106.5–108°.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.44; H, 7.59; N, 7.93.

The compound is readily soluble in cold water, and causes sodium carbonate solution to effervesce. When excess pyrrolidine was used in the original reaction, the pyrrolidine salt of the amidic acid was obtained; it was an oil, and on acidification the above free amidic acid was liberated.

4-(1-Pyrrolidinyl)-butanol-1 and its picrate. The above amidic acid (26.3 g.) was esterified with diazomethane in the usual manner, giving 17.5 g. of a colorless liquid product, b.p. 161°/8 mm., d_{20} 1.120, n_D^{20} 1.4798, M_D 47.0 (theoretical 47.0). The ester was soluble in about 10 parts of water and gave no effervescence with sodium carbonate.

The methyl ester (17.0 g.) in 100 ml. of absolute ether was slowly added at 25° with stirring to a mixture of 8.0 g. of lithium aluminum hydride and 150 ml. of absolute ether (prestirred 4 hr. under reflux). After addition, the mixture was boiled 2 hr. more with stirring.

To destroy excess hydride a minimum volume of water was cautiously added at 0°. The inorganic precipitate was removed and the ethereal filtrate extracted with a small volume of dilute hydrochloric acid. The acidic extract was basified with sodium hydroxide, saturated with sodium chloride, and extracted throughly with ether. The dried ethereal extract on evaporation yielded 10.6 g. (81%) of the colorless, liquid pyrrolidinebutanol, b.p. 103–104°/7 mm., d_{20} 0.943, n_D^{20} 1.4705, M_D 42.4 (theor. 42.4); reported[7] b.p. 113°/12 mm.

The picrate was obtained by treatment with ethereal picric acid, and was recrystallized three times from butanol-1, giving long yellow needles of m.p. 97–98°.

Anal. Calcd. for $C_8H_{17}NO\ C_6H_3N_3O_7$: N, 15.05. Found: N, 14.97.

1-(4-Triphenylmethoxybutyl)-pyrrolidinium chloride. The above free pyrrolidinebutanol (0.47 g.) was treated with 0.92 g. of triphenylchloromethane in 5 ml. of anhydrous pyridine for 15–20 hr. at 25°. Ten drops of water were added and after 30 min. the solution was vacuum-distilled to dryness. The residue was triturated with 15 ml. of ether, giving 1.10 g. of product m.p. 170–184°, which after 2 recrystallizations from benzene showed a constant m.p. of 194.5–195.5°. The trityl group content was determined by the method of Valentin.[16]

Anal. Calcd. trityl groups per molecule: 1.00. Found: 0.85.

The compound was readily soluble in ethanol or butanone but sparingly soluble in water; it gave a positive test for chloride ion.

1-(4-Bromobutyl)-pyrrolidinium bromide and chloroplatinate. To 1.9 g. of the pyrrolidinebutanol in a borosilicate glass tube was added 4.7 ml. of aqueous hydrogen bromide (saturated at 0°), and the tube sealed and heated at 150° for 3 hr. The tube content was vacuum-distilled, giving a dark brown oil which was dried over potassium hydroxide *in vacuo*, giving 3.8 g. of crude, hygroscopic solid hydrobromide.

A sample of the hydrobromide in water was treated with warm aqueous ammonium chloroplatinate, giving a bright red crystalline precipitate, which after two recrystallizations from water melted at 132.5–135°; reported[4] m.p. 133–134°.

When the above bromobutyl bromide was treated with sodium carbonate in an attempt to prepare the free bromobutylpyrrolidine, spontaneous cyclization to the spirane bromide took place; the spirane bromide was identified by conversion to the picrate (see below).

Spiro-(1,1')-bipyrrolidinium bromide and picrate. (A) From the bromobutyl pyrrolidine. The above bromobutyl bromide (0.8 g.) was dissolved in 41 ml. of 0.069*M* sodium hydroxide, and the solution heated at 90–100° for 30 min. The product was isolated by a procedure like that of von

(14) Each of the monocyclic tetramethyl intermediates in this article can exist in 12 stereoisomeric forms (6 racemic pairs). In Chart II only four of the six diastereomers are depicted (formulas XX–XXIII); each formula depicts one of two possible enantiomers. Since no official rules for naming such stereoisomers are available, we have in this article employed systematic configurational prefixes as indicated in Chart II. For example the prefix "D(2,3,3')" for stereoisomer XX signifies that the methyl groups at positions 2,3, and 3' are to the *right* of the properly oriented projection-perspective formula, and methyl group 4' to the left. The prefix "DL(2,3,3')" would represent the corresponding racemic form. For further explanation, see Ref. 13.

(15) The (+)-3,4-dimethylpyrrolidine has previously been shown to have the absolute configuration XI (see Ref. 3b). The absolute configurations of the optically active compounds now reported can be deduced from that of the dimethylpyrrolidine starting material.

(16) F. Valentin, *Chem. Zentr.*, 103, I 2160 (1932).

Braun,[4] giving 0.56 g. (97%) of the hygroscopic spirane bromide.

To the spirane bromide (0.28 g.) in 5 ml. of water was added 1 mole of saturated aqueous picric acid, giving 0.16 g. (34% based on spirane bromide) of the spirane picrate, long bright yellow needles, m.p. 259–261°. The melting point was unchanged on recrystallization from 95% ethanol.

Anal. Calcd. for $C_8H_{16}N \cdot C_6H_2N_3O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 48.17; H, 5.34; N, 15.69.

(*B*) *From dibromobutane.* To 10.0 g. of 1,4-dibromobutane was added 3.27 g. of pyrrolidine and 62 ml. of 0.74*M* sodium hydroxide, and the mixture refluxed for 1 hr. A 4.6 g. (49%) yield of the above spirane bromide was obtained. The spirane picrate obtained from this bromide was identical with that above; a mixed m.p. was not depressed.

ERYTHRO OR CIS-DIMETHYL SERIES

DL-*Erythro-2,3-dimethyl-4-oxo-4-(1-pyrrolidinyl)-butyric acid.* A well stirred mixture of 12.0 g. of *meso*-2,3-dimethylsuccinic anhydride[10] and 8.04 g. of pyrrolidine in 150 ml. of absolute ether was boiled under reflux for 2 hr. The total residue after vacuum-distillation was dissolved in sodium chloride-saturated 0.5*M* hydrochloric acid (300 ml.) and the product extracted with chloroform (4 × 100 ml.). The residue from evaporation of the chloroform extract was dried, giving 18.6 g. (99%) of product melting at 128–132°. Recrystallization from ethyl acetate (charcoal) gave 9.4 g. of colorless crystals, m.p. 130–132.5°—or 12.8 g. including the second and third crops which were nearly as pure. A sample recrystallized repeatedly from ethyl acetate and from benzene melted at 132–134°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.79; H, 8.59; N, 7.17.

The compound is soluble in butanone or water, and insoluble in hot petroleum ether.

DL-*Erythro-2,3-dimethyl-4-(1-pyrrolidinyl)-butanol-1.* The above oxobutyric acid (11.3 g.) on treatment with ethereal diazomethane gave 10.7 g. (90%) of the colorless, liquid methyl ester, b.p. 123–124°/1 mm., d_{20} 1.060, n_D^{20} 1.4728, M_D 56.5 (theoretical 56.2).

Reduction of the methyl ester (9.4 g.) with lithium aluminum hydride by the above procedure gave 5.8 g. (78%) of the colorless liquid pyrrolidinebutanol, b.p. 81–83°/0.8 mm., d_{20} 0.923, n_D^{20} 1.4679, M_D 51.6 (theoretical 51.7). The product was characterized by conversion to the dimethylspirobipyrrolidinium picrate and to the bromobutyl chloroaurate (see below).

The pyrrolidinebutanol gave a picrate of m.p. 71.5–75° and a trityl ether hydrochloride of m.p. 169–173°, but these derivatives were not further characterized. The pyrrolidinebutanol hydrobromide was very hygroscopic.

DL-*Erythro-1-bromo-2,3-dimethyl-4-(1-pyrrolidinyl)-butane hydrobromide and chloroaurate.* The dimethylpyrrolidinebutanol (1.0 ml.) was treated with saturated aqueous hydrogen bromide in a sealed tube (100°, 4 hr.) in a manner similar to that described above.

The tube contents on evaporation in vacuo gave 1.79 g. of gray-brown solid residue, m.p. 130–148°. This material was recrystallized from 4-methylpentanone-2 (charcoal), giving (including second crop) 0.98 g. (57%) of colorless transparent plates, m.p. 138–144°. The melting behavior was not changed by further recrystallization.

To 0.15 g. of this hydrobromide was added aqueous chloroauric acid (1 mole), giving 0.29 g. of rust-colored precipitate (presumably a hydrate), m.p. 99–120°. The melting point of the product dropped to 78–80° on recrystallization from ethanol, and increased to 79.5–82° on 3 additional recrystallizations from ethanol. The resulting product was apparently not solvated.

Anal. Calcd. for $C_{10}H_{20}NBr \cdot HAuCl_4$: Au, 34.34. Found: Au, 34.41.

meso-cis-3,4-Dimethylspiro-(1,1')-bipyrrolidinium bromide. (*A*) *From dibromodimethylbutane.* A mixture of 3.0 g. of *meso*-1,4-dibromo-2,3-dimethylbutane,[3d] 1.0 ml. of pyrrolidine, and excess sodium hydroxide was refluxed for 90 min. The product was isolated by the procedure (*B*) below, giving 2.13 g. (76%) of spirane bromide melting at 295–297° (capillary, decomp.). After repeated recrystallization from acetone, hygroscopic crystals of constant m.p. 295–296.5° (sealed capillary tube, decomp.) were obtained, still not entirely pure.

Anal. Calcd. for $C_{10}H_{20}NBr$: C, 51.28; H, 8.61; N, 5.98. Found: C, 49.05; H, 9.10; N, 5.76.

(*B*) *From bromobutyl bromide.* To the bromobutyl bromide (0.57 g.) was added 7.2 ml. of 0.255*M* sodium hydroxide, and the two phase mixture refluxed until clear (1 hr.). The clear solution at 0° was treated with 10 ml. of 10*M* potassium hydroxide solution, and extracted with chloroform (3 × 10 ml.). Addition of ether to the separated, dried chloroform extract precipitated 0.19 g. (45%) of the hygroscopic spirane bromide, m.p. 294–298° (cap., decomp.), identical with the above product. The product was characterized as its chloroaurate and picrate (see below).

meso-cis-3,4-Dimethylspiro-(1,1')-bipyrrolidinium picrate. A concentrated aqueous solution of the spirane bromide (prepared from dibromodimethylbutane) was added to *M*/5 aqueous trithanolamine picrate, giving bright yellow needles, m.p. 124–125.5°.

Anal. Calcd. for $C_{10}H_{20}N \cdot C_6H_2N_3O_7$: C, 50.24; H, 5.80. Found: C, 50.66; H, 5.77.

When spirane bromide prepared from the bromobutyl bromide was used, the picrate melted at 122–125.5°, and after recrystallization from 95% ethanol, at 124.5–126°. A mixed melting point with the above picrate was not depressed.

meso-cis-3,4-Dimethylspiro(1,1')-bipyrrolidinium chloroaurate. The spirane bromide (100 mg. prepared from bromobutyl bromide) in water was stirred for 30 min. with excess freshly precipitated and washed silver chloride. After removal of silver salts by filtration, the filtrate was evaporated to give the crystalline, hygroscopic chloride. This chloride on treatment with aqueous chloroauric acid tetrahydrate gave a precipitate, which was recrystallized from 95% ethanol, giving broad, bright yellow plates, m.p. 68–69°.

Anal. Calcd. for $C_{10}H_{20}NAuCl_4$: Au, 39.97. Found: Au, 39.85.

The spirane bromide prepared from dibromodimethylbutane gave a chloroaurate which was shown by melting point and mixed melting point to be identical with the above.

THREO OR TRANS DIMETHYL SERIES

DL-*Threo-2,3-dimethyl-4-oxo-4-(1-pyrrolidinyl)-butyric acid.* Racemic 2,3-dimethylsuccinic anhydride[10] (11.2 g.) was treated as for the *meso* anhydride (see above). However, the ether extract residue was dissolved in 200 ml. of chloroform, and the solution extracted with 1*M* hydrochloric acid (2 × 50 ml.). The combined aqueous extract was then saturated with sodium chloride and extracted with chloroform (3 × 50 ml.). The combined chloroform solutions (350 ml.) on vacuum-distillation gave a solid residue which was recrystallized from ethyl acetate (charcoal), giving 12.0 g. (70%, including second and third crops) of product melting at 104–107°. The melting behavior was unchanged by further recrystallization from ethyl acetate or benzene-petroleum ether.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.55; N, 6.92.

DL-*Threo-2,3-dimethyl-4-(1-pyrrolidinyl)-butanol-1.* The above oxobutyric acid (7.7 g.) with ethereal diazomethane gave 6.8 g. (83%) of the colorless, liquid methyl ester, b.p. 174–175°/12 mm., d_{20} 1.058, n_D^{20} 1.4724, M_D 56.5 (theoretical 56.2).

On reduction of the ester (5.7 g.) as for the *erythro* diastereomer, 3.6 g. (79% based on ester) of the colorless, liquid pyrrolidinebutanol were obtained, b.p. 134–135°/12 mm., d_{20} 0.929, n_D^{20} 1.4712, M_D 51.5 (theoretical 51.7). The product

was characterized by conversion to the bromobutyl chloroaurate (see below). A picrate of m.p. 83–88° and a crude trityl ether hydrochloride of m.p. 130–148° were also obtained, but were not fully characterized.

DL-*Threo-1-bromo-2,3-dimethyl-4-(1-pyrrolidinyl)-butane hydrobromide and chloroaurate.* From 2.0 ml. of the pyrrolidinebutanol by the above (*erythro*) procedure there was obtained 3.33 g. of crude gray-brown product, m.p. 133–142°. This material was twice recrystallized from 4-methylpentanone-2 (charcoal), giving 1.2 g. (36%) of colorless flakes, m.p. 130–137°. The melting point was unchanged by further recrystallization. The crystals were readily soluble in ethanol, and insoluble in benzene.

The hydrobromide was converted to the chloroaurate by the above (*erythro*) procedure. The crude product (presumably hydrated) melted at 131–149°, but after recrystallization from ethanol, pure deep red crystals of m.p. 97–99° were obtained.

Anal. Calcd. for $C_{10}H_{20}NBr \cdot HAuCl_4$: Au, 34.34. Found: Au, 34.44.

DL-*Trans-3,4-dimethylspiro-(1,1')-bipyrrolidinium bromide.* (*A*) *From dibromodimethylbutane.* From DL-1,4-dibromo-2,3-dimethylbutane[3d] treated as for the *meso* epimer (see above) there was obtained 5.2 g. (68%) of crude product, m.p. 264–268°. After recrystallization from ethanol-butanone (1:8) there was obtained (including second crop) 4.1 g. of colorless crystals, m.p. 267–269° (sealed capillary). The product was hygroscopic, but less so than its *meso* epimer, and melted without decomposing.

Anal. Calcd. for $C_{10}H_{20}NBr$: C, 51.28; H, 8.61; N, 5.98; Br, 34.13. Found: C, 51.44; H, 8.60; N, 5.74 Br, 34.64.

A picrate of m.p. 113–114.5° was obtained, but was not fully characterized.

(*B*) *From the bromobutyl bromide.* The *threo* bromobutyl bromide (0.5 g.) was cyclized by the above (*erythro*) procedure, but using a reflux time of only 10 min. On isolation, 0.23 g. (63%) of product melting at 261–265° was obtained, and shown to be identical with the product (A) above.

DL-*Trans-3,4-dimethylspiro-(1,1')-bipyrrolidinium chloroaurate.* The spirane bromide (prepared from bromobutyl bromide) was treated successively with silver chloride and chloroauric acid (see above *erythro* procedure). From the hygroscopic chloride a crude chloroaurate of m.p. 94–97° was obtained, and after three recrystallizations from ethanol it gave bright yellow plates of m.p. 97–98°.

Anal. Calcd. for $C_{10}H_{20}NAuCl_4$: Au, 39.97. Found: Au, 39.78.

The spirane bromide prepared from dibromodimethylbutane gave a chloroaurate which was shown by melting point and mixed melting point to be identical with the above.

TETRAMETHYL SERIES

2,3-Dimethyl-4-oxo-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butyric acid (mixture of DL*(2,3,3')diastereomer, XX, and* DL *(2,3,4') diastereomer, XXI).* Treatment of DL-3,4-dimethylpyrrolidine[3c] with *meso*-2,3-dimethylsuccinic anhydride[10] by the same procedure used for treatment of pyrrolidine itself (see above) gave 5.3 g. of crude mixed diastereomers, m.p. 115–122°. After several recrystallizations from benzene, crystals of m.p. 142–147° were obtained. Apparently the purified material still contains both of the *erythro/trans* diastereomers, but the ratio is not known.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.52; H, 8.72; N, 5.93.

2,3-Dimethyl-4-oxo-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butyric acid (mixture of DL*(2,3')diastereomer, XXII, and* DL*(2,4')diastereomer, XXIII).* The DL-3,4-dimethylpyrrolidine[3c] (2.5 g.) by treatment with DL-2,3-dimethylsuccinic anhydride[10] (see above *erythro* dimethyl oxobutyric acid procedure) gave a residue from the ether evaporation which was dissolved in chloroform (100 ml.), and the solution extracted with 1*M* hydrochloric acid and then with water (15 ml.; 10 ml.). On evaporation of the dried chloroform phase, 5.4 g. (97%) of crystals melting at 92–105° was obtained.

Anal. Calcd. for $C_{12}H_{21}NO_3$: N, 6.16. Found: N, 6.12.

The product, presumably a mixture of the two possible *threo/trans* diastereomers, XXII and XXIII, was readily soluble in ether and slightly soluble in water.

2,3-Dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butanol-1 picrate (single pure diastereomer DL*(2,3'), XXII.* The above mixture of *threo/trans* diastereomeric acids (5.3 g.) with diazomethane gave 4.8 g. (85%) of colorless liquid ester (presumably a diastereomeric mixture), b.p. 133–135°/2 mm., d_{20} 1.033, n_D^{20} 1.4651, M_D 64.6 (theoretical 65.5).

This ester (4.4 g.) on lithium aluminum hydride reduction gave 3.1 g. (87%) of colorless liquid pyrrolidinealkanol (presumably a diastereomeric mixture), b.p. 101–102°/2 mm.

By treatment of 2.92 g. of this pyrrolidinealkanol with ethanolic picric acid (3.34 g.), a picrate was obtained, and recrystallized four times from benzene, giving 2.9 g. of pale yellow crystals, m.p. 115–117°.

Anal. Calcd. for $C_{12}H_{25}NO \cdot C_6H_3N_3O_7$: C, 50.48; H, 6.59; N, 13.08. Found: C, 51.21; H, 6.21; N, 12.89.

This picrate is believed to consist of a single pure diastereomer, DL-XXII.

A 2.8 g. portion of the picrate in dilute aqueous hydrogen chloride was extracted with benzene, and the aqueous phase basified, salt-saturated, and extracted with ether. From the ethereal extract was obtained 0.94 g. (74%) of regenerated free pyrrolidinealkanol, b.p. 110–112°/4 mm., d_{20} 0.905, n_D^{20} 1.4595, M_D 60.3 (theoretical 60.9).

Dextrorotatory 2,3-dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butanol-1 picrate (single pure diastereomer D*(2,3')A, XXII).* When the above amidic acid preparation was repeated with dextrorotatory dimethylpyrrolidine[3a,b] and racemic dimethylsuccinic anhydride,[10] an amidic acid mixture with $[\alpha]_D^{23}$ +16.3° (ether, *c* 1) was obtained. With diazomethane, a methyl ester mixture with $[\alpha]_D^{25}$ +8.7° (ether, *c* 1) resulted. On reduction, a pyrrolidinealkanol mixture with $[\alpha]_D^{26}$ 5.7° (benzene, *c* 1) resulted. The picrate of this product after repeated recrystallizations from benzene attained a constant m.p. of 114.5°–117°. A mixed melting point with the above racemic picrate was not depressed.

This picrate appears to consist of a single pure diastereomer and is probably one of the active forms of the above racemic picrate.

1-Bromo-2,3-dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butane hydrobromide (single pure diastereomer DL*(2,3'), XXII).* The pure liquid racemic pyrrolidinealkanol (regenerated from picrate) was treated by the above (*meso* dimethyl) procedure, giving 0.85 g. of a light-brown powder, m.p. 143–148° (sintered 125°). A sample recrystallized twice from 4-methylbutanone-2 (charcoal) gave colorless crystals of m.p. 152–165°. The product was characterized by conversion to the spirane bromide and picrate (see below).

DL-*trans/trans-3,4,3',4'-Tetramethylspiro-(1,1')-bipyrrolidinium bromide and picrate.* The above bromobutyl bromide (0.27 g., m.p. 143–148°) was mixed with 3.98 ml. of 0.205*M* sodium hydroxide, and the turbid mixture refluxed for 30 min. From the mixture was isolated by the above procedure 0.093 g. of product melting at 314° (cap., decomp.). Recrystallization from butanone gave the DL-*trans/trans* spirane bromide, m.p. 318° (cap., decomp.); reported[3a,b] m.p. 323–324° (cap., decomp.).

A sample was treated with triethanolamine picrate, giving after recrystallization from aqueous ethanol long yellow needles of the DL-*trans/trans* spirane picrate, m.p. 130–135.5°; reported[3a,b] m.p. 134.5–136°.

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Reversible Oxidation of Phthalocyanines

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Phthalocyanines can be reversibly oxidized in nonaqueous media to substances soluble in organic solvents and from which the phthalocyanines can be regenerated by reduction. Several different classes of suitable oxidizing agents were found. The properties of the oxidation products suggest that they are formed by the addition of a molecule of the oxidant to the phthalocyanine molecule but modified by solvolysis in the case of reactive solvents. Zinc $\alpha,\beta,\gamma,\delta$-tetraphenylporphine can also be reversibly oxidized in benzene by benzoyl peroxide.

The oxidation of phthalocyanines has been reported by several investigators.[1-8] In these studies the oxidation was mostly destructive because either the oxidants or the conditions were not suitable for the formation of reversible oxidation products except in traces or only as transient intermediates which were rapidly hydrolyzed. In no case was the oxidation product isolated and analyzed.

More recently, however, F. Baumann and his colleagues have described[9,10] products obtained by reacting a mole of copper phthalocyanine or cobalt phthalocyanine with a great excess of one of two oxidizing agents: eleven moles of bromine in methanol or fifteen moles of concentrated nitric acid in nitrobenzene. The final products are soluble in organic solvents, are reduced to phthalocyanines, and are related to the oxidation products discussed in this paper.

The operable oxidants which were tested can be divided into four groups: peroxides and hydroperoxides[11]; chlorine and bromine[12,13]; organic hypochlorites[14]; and N-halogen compounds. The methods of preparing reversible oxidation products of phthalocyanines with these oxidants have already been described in the indicated references, but additional work, particularly with benzoyl peroxide, has shed new light on the subject.

It was found that benzoyl peroxide reacts with copper phthalocyanine in chloroform, very much faster than its rate of spontaneous decomposition, to give well defined oxidation products.

More specifically, about 70% of the benzoyl peroxide (initial concentration: 0.14 molar) reacts with an excess of finely divided copper phthalocyanine in U.S.P. chloroform (0.57% by weight of alcohol) at 30° within the first 2 hr. This rate is about 1800 times greater than the rate of spontaneous decomposition of the peroxide in chloroform at the same temperature as determined by Cass.[15] No carbon dioxide is evolved and the rate is not affected by the presence or absence of molecular oxygen. The rate, however, is about 60% lower in pure chloroform and the oxidation product, instead of yielding a bright pigment on reduction as in the case of the product obtained in chloroform containing alcohol, gives a dull, dark blue precipitate.

Although no accurate rate measurement was made, it was evident that the relative order of reactivity of the peroxides is: bis(2,4-dichlorobenzoyl) peroxide > bis(4-chlorobenzoyl) peroxide > benzoyl peroxide.

It is concluded from these facts that the reaction between benzoyl peroxide and copper phthalocyanine (I, Fig. 1) does not involve the initial decomposition of the peroxide into benzoate free radicals, but that the decomposition of the peroxide is induced by the phthalocyanine as in the reactions discussed by several investigators.[17-20] The high rate of reaction, the absence of carbon dioxide, and the relative order of reactivity of the peroxides are consistent with this type of reaction.

The course of the reaction is shown in Fig. 4. The

* Present address: Elastomer Chemicals Department.

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upper right hand portion of Fig. 1 represents the phthalocyanine molecule, A:B the oxidant, the broken arrows indicate the movement of a single electron, and the solid curved arrow the movement of a pair of electrons. In certain respects this mechanism is similar to the one proposed by Horner and Betzel[19] for the reaction between benzoyl peroxide and trialkylamines.

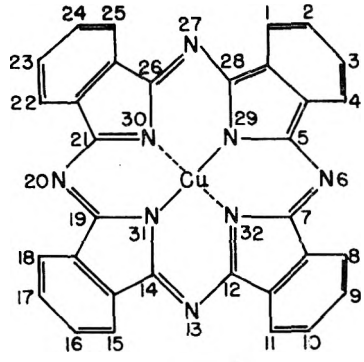

FIG. 1.—I[15]

It will be noted that the *o*-quinoid ring is changed into an *o*-phenylene ring and a carbonium ion is formed with the electron-deficient carbon atom at position 28. The reaction occurs more readily in the presence of alcohol because an ion is formed. By the movement of other pairs of electrons, the electron-deficient carbon atom can also be located at equivalent positions 26, 21 or 19 without converting any of the *o*-phenylene rings into an *o*-quinoid ring. Position 21 is thought to be the most favorable because the molecule can then be folded along the 5–21 axis thus destroying the extensive resonance of the planar phthalocyanine molecule without distorting too much the central coordination system consisting of the metal and the four nitrogen atoms. Observe that no ring is broken in this reaction.

The carbonium ion resulting from the reaction of benzoyl peroxide and copper phthalocyanine can react in several ways. In the absence of enough hydroxylic solvent it reacts with the benzoate anion forming II, A and B = benzoate Fig. 2. Since atoms 5 and 21 are allylic, the benzoate groups can be replaced by alkoxy groups. Hence, by diluting the chloroform solution of the oxidation product with methanol, II, A = benzoate, B = methoxy is first formed and then II, A and B = methoxy. The products which are actually recovered are in agreement with these structures.

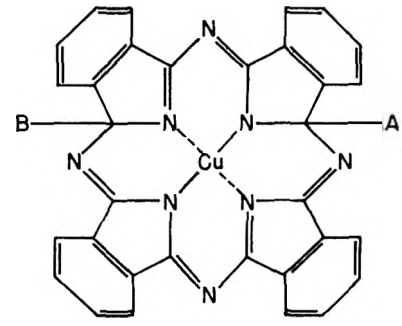

FIG. 2.—II[21]

A dark, reddish brown solution is obtained by filtering the reaction mixture of copper phthalocyanine and benzoyl peroxide in U.S.P. chloroform at the end of 2 hr. If this solution is concentrated and diluted with methanol, a product is rapidly deposited whose composition corresponds to that of II, A = benzoate, B = methoxy, and another

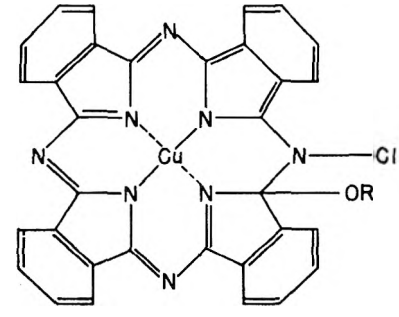

FIG. 3.—III

crop of crystals is recovered from the filtrate on long standing whose composition corresponds to that of II, A and B = methoxy. These products are less soluble in methanol than in chloroform, are hydrolyzed by mineral acid to give four moles of phthalimide and four moles of ammonia per mole, and yield the expected amount of copper phthalocyanine on reduction.

These structures are also supported by the infrared spectra. Fig. 5a is the infrared spectrum of II, A = benzoate, B = methoxy and Fig. 5b is that of II, A and B = methoxy. The basic pattern of the two spectra is the same and the region covered by 6.0–6.3 μ is consistent with the presence of two different types of C=N bonds (the peripheral and the inner, respectively), and the aromatic C=C bond. The strong band at 5.8 μ in Fig. 5a is evidence for the presence of the benzoate group and the

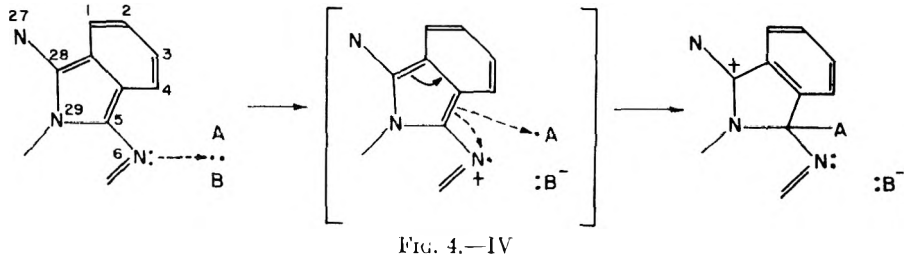

FIG. 4.—IV

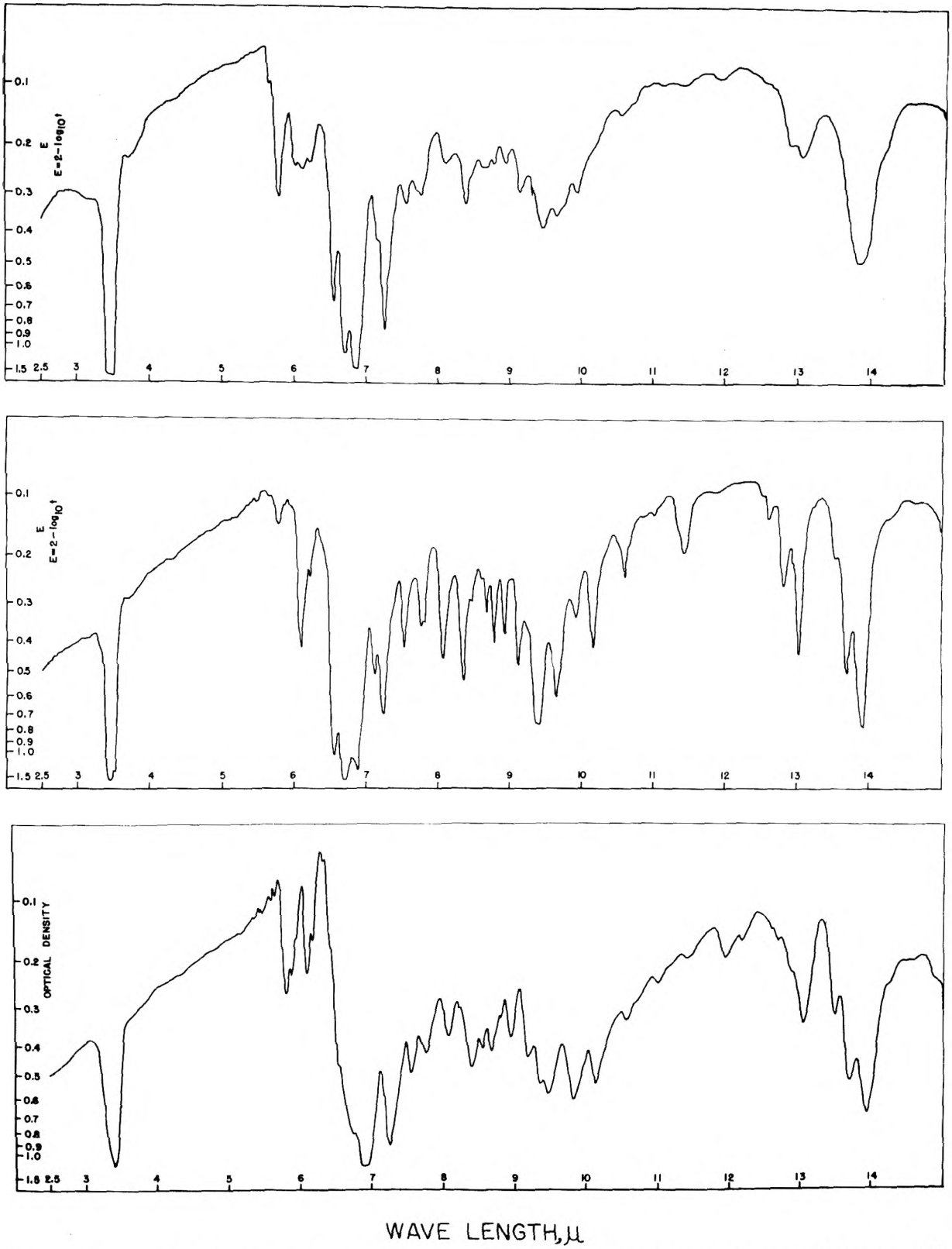

FIG. 5.—INFRARED SPECTRA OF THE REVERSIBLE OXIDATION PRODUCTS OF COPPER PHTHALOCYANINE. Nujol mull, 0.025 mm., NaCl prism. Top: (Fig. 5a), (Fig. 2, A = benzoate, B = methoxy). Middle: (Fig. 5b), (Fig. 2, A and B = methoxy). Bottom: (Fig. 5c), (Fig. 3, R = *t*-butyl).

weak band at 8.9μ suggests the presence of C—O—CH_3. The 5.8μ band in Fig. 5b is much weaker indicating the possibility that the carbonyl band is due to a minor constituent, and the stronger band at 8.9μ is consistent with the presence of two C—O—CH_3 groups.

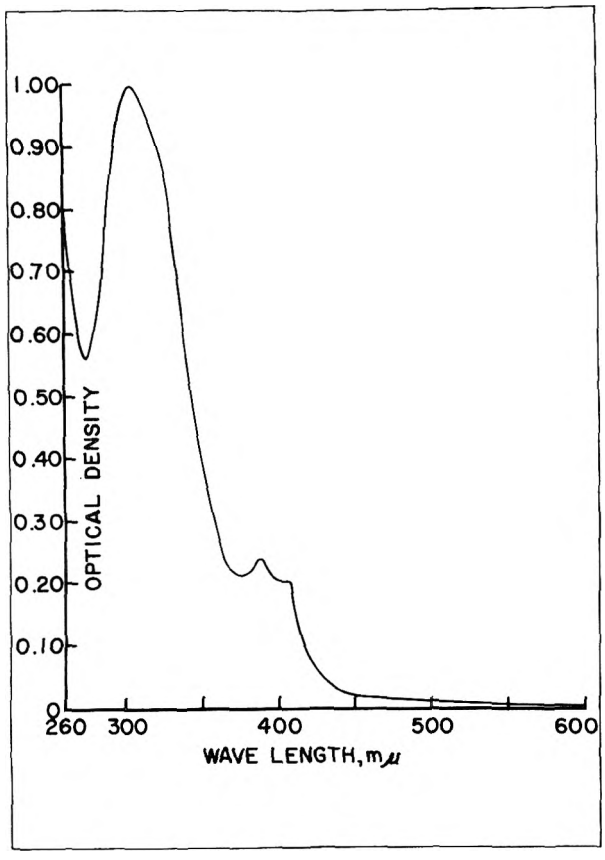

FIG. 6.—ULTRAVIOLET SPECTRUM OF (FIG. 2, A AND B = METHOXY). One centimeter chloroform solution. 0.0156 gram per liter (2.45×10^{-5} molar). Extinction coefficient = 41,000 at 304 mμ.

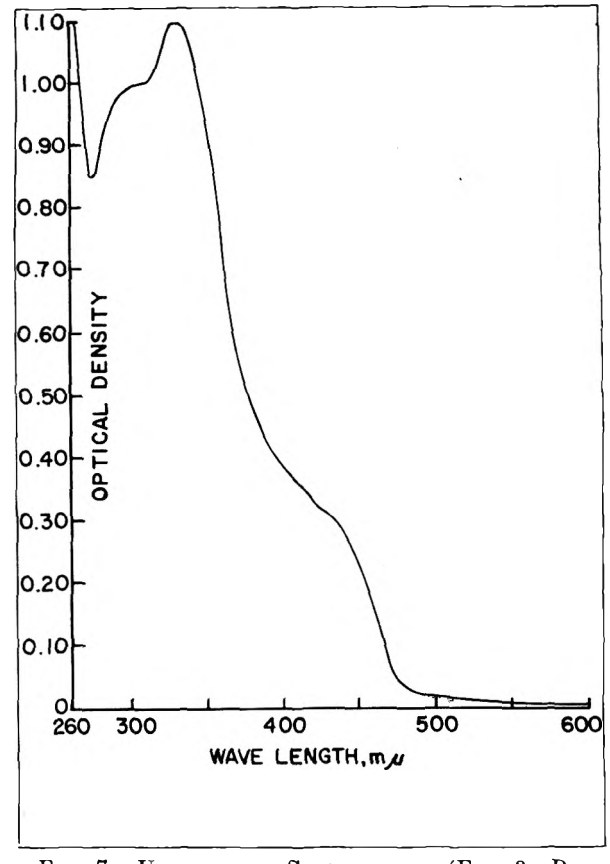

FIG. 7.—ULTRAVIOLET SPECTRUM OF (FIG. 3, R = TERTIARY-BUTYL). One centimeter chloroform solution. 0.0241 gram per liter (3.52×10^{-5} molar). Extinction coefficient 28,000 at 302 mμ and 31,000 at 330 mμ.

In contrast to phthalocyanines which are blue or green solids of high tinctorial power, the reversible oxidation products are yellowish or reddish solids of low tinctorial power. Fig. 6 is the ultraviolet spectrum of II, A and B = methoxy. It has a peak at 304 mμ and is nearly identical with the spectrum of II, A = benzoate, B = methoxy.

The reaction of phthalocyanines with chlorine in methanol follows a similar course. Mixtures of II, A = chlorine, B = methoxy and II, A = hydroxyl, B = methoxy are obtained by reacting copper phthalocyanine with chlorine[12,13] and drowning the filtrate in aqueous sodium carbonate or sodium hydroxide. In this case the initial carbonium ion reacts with methanol to give II, A = chlorine, B = methoxy some of which is converted into II, A = hydroxyl, B = methoxy by the base. The ultraviolet spectra of these products are also very similar to Fig. 6.

The elementary analyses of the crystalline oxidation product, obtained by reacting copper phthalocyanine and *tertiary*-butyl hypochlorite[14] in methanol, correspond to those of III, R = *t*-butyl. Fig. 7 is its ultraviolet spectrum and Fig. 5c is its infrared spectrum.

Note that the structure of this oxidation product is different from that of the others: the chlorine is on a peripheral nitrogen atom and there is an *o*-quinoid ring in the molecule. Fig. 3 shows the occupation of positions 6 and 7 by the substitutents, but isomers are possible at positions 6–12, 6–14, and 13–14. The chlorine is thought to be on the nitrogen atom because chlorine gas is generated when it is treated with concentrated sulfuric acid, and although it contains no chlorine which reacts with caustic or silver nitrate, chloride ions are found in the filtrate after its reduction to copper phthalocyanine with a reducing agent free from chloride ions. Its ultraviolet spectrum has peaks at 302mμ and 330mμ, the latter not being found in the spectra of the others. Its infrared spectrum resembles Fig. 5b more closely than Fig. 5a. The strong absorption in the region of 5.8–6.0μ cannot be accounted for since it is almost certain that none of the carbon atoms of the phthalocyanine molecule has been changed into a carbonyl group, an event which requires the opening of one of the nonbenzonoid rings.

It is concluded, therefore, that hypochlorites merely add to a peripheral C=N bond or one of its conjugated equivalents, the chlorine going on the nitrogen atom. The N-halogen oxidants might also react in this manner but, aside from establishing the formation of reversible oxidation products, no

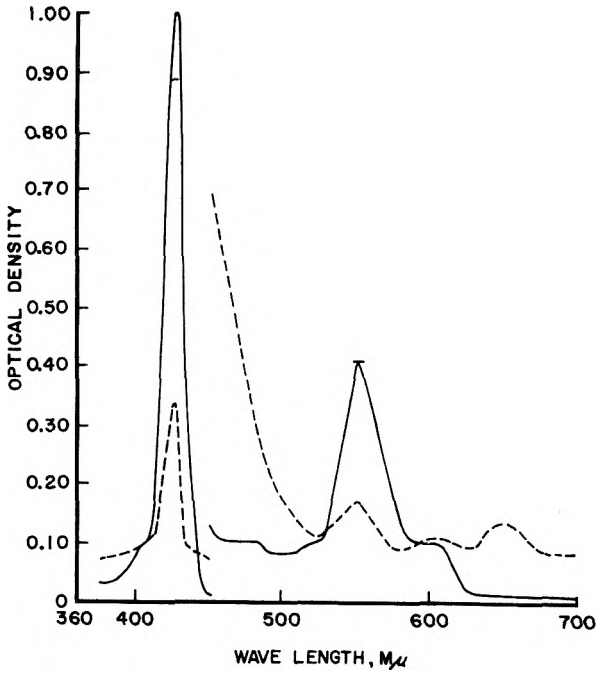

FIG. 8.—ULTRAVIOLET SPECTRUM OF ZINC $\alpha,\beta,\gamma,\delta$-TETRAPHENYLPORPHINE. One centimeter thiophene-free benzene solutions. Concentration up to 450 mμ: 0.00197 gram per liter (2.9×10^{-6} molar). Concentration above 450 mμ: 0.0197 gram per liter (2.9×10^{-5} molar). Solid line—before reaction with benzoyl peroxide: Extinction coefficient 345,000 at 425 mμ and 14,100 at 550 mμ. Dashed line—after reaction with 8.2×10^{-6} molar benzoyl peroxide at 24–27° for 20 hr. in the dark. Short horizontal lines at 425 mμ and 550 mμ indicate the extent of recovery of the absorption bands at these wave lengths on treating the oxidized solution with ascorbic acid.

further work was done with this class of oxidants.

The reversible oxidation of zinc $\alpha,\beta,\gamma,\delta$-tetraphenylporphine[22] was briefly investigated spectrophotometrically without isolating the oxidation product. The compound is oxidized in benzene by benzoyl peroxide to an unidentified product from which the original compound is regenerated by methanolic ascorbic acid. The porphine, however, is irreversibly oxidized if allowed to remain in contact with an excess of benzoyl peroxide. The ultraviolet spectra of zinc $\alpha,\beta,\gamma,\delta$-tetraphenylporphine and its oxidation product are shown in Fig. 8.[23–27]

EXPERIMENTAL

Tertiary-butyl hypochlorite was prepared according to Teeter and Bell.[28] Pure chloroform was made from U.S.P. chloroform by the conventional method. All other materials were either laboratory samples or commercial products used without further purification. No accurate rate measurements were made because it was difficult to establish and maintain standard conditions, especially to control the particle size of the phthalocyanines.

The ultraviolet and visible spectra were determined with a Cary Model 11 Recording Spectrophotometer. The infrared spectra were obtained with a Perkin-Elmer Model 12-C Spectrophotometer. The identities of the phthalocyanines recovered by reduction were determined by x-ray diffraction[29] with a Norelco 90° Diffractometer using Cu $K\alpha$ radiation.

Copper phthalocyanine and benzoyl peroxide. Twenty-one and three-tenths g. of *alpha*-copper phthalocyanine (0.037 mole), range of particle size 0.05 to 0.1 μ, found: N, 19.7; Cu, 10.8; required: N, 19.5; Cu, 11.0) and 7.02 g. of benzoyl peroxide (0.029 mole) in 217 ml. of U.S.P. chloroform containing 1.84 g. of ethanol (0.04 mole) were agitated on a magnetic stirrer for 2 hr. at 27–30°. The flask was connected to a gas bubbler containing aqueous barium hydroxide and showed that no gas was evolved during the reaction. The temperature was maintained spontaneously.

The reaction mixture was filtered and the unreacted phthalocyanine was washed with chloroform and dried. It weighed 9.95 g. Hence, 11.35 g. of phthalocyanine (0.0197 mole) had dissolved. Since there was no direct method of determining the peroxide in the reaction mixture, it was assumed that it took a mole of peroxide to dissolve a mole of phthalocyanine. On this basis 0.0197 mole of peroxide had reacted in 2 hr. or 68%.

The following data were obtained by aliquoting the filtrate but they are presented as if the entire sample had been used for each analysis.

The filtrate (296 ml.) contained 10.5 g. of copper phthalocyanine (0.0182 mole) recoverable by reduction with ascorbic acid. The filtrate was evaporated under vacuum to about 30 ml. and stirred into 300 ml. of anhydrous methanol. The precipitate which formed rapidly was filtered and dried at 85°. Four and nine-hundredths g. of greenish brown powder (0.0056 mole) were obtained.

Anal. Calcd. for II, A = benzoate, B = methoxy (Fig. 2), $C_{40}H_{24}CuN_8O_3$: N, 15.4; Cu, 8.73; phthalimide, 80.5; ammonia, 9.3; copper phthalocyanine, 79.1; benzoic acid, 16.75. Found: N, 15.8; Cu, 9.1; phthalimide, 73; ammonia, 8.8; copper phthalocyanine, 68; benzoic acid, 10.8.

Another crop of crystals was obtained from the last filtrate on standing overnight at room temperature. Three and eighty one-hundredths g. of purplish brown crystals (0.006 mole) were recovered by filtering and drying at 85°.

Anal. Calcd. for II, A and B = methoxy, $C_{34}H_{22}CuN_8O_2$: N, 17.58; Cu, 9.96; phthalimide, 91.8; ammonia, 10.65; copper phthalocyanine, 90.4. Found: N, 17.2; Cu, 9.8; phthalimide, 82; ammonia, 11.64; copper phthalocyanine, 87.

Phthalimide was determined gravimetrically by hydrolyzing 0.5 g. of the oxidation product with 20 ml. of methanol and 2 ml. of concentrated hydrochloric acid for 10 min. at room temperature, then adding 80 ml. of water and concentrating on a steam bath to 45 ml. The suspension was chilled in ice water, the crystals of phthalimide were collected on a Gooch crucible, dried, and weighed. They melted at 235° (lit. 238°) and contained 9.4% N; required for $C_8H_5NO_2$: N, 9.5.

Ammonia was determined by making the filtrate from the phthalimide analysis alkaline with sodium hydroxide

(21) This general structure was suggested by R. A. Brooks and first published in (11).

(22) Professor Melvin Calvin supplied the sample of this compound and his kindness is gratefully acknowledged.

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and distilling off the ammonia into standardized hydrochloric acid.

Copper phthalocyanine was determined gravimetrically by dissolving 0.5 g. of the oxidation product in 50 ml. of methanol, adding 0.25 g. of ascorbic acid and warming on a steam bath for 20 min. One hundred fifty ml. of water were then added, neutralized with sodium carbonate, heated for 1 hr., filtered, washed with methanol and ether, and dried at 85°. The blue crystals were identified as *alpha*-copper phthalocyanine by x-ray diffraction. It took 1.2 moles of ascorbic acid to reduce a mole of the oxidation product, and the excess is thought to be due to the difficulty of the end point.

Benzoic acid was estimated by concentrating the filtrate from the copper phthalocyanine analysis to 100 ml., acidifying with sulfuric acid, extracting with ether, and evaporating to dryness. The white crystals obtained by recrystallizing the residue melted at 122°; mixed melting point with an authentic sample of benzoic acid 122°.

Similar results were obtained when the reaction was run in an atmosphere of nitrogen instead of air. When purified chloroform was substituted for the U.S.P. material, 0.0082 mole of benzoyl peroxide reacted in 2 hr. and the filtrate contained only 1.36 g. of copper phthalocyanine (0.0024 mole) recoverable by reduction.

Metal-free phthalocyanine and phthalocyanines of magnesium, zinc, iron, cobalt, and nickel are also reversibly oxidized but perchlorinated copper phthalocyanine is resistent to oxidation.

Phthalocyanines react more readily in the *alpha*-form than in the *beta*-form of crystals.

The relative order of reactivity of the peroxides, estimated by observing the start of the formation of the oxidation products as judged by sight and confirmed by spot-testing with a reducing agent, is: bis(2,4-dichlorobenzoyl) peroxide > bis(4-chlorobenzoyl) peroxide > benzoyl peroxide > lauroyl peroxide > *tertiary*-butyl hydroperoxide. Perbenzoic acid also oxidizes phthalocyanines. Neither anhydrous nor aqueous hydrogen peroxide gave any measurable quantity of the oxidation product.

Ether, acetone and 2-alkoxyethanols are satisfactory solvents for use with peroxides. No advantage is gained by deviating from room temperature.

The oxidation products are stable if protected from reducing agents and hydrolytic conditions. They are brownish solids which do not melt but are converted into phthalocyanines between 140–220°. Any reducing agent will regenerate the phthalocyanines which are always obtained in the *alpha*-form of crystals.

Copper phthalocyanine and chlorine. Five g. of *beta*-copper phthalocyanine (0.0087 mole) were suspended in 100 ml. of anhydrous methanol and stirred while 1.5 g. of chlorine gas (0.021) were passed into the mixture in 5 min. The charge was stirred for 5 min. more and filtered directly into 100 ml. of water containing 10 g. of sodium carbonate (0.095 mole). The precipitate was filtered, washed with water, and dried at 50°. Two and a half g. of yellow powder were obtained.

Anal. It is difficult to assign an exact composition to the oxidation products prepared by this method because they are contaminated by various substances, such as copper oxide and phthalimide, which are insoluble in aqueous sodium carbonate. Found: N, 15.4; Cu, 9.0; Cl, 2.9, copper phthalocyanine by reduction, 72.

Iron phthalocyanine and chlorine. Twenty-two and seven-tenths g. of very finely ground iron phthalocyanine (0.04 mole) were suspended in 360 ml. of anhydrous methanol and stirred vigorously. Six and a quarter g. of chlorine gas (0.088 mole) were passed into the suspension in 5 min. during which period the temperature of the reaction mass rose spontaneously from 24° to 33°. The charge was stirred for 5 min. more and filtered directly into 400 ml. of water containing 40 g. of sodium carbonate (0.38 mole). The precipitate was filtered, washed with dilute aqueous sodium carbonate, and dried in a vacuum oven at 50°. Fourteen and a half g. of yellow powder were obtained.

Anal. As in the previous example and for the same reason it is difficult to assign an exact composition to this oxidation product. Found: N, 16.3; Cl, 1.3; Fe, 9.44; iron phthalocyanine by reduction, 87.

Iron phthalocyanine possesses interesting catalytic properties, such as for the decomposition of hydrogen peroxide and organic hydroperoxides and for the autoxidation of many substances. Dispersion of iron phthalocyanine on different supports can be prepared conveniently by treating the supports with a solution of the above product and depositing the phthalocyanine *in situ* by reduction with, for example, ascorbic acid.

Copper phthalocyanine and tertiary-butyl hypochlorite. Fifty g. of *alpha*-copper phthalocyanine (0.087 mole) were vigorously agitated with 24 g. of *t*-butyl hypochlorite (0.221 mole) in one liter of anhydrous methanol at 25° for 70 min. The reaction mass was filtered and the filtrate was allowed to stand at room temperature for 3 days. Dark, reddish brown transparent crystals, consisting of stout needles pointed at both ends and measuring up to 600 by 40 μ, deposited during this period. They were removed by filtration, washed with methanol and dried at 82°. Three and fifty-five-hundredths g. of crystals were recovered.

Anal. Calcd. for III, R = *t*-butyl (Fig. 3), $C_{36}H_{25}ClCuN_8O$: N, 16.36; Cu, 9.28; Cl, 5.18, copper phthalocyanine by reduction, 84.1. Found: N, 16.98; Cu, 9.48; Cl, 5.26, copper phthalocyanine 75.

Reduction of the product dissolved in 2-methoxyethanol with titanium trichloride, hydriodic acid or hydrogenation showed that two equivalents of reducing agents are required to produce a mole of copper phthalocyanine. Chlorine is evolved when these crystals are treated with either concentrated sulfuric acid or aqueous hydrochloric acid.

An identical oxidation product was obtained by treating *beta*-copper phthalocyanine in the same way.

Zinc $\alpha,\beta,\gamma,\delta$-tetraphenylporphine and benzoyl peroxide. Thiophene-free benzene solution of the porphine containing 0.00197 g. per liter is a purple solution which gave spectrum of Fig. 8, solid line. To this solution was added 0.00198 g. of benzoyl peroxide. After standing at 24–27° for 20 hr. in the dark, this solution had become yellow and gave spectrum of Fig. 8, dashed line. The optical density at 425mμ had dropped from 1.00 to 0.34, and that at 550mμ from 0.041 to 0.017. On the other hand, new weak peaks had developed at 450mμ and 645mμ. Twenty ml. of the oxidized solution were mixed with 5 ml. of methanol saturated with ascorbic acid, allowed to remain at 24–27° for 20 hr. in the dark, and washed with water to remove the methanol and excess ascorbic acid. The dried benzene solution was purple again and gave a spectrum similar to Fig. 8, solid line except that the optical density at 425mμ was 0.89 instead of 1.00. The oxidized solution did not regenerate a purple solution on treatment with ascorbic acid when it had aged for 3 days.

The optical density at 425mμ was reduced to 0.08 in 20 hr. when the concentration of benzoyl peroxide was increased to 220×10^{-6} mole, and a definite peak was developed at 450mμ (optical density: 0.09).

It was found that *t*-butyl hydroperoxide and α-cumyl hydroperoxide also oxidize the porphine but very much more slowly than benzoyl peroxide.

Acknowledgment. The author wishes to express his thanks to H. B. Gottlieb for supplying many of the phthalocyanines, to R. C. Ferguson for interpreting the infrared spectra, and to H. E. Schroeder for his advice.

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Halogen Reactivities. VIII.[1] 2-Halofurans

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The kinetics of nucleophilic displacement with piperidine of 2-halofurans, 5-methyl-2-iodofuran, and 5-chloro-2-furoylpiperidide have been investigated. The reactivity is compared with the benzene analogs and an unexpected reaction of 2-iodofuran with piperidine is discussed.

The general nonreactivity of the carbon to halogen bond in the halofurans has long been a source of difficulty in preparative reactions as evidenced by recent attempts to prepare 2-methoxyfuran directly from the halofurans.[3] Recent interest in the kinetics of halocompounds has made available the data necessary for a comparison of the halofurans with other well known compounds. Because of the difficulty in using methoxide as a nucleophilic reagent, piperidine has been used as an alternate not only for convenience but also to permit comparisons with other preciously investigated compounds. The method and apparatus used in these determinations was that previously reported.

Table 1 lists the values obtained in this work and those necessary for comparative purposes.

TABLE I

Compound	ΔE^* (kcal.)	ΔF^* (kcal.)[a]	ΔS^* (e.u.)[a]	log PZ^a
2-Chlorofuran	21.89 ± 0.36	41.23 ± 0.03	−42.1 ± 1.5	7.8
Chlorobenzene[1]	26.8 ± 1.4	43.3 ± .05	−42.4 ± 3.0	7.71
2-Bromofuran[4]	21.69 ± 0.33	39.08 ± .02	−39.1 ± 1.3	8.4
Bromobenzene[1]	24.1 ± 0.4	41.4 ± .02	−42.3 ± 1.0	7.73
Iodobenzene[5]	23.6	40.7	−38.2	8.75
2-Iodofuran	30.85 ± 0.38	38.74 ± .02	−18.8 ± 1.2	12.9
5-Methyl-2-iodofuran	26.65 ± 0.75	39.47 ± .03	−29.1 ± 2.4	10.6
5-Chloro-2-furoyl-piperidide	17.22 ± 0.85	31.05 ± .03	−37.1 ± 2.8	—

[a] Calculated from rate constants at 200°C.

From a comparison of the results on chloro and bromo furans and benzenes it is apparent that both types of compounds have essentially the same steric requirements. Although the benzene compounds have a slightly higher activation energy, the rate controlling free energy of activation shows that the furans have a slightly more reactive carbon to halogen bond than the benzene analogues. Chlorofuran has the same reactivity as bromobenzene and chloro- and bromofuran have about a tenfold greater rate of reaction than the corresponding benzene compounds.

The slightly greater reactivity of the halofurans is attributed to the oxygen atom which could increase the positive character of the carbon bearing the halogen by an inductive effect. The over-all effect would be expected to be slight because of the opposed mesomeric effect and the possible repulsion of a nucleophilic reagent by the basic oxygen. A study[6] of carboxypiperidide substituted halogen compounds showed that the furans have a lower free energy of activation by 4.8 kcal and 500 fold greater reactivity. Reactivity of the halogen would be expected to be greatly enhanced by the mesomeric effect caused by the electron withdrawal of the carboxypiperidide group in addition to the inductive effect of the oxygen atom.

In an attempt to compare the kinetics of the various halogen substituted furoylpiperidides, the results shown in Table I were obtained for 5-chloro-2-furoylpiperidide. The rate constants were erratic showing a definite increase with time which was shown not to be due to piperidine hydrochloride catalysis as indicated in Table 3. Because definite trends were observed, valid comparative results probably cannot be obtained.

The results obtained for 2-iodofuran did not fit in with the expected trends as may be seen by comparing the other 2-halofurans and the halobenzenes. The tremendous increase in activation energy and the large difference in entropy of activa-

(1) Paper VII: Richardson, Brower, and Amstutz, *J. Org. Chem.*, **21**, 890 (1956).

(2a) Taken from the Ph.D. Thesis of Donald G. Manly, Quaker Oats Fellow in Organic Chemistry 1954–56. (2b) Present address, Research Laboratories, The Quaker Oats Co., Barrington, Ill.

(3) Manly and Amstutz, *J. Org. Chem.*, **21**, 516 (1956).

(4) Recalculated values; see Petfield and Amstutz, *J. Org. Chem.*, **19**, 1944 (1954).

(5) Berliner, Quinn, and Edgerton, *J. Am. Chem. Soc.*, **72**, 5305 (1950).

(6) Paper IX, to be published.

TABLE II

Compound	T_{corr} (°C.)	k (hr.$^{-1}$)
2-Chlorofuran	202.50	0.00285 ± 0.00005
	222.19	.00731 ± .00100
	231.29	.01064 ± .00048
	235.90	.01336 ± .00041
2-Bromofuran[4]	199.3	.02234 ± .00037
	207.7	.03171 ± .00054
	216.3	.04937 ± .00090
	231.2	.09735 ± .00254
2-Iodofuran	175.24	.00756 ± .00033
	179.57	.01053 ± .00034
	182.81	.01474 ± .00100
	188.49	.02033 ± .00017
	196.31	.03572 ± .00078
	214.38	.12093 ± .00075
5-Methyl-2-iodofuran	183.96	.00183 ± .00012
	192.06	.01326 ± .00048
	197.25	.01795 ± .00077
	202.30	.02428 ± .00081
5-Chloro-2-furoyl-piperidide	90.60	.01015 ± .00059
	95.73	.01599 ± .00057
	97.84	.01666 ± .00122
	102.45	.02091 ± .00223
	109.04	.03213 ± .00193

TABLE III

KINETICS OF 5-CHLORO-2-FUROYL PIPERIDIDE CONTAINING PIPERIDINE HYDROCHLORIDE

Time (Hr.)	k (hr.$^{-1}$)		
	A[a]	B[b]	Δk[c]
0.5	0.01820	0.00932	0.00888
1.0	.01801	.01618	.00183
1.5	.01881	.01753	.00128
2.0	.01924	.01861	.00063

[a] A N = 0.1999. Not containing piperidine hydrochloride. [b] B containing piperidine hydrochloride at a concentration of 0.00451N. [c] T_{corr} = 101.10°C.

tion or PZ factor was entirely unexpected whereas the lower free energy of activation was consistent with the faster rate of reaction. The fact that the rate of reaction is faster while the activation energy is higher is quite unusual and implies a different reaction mechanism. The well known ability of furan compounds to undergo 2,5 addition[7] suggests the possibility of a similar type reaction with piperidine.

To provide evidence for a preliminary addition of piperidine, the kinetics of 5-methyl-2-iodofuran were investigated. With the 5-position blocked, a 2,5 addition would be highly improbable. The entropy of activation or PZ factor of 5-methyl-2-iodofuran appears to be consistent with nucleophilic displacement and the free energy of activation is likewise consistent with the previously reported[8] deactivation by a methyl group. The results also eliminate the possibility of a 2,3 addition. Since the data are in agreement with the expected values, it is quite probable that 2-iodofuran did undergo a multistage reaction rather than nucleophilic displacement.

(7) Rinkes, *Rec. trav. chim.*, **50**, 981 (1931). Clauson-Kaas, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd*, **24**, 18 (1947); *C. A.*, **42**, 1930 (1948).

EXPERIMENTAL

Apparatus, techniques, and calculations were the same as in previous papers.[1]

2-Chlorofuran, b.p. 77.1–77.6° was prepared by decarboxylation of 5-chloro-2-furoic acid.

2-Iodofuran, b.p. 61–62°/57 mm. was prepared by iodination of 2-furylmercuric chloride.[9]

5-Methyl-2-iodofuran, b.p. 56–57°/20 mm. was prepared in 46% yield by iodination of 5-methyl-2-furylmercuric chloride.[10]

5-Chloro-2-furoylchloride was prepared in 89% yield from the acid and thionyl chloride, b.p. 85–86°/16 mm. and m.p. 29–30°.

5-Chloro-2-furoylpiperidide: Piperidine (17.9 g.) in 22 ml. of ether was added dropwise to a rapidly stirred solution of 16.5 g. of 5-chloro-2-furoylchloride in 40 ml. of ether. After an additional hour the mixture was filtered and the ether filtrates were evaporated and distilled to give 18 g. (89%) of the product, b.p. 137–139°/3 mm.

Anal. Calc'd for $C_{10}H_{12}ClO_2N$: C, 56.3; H, 5.67; N, 6.58. Found: C, 56.5; H, 5.87; N, 6.32.

Acknowledgement. The authors wish to express their appreciation to Mr. Andrew P. Dunlop and The Quaker Oats Co. for the financial support of this work.

BETHLEHEM, PA.

(8) Berliner and Monack, *J. Am. Chem. Soc.*, **74**, 1574 (1952).

(9) Gilman, Mallory, and Wright, *J. Am. Chem. Soc.*, **54**, 733 (1932).

(10) Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ACTON TECHNICAL COLLEGE]

Abnormal Substitution Reactions of Anthracene and Phenanthrene

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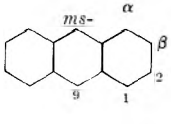
A reinterpretation has been attempted of the abnormal sulfonation and Friedel-Crafts acylation reactions of anthracene and phenanthrene. In each system it is believed that rapid initial substitution occurs at the hydrocarbon's most reactive position. This may be followed, provided solubility relationships are favorable, and because steric circumstances are apt, by a slower removal of the substituent and slow essentially irreversible substitution at the less reactive positions of the hydrocarbon.

In spite of the continued interest which is being shown in the reactivity of polycyclic aromatic systems, no satisfactory general explanation seems to have been advanced for those substitution reactions which proceed abnormally. These generally comprise sulfonation and Friedel-Crafts acylation processes. The hitherto neglected importance of reversibility in acylation reactions generally has recently been emphasized.[1] It is the purpose of this communication to reassess the evidence concerning the reversibility of the sulfonation reactions in the anthracene and phenanthrene fields, to supply further evidence of reversibility in acylation reactions, and to examine the factors governing reversibility in these systems.

Anthracene (I). The *meso* position is the most reactive in anthracene being preferentially substituted in most reactions excepting Friedel-Crafts and sulfonation reactions. Thus, sulfonation usually gives the 1- and 2-sulfonic acids only, as initial products. This result has been described as anomalous,[2,3] and the abnormal orientation ascribed to steric hindrance to the approach of the SO_3H^+ reagent.[*cf.* 4] An alternative explanation was envisaged by Clar,[5, *cf.* 6] *viz.* that primary attack occurs in the *meso* positions, and is followed by a wandering of the $-SO_3H$ group to the outer positions. The observed desulfonation of anthracene-9-sulfonic acid by means of dilute mineral acid[7] has now been confirmed, providing evidence favoring Clar's hypothesis. The reported formation, as intermediates in this reaction, of anthranol and sulfur dioxide[7] could not be confirmed, and a direct reversal of sulfonation is therefore preferred as a mechanism. The sodium salt of the related dianthryl-9-sulfonic acid could similarly be split to dianthryl and sulfuric acid without a trace of sulfur dioxide being formed, as claimed earlier.[7]



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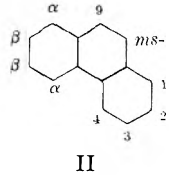

II

Sulfonation at the *meso*-position of anthracene may therefore be regarded as rapidly reversible, a consequence no doubt of the high reactivity at the *meso*-position, and of the steric instability of the bulky sulfonic acid group at this hindered position (see below). The α-positions may likewise be considered to be reversibly substituted, though more slowly, since anthracene-1,8-disulfonic acid is slowly desulfonated to anthracene by 75% sulfuric acid.[8] An actual isomerization of anthracene-1-sulfonic acid to the 2-sulfonic acid by the action of hot sulfuric acid has not been observed, further sulfonation intervening.[9] No comparable evidence of mobility appears to exist for the 2-anthryl position, which may be assumed to be stable. The ease of desulfonation seems therefore to decrease in the expected order of reactivity of these positions to electrophilic reagents (here H^+).

Recently, Gold and Long[10] have determined the rate of isotopic interchange at the 9-anthryl-position using deuterium-labeled anthracene and concentrated sulfuric acid. It was found that some loss of anthracene resulted through sulfonation, which was, however, slower than the isotope exchange. In view of the probably very rapid reversible sulfonation at the 9-anthryl-position, the observed exchange might in part be due to such a process, and unlikely to be wholly due to the mechanism put forward.

Certain uncatalyzed Friedel-Crafts type reactions cause substitutions in the 9- position of anthracene exclusively,[11,12] thus proceeding normally;

(1) Gore, *Chem. Revs.*, **55**, 229 (1955).
(2) deBruyn, *Ann. chim. Paris*, xi, **20**, 551 (1945).
(3) Braude and Fawcett, *J. Chem. Soc.*, 800 (1950).
(4) Badger, *The Structures and Reactions of the Aromatic Compounds*, University Press, Cambridge, 1954, p. 305.
(5) Clar, *Aromatische Kohlenwasserstoffe*, Springer Verlag, 1952, p. 177.
(6) Fukui, Yonezawa, and Shingu, *J. Chem. Phys.*, **20**, 722 (1952).
(7) Minaev and Fedorov, *J. Russ. Phys. Chem. Soc.*, **61**, 143 (1929).
(8) Berkenheim and Snamenskaya, *Zhur. Obshchei Khim.*, **4**, 31 (1934).
(9) Battegay and Brandt, *Bull. soc. chim. France*, 4, **33**, 1667 (1923).
(10) Gold and Long, *J. Am. Chem. Soc.*, **75**, 4543 (1953).
(11) Nenitzescu, Isacescu, and Ionescu, *Ann.*, **491**, 210 (1931).
(12) Liebermann and Zsuffa, *Ber. deut. chem. Ges.*, **44**, 202 (1911).

catalyzed acylations, however, have been regarded as abnormal. *Meso*-substitution is effected under quite mild experimental conditions, and usually with carbon bisulfide or other solvent, from which the reaction complex invariably precipitates, thus preventing subsequent reaction.[1] Moreover, abnormal products are obtained by use of solvents of good solvent power, such as nitrobenzene, which allows subsequent rearrangement to take place in solution of the *meso*- product first formed. For example, 9-anthryl methyl ketone, obtainable under mild conditions, can be converted into mixtures of 1- and 2-anthryl methyl ketones[2,15-16] under the more strenuous conditions approximating those for the preparation of the latter ketones. The migration hypothesis was first advanced by Linstead,[15] and indeed was very attractive. However, such observed migrations may alternatively be considered to have no parallel in the actual acylation process, particularly in nitrobenzene solution, where a solvated reaction complex is undoubtedly formed, which may not find spatial accommodataion in the sterically hindered *meso*- position and would thus enter the outer rings.[1] In one particular benzoylation experiment quoted in the literature,[17] the acyl group could enter the *meso*-position (giving a 79% yield) under specially mild conditions: at $-10°$ and reaction time 5 min., supporting the migration hypothesis for substitution in the outer positions.

This has now been established unequivocally for acetylation in the case of benzene as solvent. A reaction, which is usually prolonged for 20 hr. to give 1- and 2-anthryl methyl ketones only, when interrupted after 3 hr. is found to give only 9-anthryl methyl ketone.

In such a system it is most unlikely that a reagent of large steric requirements is involved in the initial substitution stage.[18] In the system undergoing rearrangement it would appear that the over-all rate of substitution at the outer positions, very probably by a reagent of large steric requirements, is faster than the attack at the *meso*-positions by a reagent of small size, presumably the free acyl cation. One of the causes of the rapid rearrangement is therefore probably this duality of mechanism. It should be noted that of the two outer positions of anthracene the 1- position is the one substituted to a greater extent in nitrobenzene solution, which is in contrast to the case of naphthalene, in which the 2-position is favored.

In support of the concept of a deacylation-reacylation process is the smooth conversion of 9-anthryl methyl ketone to 9-anthryl phenyl ketone[14] under conditions identical with the preparation of the latter compound,[19] and the ready removal of the acyl substituent by boiling of 9-anthryl methyl ketone,[20] 9-anthryl phenyl ketone[19] or indeed 9-anthraldehyde (see Experimental) with a solution of sulfuric acid in glacial acetic acid. The deacylations with orthophosphoric acid of certain *o*-alkyl substituted acetophenones,[21-24] with nitric acid of acetylated pyrroles,[25] and with trichloroacetic acid of 3-acetyl guiaazulene,[26] appear to be analogous. The deacylation process clearly involves an electrophilic attack by H^+ with probable formation of the usual σ-complex transition state.

Summarizing then, the initial accumulation of the 9-isomer in anthracene acylations is due to its faster formation and low solubility of the ketone complex. The ultimate formation of the 1- and 2-isomers is the result of slow deacylation of the 9-isomer and the greater thermodynamic stability of the 1- and 2- isomers.

Phenanthrene (II). Studies of the reactivity of this hydrocarbon have led to conflicting results. In general the 9- position is the one most readily attacked, followed by the 1- position, *e.g.* nitration.[27] Both the Friedel-Crafts acylation and sulfonation reactions show the usual "abnormal" features. Werner[28, *cf.* 29] first noted that a low temperature of sulfonation favors formation of the 9-sulfonic acid, *i.e.* the normal product. At 120–130° this acid was reported to be formed only in traces, and at 170–180° not at all. At the higher temperatures phenanthrene 2- and 3-sulfonic acids predominate. Fieser[30] next showed that a reaction with sulfuric acid at 60° gave mainly phenanthrene 2- and 3-sulfonic acid, with less of the 9- and 1-acids, while at 120° increased yields of the 2- and 3-acids but no 1- and 9-acids were obtained. Fieser investigated the possibility of reversible sulfonation by heating the 9-, 2-, and 3-sulfonic acids separately with sulfuric acid. This failed to reveal any rearrangement, because of further sulfonation. It must be stressed, however, that in Fieser's[31] elucidation

(13) British Patent 289,585 (J. Y. Johnson to I. G. Farbenindustrie, A. G.).
(14) Batten, *D.I.C. Thesis, London*, 1933.
(15) Linstead, *Ann. Repts. on Progr. Chem. Chem. Soc. London*, **35**, 254 (1937).
(16) French Patent **633,071** (I. G. Farbenindustrie, A.G.).
(17) Krollpfeifer and Schutz, *Ber. deut. chem. Ges.*, **56**, 2360 (1923).
(18) Gore, *Chemistry & Industry*, 1954, 1385.
(19) Cook, *J. Chem. Soc.*, 1282 (1926).
(20) Krollpfeifer, *Ber. deut. chem. Ges.*, **56**, 2363 (1923).
(21) Klages and Lickroth, *Ber. deut. chem. Ges.*, **32**, 1562 (1899).
(22) Arnold & Rondesvedt, *J. Am. Chem. Soc.*, **68**, 2177 (1946).
(23) Schubert and Latourette, *J. Am. Chem. Soc.*, **74**, 1829 (1952).
(24) Baddeley, *J. Chem. Soc.*, 232 (1944).
(25) Fischer and Zerweck, *Ber. deut. chem. Ges.*, **55**, 1949 (1922).
(26) Galloway, Reid, and Stafford, *Chemistry & Industry*, 1954, 724.
(27) Dewar and Warford, *Chemistry & Industry*, 1956, 98.
(28) Werner, Frey, Kunz, Lowenstein, Rekner, and Wack, *Ann.*, **321**, 248 (1902).
(29) Sandqvist, *Ann.*, **392**, 76 (1912).
(30) Feiser, *J. Am. Chem. Soc.*, **51**, 2460 (1929).
(31) Feiser, *J. Am. Chem. Soc.*, **51**, 2471 (1929).

of the structures of his disulfonic acids it was assumed that no rearrangement occurred either prior to or subsequent to further sulfonation. Ioffe later showed in a careful study of this reaction that the 9-sulfonic acid was formed even at higher temperatures, contrary to previous reports,[28] but quickly rearranged to other monosulfonic acids, the yield falling off to zero within a half to one hour. The 3-isomer was also shown to rearrange slowly to the 2-isomer. It appears to follow then[33] that in the sulfonation of this hydrocarbon there is competition between the formation and hydrolytic fission of sulfonic acids, proceeding at different rates for the different isomers, leading initially to appreciable amounts of the *meso*- and α-isomers and ultimately to an accumulation of the β-isomers, which are most stable to hydrolysis. The β-sulfonation of phenanthrene should therefore no longer be regarded as due to steric hindrance to attack at the α- positions.[34]

In most acylation reactions the 2- and 3-positions are favored, even in carbon bisulfide suspensions, though better over-all yields have been obtained in the presence of nitrobenzene.[1] *Meso*-substitution has been reported in a number of cases[35-37] using carbon bisulfide, a low yield being obtained in each case. An early acetylation of phenanthrene[35] was claimed to afford mainly the *meso*-isomer, but this claim was disproved some years later.[38] Since the reaction conditions cited were sufficiently mild, and as carbon bisulfide was being used as solvent, it was suggested[39] that the *meso*-isomer should here predominate, being first formed and precipitated from the solution as its aluminum chloride complex. This has recently been confirmed by Bavin and Dewar,[36] who showed that the *meso*-isomer is the main product, but that the β- isomers are formed likewise.

A report of *meso*-benzoylation of phenanthrene[35] in carbon bisulfide was not confirmed by later workers,[40,41] a 9% yield of 1-phenanthryl phenyl ketone being isolated instead, this being facilitated by the low solubility of its aluminum chloride complex. In the present work, by a modification of the experimental procedure, the yield of this ketone could be raised to 19%. The 1-position of phenanthrene is therefore of appreciable reactivity, and may be substituted under mild reaction conditions.[cf. 36] Benzoylation in nitrobenzene solution[40,41] gives mainly the 3-isomer with lesser amounts of the 1- and 2-phenanthryl phenyl ketones. The general similarity between the acylation and the sulfonation of phenanthrene is emphasized by evidence, here presented, that 3-phenanthryl methyl ketone is slowly converted to the 2-isomer under Friedel-Crafts acetylating conditions. Treatment in nitrobenzene solution of phenanthrene with 1.4 equivalents of acetyl chloride and 2.2 equivalents of aluminum chloride gives mixtures of 2- and 3-phenanthryl methyl ketones, which may be separated quantitatively. After 6 hr. at 25°, the reaction mixture affords a 16% yield of 2- and a 62% yield of 3-phenanthryl methyl ketone (confirming values of 15% and 65%, respectively, previously reported[38]). On allowing the reaction to proceed at 25° for 17 hr., the yields are, respectively, 26% and 50%, indicating that during 11 hr. some 20% of the 3- ketone is converted to the more stable 2-ketone.

Strong circumstantial evidence therefore exists for some reversibility of acylation reactions with phenanthrene, the *meso*- and the 1-positions being initially formed but of lower stability than the 2- and 3-isomers which ultimately accumulate. However, treatment of 9-phenanthryl methyl ketone under Friedel-Crafts conditions with aluminum chloride or bromide[41] has failed to show any of the expected isomerization. This may perhaps be due to the absence of added hydrogen halide, without which reversible acylation cannot proceed.[1] Also, the sulfuric acid/acetic acid reagent is unable to deacylate either 9-phenanthraldehyde or 1-phenanthryl phenyl ketone; this is perhaps not unexpected since acyl groups must be displaced out of coplanarity much more in the *meso* anthyl series than in either position of the phenanthrene molecule,[42] the former therefore being the more easily replaceable.

In conclusion, it is of interest to consider briefly in what way the Friedel-Crafts acylation and sulfonation reactions are unusual and lead to the formation of abnormal isomers in the polycyclic aromatic series. The most reactive positions in anthracene and phenanthrene are the most central ones, which happen at the same time to be the sterically less accessible positions. When a substituent has entered the *meso*- position, it will cause interference to, and will therefore be twisted out of plane by, the *peri*- hydrogen atom(s). This is the position in particular where the entering group is a bulky solvated sulfonic acid group of an aluminum chloride-complexed acyl group. This out-of-plane distortion will cause an appreciable lowering of resonance stabilization, to below that possible at the unhindered positions, and proton catalyzed rearrangement will therefore proceed.

(32) Ioffe, *Zhur. Obshchei Khim.*, **3**, 448 (1933).
(33) Ioffe, *Org. Chem. Ind. U.S.S.R.*, **7**, 374 (1940).
(34) Feiser and Feiser, *Organic Chemistry*, D. C. Heath and Company, Boston, 1950, p. 805.
(35) Willgerodt and Albert, *J. prakt. Chem.*, 2, **84**, 383 (1911).
(36) Bavin and Dewar, *J. Chem. Soc.*, 166 (1956).
(37) Clar, *Ber. deut. chem. Ges.*, **62**, 350 (1929).
(38) Mosettig and de Kamp, *J. Am. Chem. Soc.*, **52**, 3704 (1930).
(39) Gore, personal communication to Dewar (1954).
(40) Bachmann, *J. Am. Chem. Soc.*, **57**, 555 (1935).
(41) Bachmann and Boatner, *J. Am. Chem. Soc.*, **58**, 2097 (1936).
(42) Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

EXPERIMENTAL

Acetylation of anthracene. (*a*) A mixture of 300 g. of benzene, 54 g. of anthracene and 72 g. of acetyl chloride was stirred at 0°, and 120 g. of powdered aluminum chloride was added in portions, the temperature being maintained at 5–10°. Stirring was continued for a further 2.50 hr. The red complex which had precipitated was collected on a sinter-funnel, washed with dry benzene, and hydrolyzed by adding to a stirred mixture of ice and 5 *N* hydrochloric acid. The benzene extract was washed with water, dried over sodium sulfate, filtered through a short column of alumina, and the filtrate evaporated. The residue was finally heated at 1 mm. and 100°, in order to remove acetophenone, and yielded 36 g. of 9-anthryl methyl ketone, m.p. 76°, on crystallization from benzene.

(*b*) As for (*a*). Stirring was continued for 1 hr., after addition of the aluminum chloride, at 5–10°, and then for 20 hr. at 20°. The product was isolated as in (*a*). The chromatographed mixture was crystallized from benzene, to give 4.2 g. of 2-anthryl methyl ketone, m.p. 185–186°; the mother liquors were evaporated and the residue crystallized from ethyl acetate, giving 22 g. of 1-anthryl methyl ketone, m.p. 105–106°.

Deformylation of 9-anthraldehyde. A solution of 1 g. of 9-anthraldehyde in 18 ml. of glacial acetic acid was treated with 2 ml. of concentrated sulfuric acid, and the mixture refluxed for 80 min., when an aliquot no longer gave a positive test with 2,4-dinitrophenylhydrazine solution, and then diluted with water. The precipitate (0.7 g.) on recrystallization from dilute acetic acid afforded 0.4 g. of anthracene, m.p. and mixed m.p. 210–212°, which on oxidation with chromic acid in glacial acetic acid gave anthraquinone, m.p. and mixed m.p. 282°–283°.

Sodium anthracene 9-sulfonate. Prepared and purified according to the method of Minaev and Fedorov.[7] Treatment of the salt with 3 *N* hydrochloric acid immediately produced, in the cold, some sulfur dioxide. Subsequent boiling produced no further amounts of the gas. The reported formation of anthracene was confirmed, but anthranol could not be detected.

Sodium 9,9'-dianthryl-10-sulfonate was prepared by the method of Minaev and Fedorov.[7] One gram of the salt was boiled for 3.5 hr. with 25 ml. of 4 *N* hydrochloric acid and 20 ml. of acetic acid. The reaction mixture on dilution with water gave 0.7 g. of dianthryl, m.p. 311–312°, after recrystallization from acetic acid.

1-Phenanthryl phenyl ketone. A mixture of 114 ml. of benzoyl chloride and 150 g. of aluminum chloride was heated until a clear solution resulted. The mixture was cooled, 850 ml. of carbon bisulfide was added, and the complex dissolved by stirring. One hundred seventy-five grams of phenanthrene was added to this solution during 20 min. Evolution of hydrogen chloride, at first rapid, ceased after a further 20 min., when the mixture was cooled to 0°. The precipitated complex was collected and decomposed by adding to a mixture of ice and 10 *N* hydrochloric acid. The residual carbon bisulfide was allowed to evaporate, and 38 g. of 1-phenanthryl phenyl ketone, m.p. 141–142°, was collected by filtration. A further crop of 2.4 g. of the ketone was obtained by extracting the above filtrate with chloroform, washing the extract with water, concentrating to 120 ml., adding 50 ml. of ether and setting aside at 0°. The pure ketone, obtained by recrystallization from acetone, had a melting point of 148–149.5° (literature m.p. 148–149°[40,41]).

Acetylation of phenanthrene. Using the method of Mosettig and de Kamp,[38] the reaction mixture being kept at 25°, (*a*) after 6 hr. a 16% yield of 2-phenanthryl methyl ketone, m.p. 142.5–143.5°, and a 62% yield of 3-phenanthryl methyl ketone, m.p. 72.5–73.5°, were obtained by careful fractional crystallization; (*b*) after 17 hr. the yields were 26% and 50%, respectively.

Attempted deacylations. (*a*) *1-Phenanthryl phenyl ketone.* A solution of 1 g. of the ketone in 50 ml. of glacial acetic acid, containing 5 ml. of concentrated sulfuric acid, was refluxed for 4.5 hr., and then poured into water. The product (0.98 g.) was the unchanged ketone, m.p. and mixed m.p. 144–145°.

(*b*) *9-Phenanthraldehyde.* One gram of the aldehyde was treated as in (*a*) for 3.5 hr. The product (0.9 g.) proved to be unchanged aldehyde, m.p. 94°, pure (m.p. and mixed m.p. 100°) after one recrystallization.

LONDON, ENGLAND

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Naphthyridines. II. Synthesis of 1,7-Naphthyridines by Borsche Synthesis[1,2]

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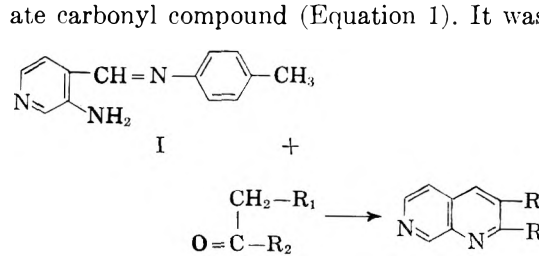
The preparation of six new 1,7-naphthyridines (II–VII) by condensation of the appropriate carbonyl compound with N-(3-amino-4-picolylidene)-*p*-toluidine is described.

In an earlier communication[2] the synthesis of two 1,7-naphthyridines using the Borsche[3] modification of the Friedlander synthesis was reported. The preparative sequence employed consisted of the synthesis of N-(3-amino-4-picolylidene)-*p*-toluidine (I) and the condensation of I with an appropriate carbonyl compound (Equation 1). It was suggested that the synthesis might be expected to be a general one for the preparation of 1,7-naphthyri-



(1) This work was supported in part by grant G-1090 of the National Science Foundation.

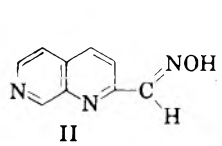
(2) Paper I, Baumgarten and Krieger, *J. Am. Chem. Soc.*, **77**, 2438 (1955).

(3) Borsche, Doeller, and Wagner-Roemich, *Ber.*, **76**, 1099 (1943); Borsche and Barthenhier, *Ann.*, **548**, 50 (1941); Borsche, Wagner-Roemich, and Barthenhier, *Ann.*, **550**, 165 (1942); Borsche and Ried, *Ann.*, **554**, 269 (1943).

dines. We have examined this synthesis further and report here its successful use in the preparation of six new 1,7-naphthyridines. Several modifications made in the synthesis of I are described in the Experimental section.

The condensation of I with isonitrosoacetone gave 1,7-naphthyridine-2-aldoxime (II) in 56% yield. From the condensation of dimethyldihydroresorcinol (methone) with I, 2,9-diaza-6,8-dihydro-7,7-dimethyl-5-oxoanthracene (III) was obtained in 20% yield. With cyclopentanone and *p*-methylcyclohexanone, I gave 7,9-diazabenz[f]indane (IV) and 2,9-diaza-5,6,7,8-tetrahydro-6-methylanthracene (V) in 56% and 58% yields, respectively. From acetylacetone and I, 2-methyl-3-acetyl-1,7-naphthyridine (VI) was obtained in 16% yield. The conditions used in each of these reactions were essentially the same as those described by Borsche[3] for the synthesis of quinoline derivatives.

Other experiments[4] in progress in this laboratory have shown that 2-aryl-3-nitroquinolines may be prepared in good yields by the reaction between ω-nitroacetophenones with *o*-aminobenzaldehyde or with *o*-aminobenzaltoluidine. The reaction between I and ω-nitroacetophenone gave 3-nitro-2-phenyl-1,7-naphthyridine (VII) but only in very low yield (10%).



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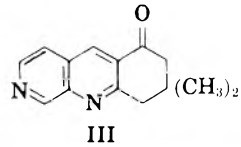

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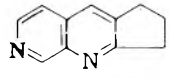
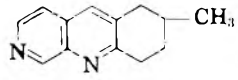


IV



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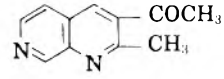
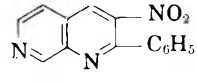


VI



VII

The success of the Borsche procedure in the examples described here, which were selected to cover a reasonably large range of diverse structures, suggests that this synthesis should show the same generality of application as that shown by the well studied Borsche quinoline synthesis. The principal limitation of the method as applied to 1,7-naphthyridines appears to be the low yields encountered in the preparation of I.

EXPERIMENTAL[5]

N-(3-Amino-4-picolylidene)-p-toluidine (I) was prepared as described previously[2,6] from 2-amino-4-picoline with modifications in the individual steps as outlined in the following sections.

3- and 5-Nitro-2-chloro-4-picoline. A mixture of 113 g. (0.73 mole) of the crude mixed 3- and 5-nitro-2-hydroxy-4-picolines,[6] 125 ml. of phosphorus oxychloride and 20 g. of phosphorus pentachloride was heated to 110–120° in an oil bath for 4 hr. The mixture was cooled and poured slowly into ice water with stirring. When the hydrolysis of the excess phosphorus oxychloride was complete, the chloro compound was steam distilled from the acidic hydrolysis mixture. The distillate was extracted with ether. The ethereal solution was dried over magnesium sulfate, filtered, and evaporated on the steam bath. The residual mixture of 3- and 5-nitro-2-chloro-4-picoline, 111 g. (90%), was satisfactory for use in the following reaction. In other experiments the yields ranged from 80–95%, about 30% higher than reported earlier.

3-Nitro-4-picoline. A mixture of 64 g. (0.37 mole) of the crude mixed chloronitropicolines and 120 ml. of glacial acetic acid was stirred and heated to boiling under reflux using a wire gauze and a burner. Heating was continued while 100 g. (1.57 mole) of copper powder (Baker, purified) was added in portions over a period of 30 min. and until the mixture became too thick to stir (usually after an additional 15 min.). The setup was rearranged for steam distillation and the product was isolated as described previously[6] (4 l. of steam distillate being collected). The yield of 3-nitro-4-picoline hydrochloride was 25 g. (39%), m.p. 180–182°. In other experiments the yields ranged from 30–40%. These yields were as good as those obtained using benzoic acid and the operation was simpler.[7]

3-Nitro-4-pyridinecarboxaldehyde dihydrate. In a large number of experiments following our earlier procedure[2] the yields of recrystallized 3-nitro-4-pyridinecarboxaldehyde dihydrate, m.p. 91–93°, were in the range of 18–25%. An approximately equivalent amount of aldehyde remained in the mother liquors, as indicated by assay with 2,4-dinitrophenylhydrazine, but was not readily recovered on a small run.

N-(3-Amino-4-picolylidene)-p-toluidine. After trying many alternative procedures the following method has been adopted as giving the highest yields of very nearly pure product with a minimum of manipulation.[8] A solution of 0.75 g. (0.004 mole) of 3-nitro-4-pyridinecarboxaldehyde dihydrate and 0.43 g. (0.004 mole) of *p*-toluidine in 4 ml. of 95% ethanol was heated under reflux for 1 hr. Meanwhile solutions of 1.33 g. (0.0079 mole) of sodium sulfide pentahydrate and of 0.67 g. (0.0079 mole) of sodium bicarbonate in the minimum amounts of water were mixed and diluted with an equal volume of 95% ethanol. After 30 min. the solution was filtered. The aqueous-ethanolic solution of

(4) Baumgarten and Saylor, in press.

(5) Melting points are corrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill., and by Micro-Tech Laboratories, Skokie, Ill.

(6) Baumgarten, Su, and Krieger, *J. Am. Chem. Soc.*, **76**, 596 (1954).

(7) E. V. Brown (*J. Am. Chem. Soc.*, **76**, 3167 (1954)) has reported obtaining a 70% yield of 3-nitro-4-picoline by the action of copper and benzoic acid on pure 2-chloro-3-nitro-4-picoline. Unfortunately, Brown did not report any physical data to support the identity or purity of his product. Following his directions we obtained an apparent yield of 70% also; however, the product was found to be only 50% pure. As far as we are able to determine there is no advantage to be gained by separating the isomeric chloro compounds prior to the dechlorination and the separation (by steam distillation of the amino precursors of the chloro compounds) is tedious.

(8) We have been unable to duplicate our original yield of 77% of this material. In our original experiments[6] an ancient sample of sodium sulfide nonahydrate of dubious purity was used. Unfortunately, this material was discarded when fresh sodium sulfide pentahydrate became available to us. We have not been able to determine whether or not our original yield, which our records demonstrate to be real and not fancied, was made possible by the composition of the old sodium sulfide. This point is being studied further.

sodium hydrogen sulfide[9] was added to the hot solution above. On cooling and addition of water N-(3-amino-4-picolylidene)-*p*-toluidine was precipitated and was collected and air-dried, giving 0.42 g. (50%) of material melting at 153–154°.[10] Normally the product was pale yellow in color and did not require further purification.

1,7-Naphthyridine-2-aldoxime (II). A solution of 1.28 g. (0.0060 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine and 0.55 g. (0.0063 mole) of isonitrosoacetone in 12 ml. of ethanol and 3.0 ml. of 50% potassium hydroxide was heated for 6 hr. under reflux. The reaction mixture was steam distilled to remove the ethanol and *p*-toluidine. The solution was filtered and made acidic with acetic acid to precipitate the oxime. The crude, dried oxime, 0.89 g., m.p. 235–245°, was recrystallized from ethanol (charcoal) giving 0.5 g. (56%) of 1,7-naphthyridine-2-aldoxime, m.p. 245–246°, as a pale yellow powder.

Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.50; H, 3.98; N, 24.31.

2,9-Diaza-6,8-dihydro-7,7-dimethyl-5-oxoanthracene (III). A mixture of 0.21 g. (0.001 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine, 0.14 g. (0.001 mole) of dimethyldihydroresorcinol and three drops of piperidine was heated on the steam bath for 8 hr. After cooling, the brown mass was pulverized and extracted with ether. Evaporation of the ether gave 0.16 g. (71%) of crude product, m.p. 140–152°. After 4 recrystallizations from Skellysolve C,[11] 45 mg. (20%) of 2,9-diaza-6,8-dihydro-7,7-dimethyl-5-oxoanthracene, m.p. 152–155°, was obtained as colorless flakes.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.23; H, 6.00; N, 12.15.

7,9-Diazabenz[f]indane (IV). A solution of 0.465 g. (0.0022 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine and 0.185 g. (0.0022 mole) of cyclopentanone in 5 ml. of ethanol and 1.5 ml. of 2*N* sodium hydroxide solution was heated for 6 hr. on the steam bath. The ethanol and *p*-toluidine were removed by steam distillation. After cooling the solution, the naphthyridine was filtered off and air-dried, giving 0.345 g. (92%) of crude product, m.p. 80–84°. After 1 recrystallization from Skellysolve C[11] the colorless needles of 7,9-diazabenz[f]indane, 0.210 g. (56%), melted at 86–87°.

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.92; H, 5.80; N, 16.62.

2,9-Diaza-5,6,7,8-tetrahydro-6-methylanthracene. (V). A solution of 0.53 g. (0.0025 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine and 0.27 g. (0.0025 mole) of 4-methylcyclohexanone in 6 ml. of ethanol and 2 ml. of 2*N* sodium hydroxide solution was heated on the steam bath for 6 hr. The ethanol and *p*-toluidine were removed by steam distillation, and the naphthyridine was extracted from the residue with ether. Evaporation of the ether gave 0.36 g. (76%) of crude product, m.p. 82–86°. After 2 recrystallizations from Skellysolve C,[11] 0.275 g. (58%) of 2,8-diaza-5,6,7,8-tetrahydro-6-methylanthracene, m.p. 86–88°, was obtained as colorless needles.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.73; H, 7.11; N, 13.85.

2-Methyl-3-acetyl-1,7-naphthyridine (VI). A mixture of 0.211 g. (0.001 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine, 0.100 g. (0.001 mole) of acetylacetone and 3 drops of piperidine was heated on the steam bath for 8 hr. After cooling, the brown mass was pulverized and extracted with ether. Evaporation of the ether gave 0.11 g. (59%) of crude product, m.p. 102–106°. After two recrystallizations from water (8 ml./0.1 g.), 0.03 g. (16%) of 2-methyl-3-acetyl-1,7-naphthyridine (colorless needles), m.p. 112–113.5°, was obtained.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.41; H, 5.55; N, 15.31.

3-Nitro-2-phenyl-1,7-naphthyridine (VII). A solution of 0.211 g. (0.001 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine and 0.166 g. (0.001 mole) of ω-nitroacetophenone in 2 ml. of absolute ethanol was heated under reflux for 2 hr. The cooled solution was diluted with water and extracted with ether. The ethereal solution was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resultant red oil was recrystallized from Skellysolve C[11] to yield 0.025 g. (10%) of 3-nitro-2-phenyl-1,7-naphthyridine (yellow prisms), m.p. 120–121°.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.72. Found: C, 67.13; H, 3.60; N, 16.31.

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(9) Hodgson and Ward, *J. Chem. Soc.*, 242 (1948).

(10) In the earlier paper[2] both the crude and purified materials were reported to melt at 146–148°. This was a typographical error on our part for the analytical sample actually melted at 152–153°.

(11) A hydrocarbon solvent, b.p. 88–98°.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

Substituted Biphenyls by Action of Benzoyl Chloride on Some β-Aroylpropionic Acids

ANDREW S. KENDE AND EDWIN F. ULLMAN

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The reaction of three β-aroylpropionic acids with benzoyl chloride is shown to give substituted phthalides in the biphenyl series. The ultraviolet and infrared spectra of these products and some related biphenyls are discussed.

The reaction of β-benzoylpropionic acid with benzoyl chloride was reported by Kugel[1] to yield an unidentified alkali-stable compound which had the empirical formula $C_{20}H_{14}O_3$. The structure of this product has now been investigated and the reaction extended to other β-aroylpropionic acids.

In our hands, this reaction produced a low yield of a product that had a melting point slightly higher than that of Kugel's compound. Combustion and molecular weight data required a revision of the earlier formula to $C_{27}H_{18}O_4$. The implicit stoichiometry, which can be represented as 2 $C_6H_5COCH_2CH_2COOH + C_6H_5COCl \rightarrow C_{27}H_{18}O_4 + HCl + 3H_2O$, was supported by the extension of the reaction to β-*p*-methoxybenzoyl- and β-*p*-chlorobenzoylpropionic acids to give similar condensation

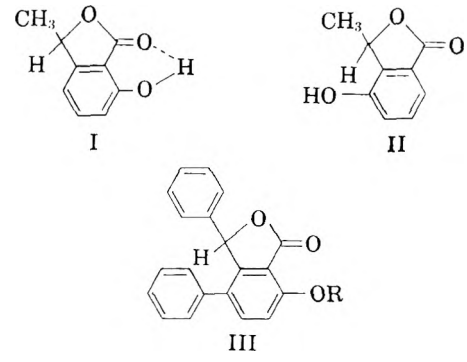
(1) Kugel, *Ann.*, 299, 61 (1898).

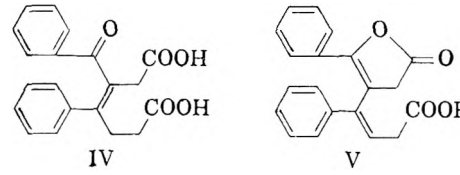
products. The appearance of a strong band at 5.66 μ and a shoulder near 5.71 μ in the infrared spectrum of each of these products gave evidence of the presence of two carbonyl groupings, at least one of which was very likely a five-membered lactone. These products displayed no olefinic character toward bromine in carbon tetrachloride or potassium permanganate in acetone.

The action of hot alcoholic potassium hydroxide on the above C_{27} compound, followed by acidification of the reaction mixture, led to the isolation of benzoic acid and a second compound whose analytical data suggested a $C_{20}H_{14}O_3$ formulation. This product exhibited hydroxyl and carbonyl absorption maxima in the infrared at 2.95 μ and 5.75 μ, respectively. The phenolic character of the hydroxyl group was easily recognized. The product gave a blue-green color with ferric chloride and readily reacted with diazomethane to give an ether which had no infrared maximum in the three-micron region but had a carbonyl band at 5.68 μ. The compound was inert toward chromium trioxide-pyridine, but readily formed a monoacetate which had a single carbonyl peak at 5.65 μ, characteristic of aryl acetates,[2] and likewise underwent benzoylation, regenerating the original C_{27} compound. The possibility that this substance contained an enolized ketone or other readily reducible group was unlikely since it was unaffected by 2,4-dinitrophenylhydrazine reagent or hydrogen over palladium on charcoal.

These results are consistent with the presence, in the C_{27} compound, of an aromatic benzoate ester and an alkali-stable five-membered lactone grouping. Of special significance is the observed decrease in wave length of the infrared carbonyl maximum of the C_{20} hydrolysis product when the phenolic hydroxyl is acylated or alkylated (*vide supra*). Such behavior would be expected of a phenolic lactone if the hydroxyl were suitably oriented to permit hydrogen-bonding to the carbonyl oxygen. For example, it has been shown[3] that on conversion of 7-hydroxy-3-methylphthalide (I) to its methyl ether the infrared carbonyl band is changed from 5.75 μ to 5.68 μ. In contrast, 4-hydroxy-3-methylphthalide (II), which is incapable of intramolecular hydrogen-bonding, and its methyl ether both absorb at 5.69 μ.

A consideration of the probable modes of condensation of two molecules of β-benzoylpropionic acid, viewed in the light of the above data, leads directly to structure III (R = C_6H_5CO—) for the C_{27} product. Although the exact sequence of steps is indeterminate, this product could arise through an initial acid-catalyzed aldol condensation and dehydration to yield IV. Cyclization to the enol-lactone V might then occur followed by cyclodehydration and aromatization to give III (R = H). Esterification of this phenol with benzoyl chloride would produce the postulated product (III, R = C_6H_5CO—).[4] This structure is compatible with all the observed properties of the compound. The extraordinary resistance of the phthalide toward alkaline hydrolysis is characteristic of 3-arylphthalides.[5] Moreover, the presence of the phenolate anion in the initial hydrolysis product (III, R=H) would further decrease the susceptibility of the carbonyl to nucleophilic attack.





To verify this structural conclusion, an ultraviolet spectral comparison with a known biphenyl was made. Since an appropriately disubstituted 4-hydroxybiphenyl was unavailable, it was necessary to employ one of the known 2- or 3-alkyl-4-hydroxybiphenyls as a model. Because of the sensitivity of the ultraviolet spectra of biphenyls to bulky 2-substituents, caused by steric interactions in the photoexcited state,[6] it was concluded that a member of the former group would be the more suitable model, provided its spectrum were compared with a derivative of III that lacked the carbonyl chromophore. The phthalide-ester III (R=C_6H_5CO—) was accordingly converted with lithium aluminum hydride to the triol VII, the identity of which was supported by an active hydrogen determination. The close similarity of the ultraviolet spectrum of this product with that of VIII (Fig. 1), obtained from lithium aluminum hydride reduction of 4-hydroxy-2-bi-

(2) Hartwell, Richards, and Thompson, *J. Chem. Soc.*, 1436 (1948).

(3) Hochstein and Pasternack, *J. Am. Chem. Soc.*, 74, 3905 (1952).

(4) Similar mechanisms can be envisaged for the condensations of β-*p*-methoxybenzoyl- and β-*p*-chlorobenzoylpropionic acids. The spectra of the products of these reactions are very similar to that of III (R = C_6H_5CO—), and in the latter case, hydrolysis of the product yielded a phenol with properties resembling those of III (R = H).

(5) Tasman, *Rec. trav. chim.*, 46, 653, 922 (1927).

(6) Beaven, Hall, Lesslie, and Turner, *J. Chem. Soc.*, 854 (1952), and references cited therein.

phenylcarboxylic acid,[7] provided convincing confirmation of the above structural arguments.

EXPERIMENTAL[8]

Condensation of β-benzoylpropionic acid was performed by heating 0.10 mole of the acid with 0.20 mole of benzoyl chloride on a steam bath for 15–18 hr. The resulting mixture was taken up in warm ethanol and allowed to stand at 0° for 2 days. The crystalline precipitate thus obtained was removed by filtration and recrystallized twice from 95% ethanol with the aid of charcoal to give nearly colorless needles of III (R = C_6H_5CO—), m.p. 194–195°. Yields averaged 7–10%.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.45; H, 4.67; mol. wt., 302. Calcd. for $C_{27}H_{18}O_4$: C, 79.79; H, 4.46; mol. wt., 406. Found: C, 80.14; H, 4.37; mol. wt. 413 (Rast).

The infrared spectrum showed major peaks at 5.65, (5.71), 6.23, 6.74, 6.89, 7.95, 8.53, 9.55, and 9.78 μ. The ultraviolet spectrum exhibited λ_{max} 228 and (285) mμ, log ε 4.58 and (3.70). The product was inert toward bromine in carbon tetrachloride or potassium permanganate in aqueous acetone.

Condensation of β-p-methoxybenzoylpropionic acid and benzoyl chloride, under the above conditions, produced a dark brown mass which, on reprecipitation from ethyl acetate-ethanol, was converted to a gummy powder. After trituration with ether-benzene, this product was recrystallized twice from benzene-ethyl acetate to give about a 5% yield of colorless flakes, m.p. 182–183°.

Anal. Calcd. for $C_{29}H_{22}O_6$: C, 74.67; H, 4.75. Found: C, 75.19; H, 5.12.

The principal infrared maxima were 5.67, (5.72), 6.22, 6.75, 8.06, 8.55, 9.29, 9.56, 9.79 μ; the spectrum was in general similar to that of III (R = C_6H_5CO—).

Condensation of β-p-chlorobenzoylpropionic acid with benzoyl chloride under similar conditions yielded a gum from which two products could be isolated. A solution of this mixture in ethyl acetate-ethanol gave, on standing, an amorphous, highly insoluble yellow powder, m.p. 245–248°.[9] The mother liquors, on longer standing, slowly deposited an almost equal quantity of a new substance which could be readily recrystallized from benzene-petroleum ether to give colorless needles, m.p. 191–192°, in 3% yield.

Anal. Calcd. for $C_{27}H_{16}O_4Cl_2$: C, 68.30; H, 3.40. Found: C, 68.73; H, 3.48.

The infrared spectrum showed maxima at 5.66, (5.72), 6.26, 6.79, 8.55, 9.20, 9.64, 9.79, and 9.87 μ. The ultraviolet absorption was very similar to that of III (R = C_6H_5CO—), with λ_{max} 229 mμ, log ε 4.63.

Hydrolysis of III (R = C_6H_5CO—) was carried out by refluxing 0.160 g. of the compound in a solution of 5% potassium hydroxide in 95% methanol for 6–10 hr. under a nitrogen atmosphere. Filtration of the cooled solution led to the isolation of a crystalline potassium salt (0.140 g.), which yielded a white curdy solid when stirred with dilute hydrochloric acid. An ether solution of this product was washed with water, dried over sodium sulfate, and evaporated to dryness. The powder so obtained was recrystallized from ether-petroleum ether to give colorless crystals (0.096 g., 82% yield), m.p. 139–140° (III, R = H).

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.45; H, 4.67; mol. wt., 302. Found: C, 79.39; H, 4.84; mol. wt., 295 (Rast).

This substance gave a blue-green color with ferric chloride solution. It was insoluble in base and was unaffected by chromium trioxide–pyridine complex, 2,4-dinitrophenylhydrazine reagent or hydrogen over palladium on charcoal in ethanol. The infrared spectrum displayed peaks at 2.95, 5.75, 6.18, 6.73, 6.88, 7.40, 7.70, 8.55, 9.09, 9.40, 10.42, and 11.95 μ. The ultraviolet absorption showed λ_{max} (252) and 310 mμ, log ε (3.87) and 3.48.

Upon acidification and dilution of the original alkaline filtrate, a second substance was isolated. Sublimation of the crude material yielded benzoic acid, identified by mixed melting point with an authentic sample.

The methyl ether III (R = CH_3) crystallized directly in 85% yield from a saturated ethereal solution of the phenol containing excess diazomethane. Recrystallization of the product from ether-ethyl acetate gave colorless needles, m.p. 222–223°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.66; H, 5.07.

The methyl ether absorbed in the infrared at 5.68, 6.17, 6.29, 6.74, 7.80, 9.05, 9.30, and 9.60 μ. The ultraviolet spectrum had λ_{max} (252) and 307 mμ, log ε (3.97) and 3.62.

The acetate III (R = CH_3CO—) was formed upon acetylation of the phenol with acetic anhydride-pyridine at room temperature. Short needles were obtained (91% yield) from petroleum ether-ether, m.p. 191–192°.

Anal. Calcd. for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 77.16; H, 4.59.

The acetate had infrared absorption at 5.65, 6.24, 6.74, 6.90, 7.30, 7.50, 8.50, 9.12, 9.45, 9.80, 10.20, and 11.16 μ. The ultraviolet spectrum had λ_{max} (253) and 290 mμ, log ε (3.78) and 3.25.

The benzoate III (R = C_6H_5CO—) prepared with benzoyl chloride in pyridine and recrystallized from petroleum ether-ethyl acetate, was shown by mixed melting point and infrared and ultraviolet spectra to be identical with the β-benzoylpropionic acid-benzoyl chloride condensation product.

Hydrolysis of the $C_{27}H_{16}O_4Cl_2$ product (0.034 g., m.p. 191–192°) was performed in the same manner as the above hydrolysis of III (R = C_6H_5CO—). An insoluble potassium salt was also obtained and was purified in a like manner to yield a crude product (0.023 g., 87% yield) which, on crystallization from petroleum ether-ether, gave white needles, m.p. 186–187°.

Anal. Calcd. for $C_{20}H_{12}Cl_2O_3$: C, 64.71; H, 3.27. Found: C, 64.63; H, 3.66.

The infrared spectrum of this product showed absorption at 2.98, 5.76, 6.23, 6.79, 7.45, 8.61, 9.22, and 9.91 μ, and the ultraviolet had λ_{max} 259 and 309 mμ, log ε 4.06 and 3.66.

Reduction of III (R = C_6H_5CO—) was carried out by adding a saturated solution of the benzoate (0.40 g.) in dry benzene to a slurry of 0.40 g. lithium aluminum hydride in 30 ml. of freshly distilled tetrahydrofuran. The mixture was refluxed overnight, allowed to cool, and then treated with

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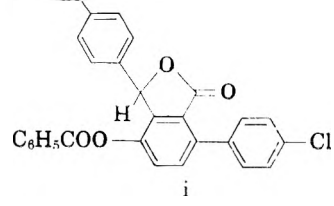
(7) Huntress and Seikel, *J. Am. Chem. Soc.*, 61, 817 (1939). We are indebted to Dr. Seikel (Wellesley College, Wellesley, Mass.) for providing a sample of this acid.

(8) Infrared spectra were of chloroform solutions unless otherwise stated, and were taken on a Perkin-Elmer 21B double beam spectrophotometer. Ultraviolet spectra were taken of 95% ethanol solutions on a Cary recording spectrophotometer. Spectral values in parentheses indicate shoulders. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(9) The infrared maximum of this compound at 5.66 μ and the maxima of its amorphous hydrolysis product at 2.90 and 5.67 μ suggest that the former might be formulated as i. Such a product could arise by a mechanism similar to the proposed mode of formation of III (R = C_6H_5CO—).



i

ethyl acetate to destroy the excess reducing agent. Addition of cold 5% sulfuric acid dissolved the precipitate. The resulting solution was extracted several times with ether. After washing with water and drying over magnesium sulfate, the extracts were evaporated to dryness to give a colorless oil (0.36 g.) which crystallized on trituration with benzene. Recrystallization from benzene-ethyl acetate yielded VII as a colorless product (0.26 g., 86% yield), m.p. 165–166°, which, after repeated recrystallizations, melted at 169–170°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 79.01; H, 5.77. An active hydrogen determination showed 0.84%, corresponding to 2.6 atoms.[10]

The infrared spectrum showed maxima at 3.00, 6.25, 6.82, 7.92, 8.57, and 8.85 μ. The ultraviolet spectrum is recorded in Fig. 1.

Reduction of 4-hydroxy-2-biphenylcarboxylic acid (0.080 g.) was performed essentially as described above. A crystalline white solid (0.045 g.) was obtained which was recrystallized several times from ether-benzene to yield VIII, m.p. 175–176°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.90; H, 5.87.

(10) Sample was incompletely soluble in the butyl ether.

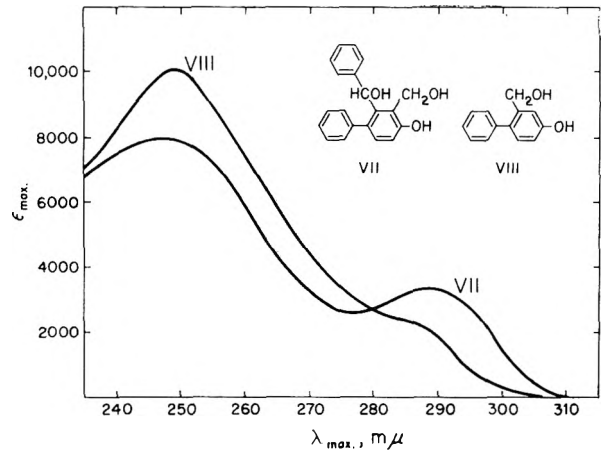


FIG. 1.—ULTRAVIOLET SPECTRA OF SUBSTITUTED 4-HYDROXYBIPHENYLS (IN 95% ETHANOL)

The ultraviolet spectrum is reproduced in Figure 1.

CAMBRIDGE, MASS.

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

Some Pyridylnitroalkenes, Nitroalkanols, and Alkylamines

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Nicotinaldehyde condenses with nitroethane to 1-(3-pyridyl)-2-nitropropene which can be reduced stepwise to 3-pyridylacetoxime and 1-(3-pyridyl)-2-aminopropane. Pyridine-4-aldehyde and nitroethane furnish 1-(4-pyridyl)-2-nitropropanol-1, while isoquinoline-3-aldehyde and nitroethane give 1-(3-isoquinolyl)-2-nitropropene.

Considerable pharmacological interest has been attached to 2-aminoethyl and 2-aminopropyl derivatives of pyridine. 2-(2-Pyridyl)-ethylamine[2] and 1-(2-pyridyl)-2-aminopropane[3] resemble histamine in pharmacodynamic behavior whereas 1-(6-methyl-2-pyridyl)-2-aminopropane,[3] and especially 1-(5-ethyl-2-pyridyl)-2-aminopropane[3] produce marked analgesia in laboratory animals. 2-(3- or 4-Pyridyl)-ethylamines[2,4] are pressor amines, and 1-(3-pyridyl)-2-aminopropane[5] especially appears to have pronounced vasoconstrictor properties.[6] It became advisable to prepare this amine by a more rewarding route than described previously,[5] and the commercial availability of nicotinaldehyde invited a synthesis *via* 1-(3-pyridyl)-2-nitropropene. This compound was formed in 67% yield from nicotinaldehyde and nitroethane under the influence of *n*-butylamine at 90°, and could be reduced stepwise with lithium aluminum hydride. 3-Pyridylacetoxime[5] was obtained in high yields first. This reaction resembles the reduction of 1-phenyl-2-nitropropene which could be stopped at phenylacetoxime.[7] When four moles of the reducing agent was used in boiling ether for 10 hr., a mixture of 43% of 1-(3-pyridyl)-2-aminopropane and 40% of 3-pyridylacetoxime was formed. The latter could be separated and reduced in the same manner, but again only 48% of 1-(3-pyridyl)-2-aminopropane was obtained. No reduction of the pyridine ring was noted although this has been reported for certain other 3-substituted pyridine derivatives.[8,9]

Of the three pyridine aldehydes, only the 3-isomer reacts with nitromethane to give an α,β-unsaturated nitro derivative.[10] The 2- and 4-isomers furnish the corresponding 2-nitroethanols under analo-

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gous conditions.[11] It has now been found that pyridine-4-aldehyde and nitroethane yield 80% of 1-(4-pyridyl)-2-nitropropanol-1 under the influence of *n*-butylamine or potassium hydroxide. This nitro alcohol could not be dehydrated by agitation with phosphorus pentoxide for 24 hr., and it was recovered unchanged when its solution in aqueous sodium hydroxide was treated with acid. Warming with acetic anhydride led to black tars with the evolution of oxides of nitrogen.

The formation of stable nitro alcohols α or γ to pyridine nitrogen has some analogies in related ring systems. Quinoline-4-aldehydes add nitroalkanes to give the corresponding 1-(4-quinolyl)-2-nitro-1-alkanols,[12,13] and isoquinoline-1-aldehyde yields 1-(1-isoquinolyl)-2-nitroethanol with nitromethane.[14] We have found that, by contrast, isoquinoline-3-aldehyde in which the formyl group is located at a slightly less reactive position[15] can be condensed with nitroethane to 1-(3-isoquinolyl)-2-nitropropene without difficulty.

These regularities may be explained on the basis of the higher inductive effect on the extraannular C—OH group exerted by the 2- and 4- positions of the pyridine ring, making an escape of hydroxide ions from the alcohol more difficult.

EXPERIMENTAL[16]

1-(3-Pyridyl)-2-nitropropene. A mixture of 3.2 g. (0.03 mole) of nicotinaldehyde, 2.67 g. (0.03 mole) of nitroethane, and 4–5 drops of *n*-butylamine was heated on a steam bath for 2.5 hr. or longer, cooled to −4°, and allowed to crystallize. The crystals were filtered and washed with petroleum ether. An additional batch of the material was obtained by extracting the filtrate with dilute acid and cautiously neutralizing the acid layer with sodium carbonate solution. Recrystallization from a small volume of ethyl acetate or from ligroin gave 3.2 g. (67%) of yellow prisms, m.p. 67.5–68°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91. Found: C, 58.56; H, 4.88.

The compound irritated the skin and caused severe dermatosis. The yellow *picrate* melted at 131° after crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{11}N_5O_9$: C, 42.75; H, 2.92. Found: C, 42.59; H, 3.04.

About 17% of unchanged nicotinaldehyde was recovered by extraction of the aqueous alkaline filtrate of the nitropropene derivative with ether.

Reduction of 1-(3-pyridyl)-2-nitropropene. (*a*) To a stirred suspension of 1.7 g. (0.04 mole) of lithium aluminum hydride in 75 ml. of dry ether at 0° was added a solution of 2.2 g. (0.0135 mole) of the nitropropene derivative. The mixture was stirred at 0° for 10 min. and at 28° for 30 min., treated with 2.8 ml. of water, and filtered after 1 hr., and the precipitate was extracted exhaustively with ether. The colorless crystalline residue from the combined ether solutions melted at 115–117° and did not depress the melting point of an authentic sample of 3-pyridylacetoxime.[5] The yield was 80–90%.

(*b*) If the reduction was carried out with a four-molar excess of lithium aluminum hydride in boiling ether for 9–10 hr., and the residue from the ether extract was distilled, a 45% yield of 1-(3-pyridyl)-2-aminopropane, b.p. 70–73° (0.2 mm.) was obtained. The *dipicrate*, m.p. 187–187.5°, did not depress the melting point of an authentic sample.[5]

The hygroscopic *dihydrobromide* crystallized from absolute ethanol, m.p. 192–193°.

Anal. Calcd. for $C_8H_{12}N_2.2HBr$: C, 32.24; H, 4.73. Found: C, 32.13; H, 5.17.

About 40% of 3-pyridylacetoxime distilled as a higher boiling fraction, and was identified by its melting point characteristics.

(*c*) 3-Pyridylacetoxime could be reduced in the same manner with two moles of lithium aluminum hydride. The yield of amine after distillation was 48%.

1-(4-Pyridyl)-2-nitropropanol-1. (*a*) A mixture of 2.14 g. (0.02 mole) of pyridine-4-aldehyde, 1.65 g. (0.022 mole) of nitroethane, and 6 drops of *n*-butylamine was allowed to stand at 25° for 5 days. After trituration with 25 ml. of ether, 2.95 g. (80%) of pale brown needles was filtered which after recrystallization from ethanol melted at 153–153.5°, dec.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53. Found: C, 52.60; H, 5.44.

The yellow *picrate* crystallized from ethanol, m.p. 149–150°, dec.

Anal. Calcd. for $C_{14}H_{13}N_5O_{10}$: C, 40.88; H, 3.19. Found: C, 40.75; H, 3.27.

(*b*) To a stirred solution of 5 g. of potassium hydroxide and 80.9 g. (1.08 mole) of nitroethane in 200 ml. of absolute methanol at 10° was added 107.1 g. (1 mole) of pyridine-4-aldehyde at such a rate that the temperature did not rise over 35°. A white precipitate appeared. After standing overnight, the viscous mixture was filtered, and the colorless nitropropanol derivative (150.6 g., 82.5%, m.p. 150–151°, dec) was washed with water and methanol. After recrystallization from ethanol the substance melted at 151–152°, dec.

Anal. Found: C, 52.35; H, 5.42.

When ammonium acetate in hot acetic acid was used as a condensing agent, a high melting polymeric solid was formed. Attempts to reduce the pure nitropropanol derivative with nickel or platinum catalysts, or with lithium aluminum hydride, remained inconclusive.

1-(3-Isoquinolyl)-2-nitropropene. When a solution of 7.81 g. (0.05 mole) of isoquinoline-3-aldehyde,[17] 4.05 g. (0.054 mole) of nitroethane and 0.5 ml. of *n*-butylamine was allowed to stand at 25° for 5 days and worked up, 4.39 g. (41%) of brown needles was obtained which, after recrystallization from ethanol, melted at 113–114°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71. Found: C, 67.29; H, 4.64.

Like other β-nitrostyrenes,[18] 1-(3-isoquinolyl)-2-nitropropene inhibited the multiplication of a variety of pathogenic and agricultural fungi.

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

Preparation and Ultraviolet Absorption Spectra of Certain Alkyl Polysulfides

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Improved procedures are here reported for the preparation of di-*n*-butyl, di-*n*-amyl, and di-isoamyl disulfides by the Bunte salt method. In addition, di-*n*-propyl, di-isopropyl, and di-*n*-butyl trisulfides have been synthesized by the interaction of the respective mercaptans and sulfur dichloride. The ultraviolet absorption spectra of these compounds have also been determined.

Di-*n*-butyl disulfide[1,2] and di-*n*-amyl disulfide[1] have already been prepared through the medium of the Bunte salts. Di-*n*-propyl trisulfide and di-isopropyl trisulfide have been prepared by Cairns, *et al.* as[3] some of the products resulting from the action of hydrogen sulfide on certain carbonyl compounds. Di-*n*-butyl trisulfide has been prepared by the reaction of thionyl chloride with *n*-butyl mercaptan.[4]

Di-*n*-butyl, di-*n*-amyl and di-isoamyl disulfides have been prepared here in percentage yields of 56.2, 53.3, and 47.3 respectively, through the medium of the corresponding Bunte salts:

$$2SO_2(ONa)SC_4H_9\text{-}n + 2KOH \longrightarrow (n\text{-}C_4H_9S)_2 + HOH + K_2SO_3 + Na_2SO_4 \quad (I)$$

Di-*n*-propyl, di-isopropyl, and di-*n*-butyl trisulfides have resulted from the action of sulfur dichloride of the respective mercaptans in percentage yields of 64.7, 46.0, and 45.0, respectively:

$$2n\text{-}C_3H_7SH + (SCl)_2 \longrightarrow 2HCl + (n\text{-}C_3H_7S)_2 \quad (II)$$

Di-*n*-butyl sulfide has been satisfactorily prepared by an adaptation of the Williamson synthesis on the interaction of sodium *n*-butyl mercaptide and *n*-butyl bromide, yield 40.7%.

The ultraviolet absorption spectra of these polysulfides were measured between 220 and 340 mm. Almost identical spectra were obtained for the three disulfides. The spectra for *n*-propyl, isopropyl, and *n*-butyl trisulfides were also nearly identical with each other. A comparison of the inflection points of the disulfide spectra with those reported by Gorin and Dougherty[5] and Koch[6] show close agreement. An interesting comparison spectrum was run using di-*n*-butyl sulfide, disulfide, and trisulfide. It is noteworthy that as the rank of these compounds increases, the absorbance becomes more intense at a much greater rate. An increase in absorbance is to be expected due to the electronic excitation on the additional sulfur atom or atoms. The first maximum in trisulfide spectra, around 251 mm. as already reported by Baer and Carmack[7] agrees quite well with the measured values herein recorded.

TABLE I

PHYSICAL PROPERTIES

	B.P., °C.	Mm.	n_D^{25}	Yield, %
$(n\text{-}C_4H_9)_2S$	121–124	26	1.4907	56.2
$(n\text{-}C_4H_9S)_2$	105–108	2	1.4872	53.5
$(n\text{-}C_5H_{11}S)_2$	124.0–126.5	10	1.4810	47.3
$(iso\text{-}C_5H_{11}S)_2$	86–89	1.5	1.5440	64.7
$(n\text{-}C_3H_7S)_2S$	86–90	8	1.5382	46.0
$(iso\text{-}C_3H_7S)_2S$	87–90	0.7	1.5287	45.0
$(n\text{-}C_4H_9S)_2S$	180–183	740	1.4493	40.7

TABLE II

WAVE LENGTHS, mμ

	Minima	Maxima
$(n\text{-}C_4H_9S)_2$	227	252
$(n\text{-}C_5H_{11}S)_2$	227	254
$(iso\text{-}C_5H_{11}S)_2$	227	252
$(n\text{-}C_3H_7S)_2S$	—	251
$(iso\text{-}C_3H_7S)_2S$	—	254
$(n\text{-}C_4H_9S)_2S$	—	251

EXPERIMENTAL

Di-n-butyl sulfide. Sodium (5.1 g., 0.22 g.-atom) was dissolved in 125 cc. of absolute ethyl alcohol in a three necked flask protected by a calcium chloride tube and an atmosphere of dry nitrogen. With stirring and cooling in an ice bath, 20.0 g. (0.22 mole) of *n*-butyl mercaptan was added, followed by 31.0 g. (0.23 mole) of *n*-butyl bromide, over a 15 min. period. After the addition had been completed, the reaction mixture was refluxed for 2 hr., cooled, the organic layer separated from the solid which had formed during reaction, and dried over calcium sulfate. Distillation of the product yielded 13.0 g. (0.09 mole) of di-*n*-butyl sulfide, yield 40.7%, b.p. 180–183°/740 mm. (lit.[8] 182°); n_D^{25} 1.4493 (lit.[9] 1.4530).

Di-n-butyl disulfide. Di-*n*-butyl disulfide was prepared by a procedure similar to that reported by Stutz and Shriner.[2] Sodium thiosulfate pentahydrate (300 g., 1.21 mole) in 500 cc. of ethyl alcohol and 400 cc. of water was stirred

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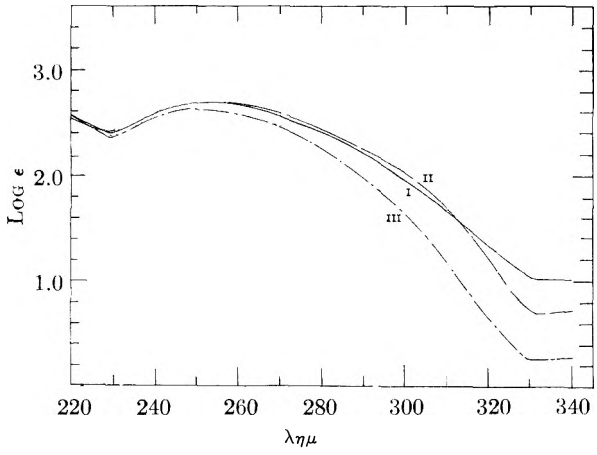

FIG. 1.—ULTRAVIOLET ABSORPTION SPECTRA OF ALKYL DISULFIDES, I, *n*-BUTYL DISULFIDE; II, *n*-AMYL DISULFIDE; III, ISOAMYL DISULFIDE.

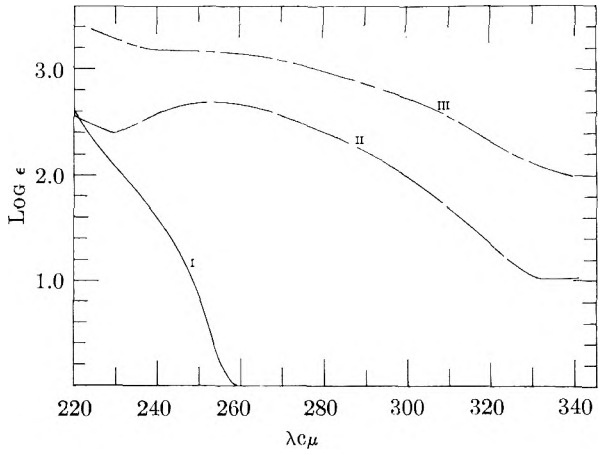

FIG. 3.—ULTRAVIOLET ABSORPTION COMPARISON SPECTRA OF *n*-BUTYL SULFIDE AND POLYSULFIDES, I, *n*-BUTYL SULFIDE; II, *n*-BUTYL DISULFIDE; III, *n*-BUTYL TRISULFIDE.

until solution had been completed, after which 137.0 g. (1.00 mole) of *n*-butyl bromide was added over a 1-hr. period. Stirring and refluxing were continued for 2 hr. On partial cooling, 140 g. (2.5 moles) of potassium hydroxide in 300 cc. of water was added with 45 min. stirring and refluxing. The organic layer was separated, washed with 200 cc. of distilled water and dried over calcium chloride. Distillation yielded di-*n*-butyl disulfide (49.9 g., 56.2%), b.p. 121–124°/26 mm. (lit.[2] 120–123°/26–30 mm.); n_D^{25} 1.4907 (lit.[2] n_D^{20} 1.4926).

Di-n-amyl disulfide. Di-*n*-amyl disulfide was also prepared by the method outlined above using the same molar proportions of reactants, including 151.0 g. (1.00 mole) of *n*-amyl bromide. Di-*n*-amyl disulfide (55.0 g., 0.27 mole) was isolated by distillation; yield 53.5%, b.p. 105–108°/2 mm. (lit.[10] 90–92°/1 mm.); n_D^{25} 1.4872 (lit.[10] 1.4875).

Di-isoamyl disulfide. Di-isoamyl disulfide was prepared as was the *n*-isomer. 1-Bromo-3-methylbutane (151.0 g., 1.00 mole) was used, yielding 48.6 g. (0.24 mole) of di-isoamyl disulfide, yield 47.3%, b.p. 124.0–126.5°/10 mm. (lit.[11] 123.5–124.0°/12 mm.); n_D^{25} 1.4810 (lit.[12] 1.4832).

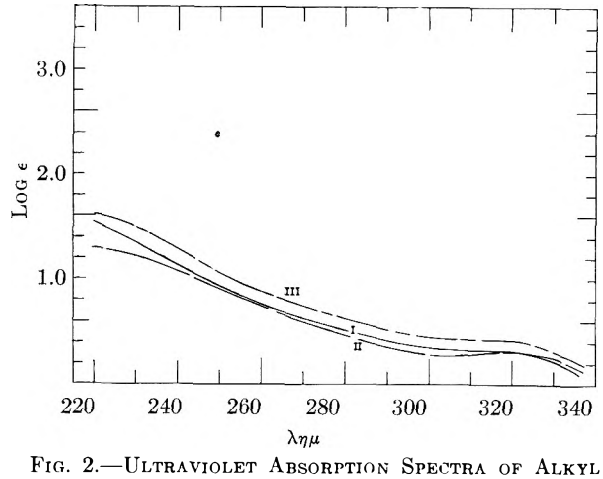

FIG. 2.—ULTRAVIOLET ABSORPTION SPECTRA OF ALKYL TRISULFIDES, I, *n*-PROPYL TRISULFIDE; II, ISOPROPYL TRISULFIDES; III, *n*-BUTYL TRISULFIDE.

Di-n-propyl trisulfide. Di-*n*-propyl trisulfide was prepared by a similar procedure, as reported by Clayton and Etzler.[13] *n*-Propyl mercaptan (30.5 g., 0.40 mole) dissolved in 300 cc. of carbon disulfide was placed in a 1 l. three-necked flask, equipped with a condenser, mechanical stirrer, and calcium chloride tube. With stirring, 20.6 g. (0.2 mole) of sulfur dichloride in 200 cc. of carbon disulfide was added over a period of 3 hr. After all the sulfur dichloride had been added, the mixture was refluxed for 1 hr. After cooling, the solvent was distilled off under reduced pressure and the residue fractionated, giving di-*n*-propyl trisulfide, 23.5 g. (64.7%), b.p. 86–89°/1.5 mm. (lit.[3] 68–69°/0.9 mm.); n_D^{25} 1.5440 (lit.[3] 1.5424)

Di-isopropyl trisulfide. By the same procedure, using 16 g. (0.21 mole) of isopropyl mercaptan and the other reactants in relative amounts, di-isopropyl trisulfide was isolated (8.5 g., 46%), b.p. 86–90°/8 mm. (lit.[3] 75–76°/5 mm.); n_D^{25} 1.5352 (lit.[3] 1.5351).

Di-n-butyl trisulfide. Similarly, using 36 g. (0.40 mole) of *n*-butyl mercaptan and other reactants in proportion, di-*n*-butyl trisulfide was isolated (19.0 g., 45%) b.p. 87–90°/0.7 mm. (lit.[11] 119–21°/6 mm.); n_D^{25} 1.5287 (lit.[4] n_D^{20} 1.5320).

Determination of the spectra. The ultraviolet spectra were measured with a Beckman Model DK-2 spectrophotometer. After the instrument was balanced, the spectra were determined using isooctane as the solvent. The solvent, spectro grade isooctane, was purchased from the Phillips Petroleum Co. The concentration of the solutions of mono- and disulfides were about 0.001*M* and of trisulfides 0.0005*M*. The solutions of the polysulfides were prepared in a more concentrated form, then diluted to the above mentioned lower grade.

Acknowledgment. The authors are indebted to The Hooker Electrochemical Co., Niagara Falls, N. Y. for a supply of sulfur dichloride.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DREXEL INSTITUTE OF TECHNOLOGY]

Triethyltin Haloacetates, Halopropionates, and Propenoates

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Table I lists the properties of fourteen new triethyltin haloacetates, halopropionates, and propenoates. All except two of the esters result from the usual preparative method $[(C_2H_5)_3Sn]_2O + 2HOCOCH_2X \rightarrow 2(C_2H_5)_3SnOCOCH_2X + H_2O$. Two esters involve altered preparative methods $[(C_2H_5)_3Sn]_2O + 2CH_3OCOC(CH_3)=CH_2 \rightarrow 2(C_2H_5)_3SnOCOC(CH_3)=CH_2 + CH_3OCH_3$ and also $(C_2H_5)_3SnI + AgOCOCH_2OH \rightarrow (C_2H_5)_3SnOCOCH_2OH + AgI$.

Previous investigations on triethyltin esters at this Institute include the preparation of triethyltin esters by two methods: the typical[1,2] $[(C_2H_5)_3Sn]_2O + 2CF_3COOH \rightarrow 2(C_2H_5)_3SnOCOCF_3 + H_2O$ and a recent modification[3] $[(C_2H_5)_3Sn]_2O + 2C_2H_5OCOCH_3 \rightarrow 2(C_2H_5)_3SnOCOCH_3 + C_2H_5OC_2H_5$. The present paper employs acids in twelve preparations and an organic ester in one preparation. Neither of these methods appears suitable for the synthesis of the hydroxyacetate, but the use of a silver salt proves adequate—as in previous[4] organogermanium preparations—$(C_2H_5)_3SnI + AgOCOCH_2OH \rightarrow (C_2H_5)_3SnOCOCH_2OH + AgI$. Transesterifications or ester exchanges often have great usefulness in organosilicon[5] or organogermanium[6] preparations, but appear to have definite limitations in trialkyltin preparations, especially with moderately strong acids, which can yield diesters[7] $(C_2H_5)_3SnOCOCF_3 + 2C_6H_5SH \rightarrow (C_2H_5)_2Sn(SC_6H_5)_2 + C_2H_6 + CF_3COOH$.

An earlier paper shows the position of triethyltin esters in a "conversion series" for the use of silver salts.[8]

This present publication contains, it seems, the first trialkyltin halopropionates and the first trialkyltin propenoates. Earlier papers report the compounds $(C_2H_5)_3SnOCOCF_3$,[1] $(C_2H_5)_3SnOCOCH_2Cl$, and $(C_2H_5)_3SnOCOCHCl_2$[7] as haloacetates; the present paper adds $(C_2H_5)_3SnOCOCH_2F$, $(C_2H_5)_3SnOCOCH_2Br$, and $(C_2H_5)_3SnOCOCH_2I$.

Nearly all the compounds in Table I have limited thermal stabilities, but $(C_2H_5)_3SnOCOC_2F_5$ and $(C_2H_5)_3SnOCO$-*n*-C_3F_7 appear rather stable at their respective boiling points of 216.5° and 224° under 760 mm. pressure. In fact, the combination of limited thermal stability and of fairly high solubility in organic solvents makes the preparation of these compounds painstaking.

Analyses in Table I include the direct determination, perhaps for the first time, of the ester group in organotin esters by titration with sodium hydroxide in ethanol.

TABLE I

PROPERTIES OF TRIETHYLTIN HALOESTERS AND PROPENOATES

Compound	M.P., °C.	OCOR		Tin		Mol. Wt.		Yield, %[a]
		Calcd.	Found	Calcd.	Found	Calcd.	Found	
$(C_2H_5)_3SnOCOCH_2F$	155–156	27.2	27.3	42.0	41.8	282.9	—	30
$(C_2H_5)_3SnOCOCH_2Br$	99.5	40.2	40.5	34.6	34.8	343.8	361	50
$(C_2H_5)_3SnOCOCH_2I$	94.5	47.4	47.9	30.4	30.6	390.8	384	60
$(C_2H_5)_3SnOCOCH_2CH_2Cl$	87.5–88	34.3	33.9	37.9	38.3	313.4	310	70
$(C_2H_5)_3SnOCOCHClCH_3$	90.5–91	34.3	34.2	37.9	38.1	313.4	303	70
$(C_2H_5)_3SnOCOCH_2CH_2Br$	84.5	42.5	42.7	33.2	33.4	357.9	—	60
$(C_2H_5)_3SnOCOCHBrCH_3$	88–89	42.5	42.8	33.2	32.9	357.9	345	40
$(C_2H_5)_3SnOCOCHBrCH_2Br$	99.5–100	52.9	53.1	27.2	27.0	436.8	—	70
$(C_2H_5)_3SnOCOCF_2CF_3$[b]	94.5	44.2	44.5	32.2	32.2	368.9	384	40
$(C_2H_5)_3SnOCO$-*n*-C_3F_7[c]	75.5	50.8	51.1	28.3	28.8	418.9	420	40
$(C_2H_5)_3SnOCOCH=CH_2$	116–117	25.6	25.6	42.9	43.5	276.9	—	70
$(C_2H_5)_3SnOCOC(CH_3)=CH_2$	75.5	29.2	29.1	40.8	40.9	291.0	—	30
$(C_2H_5)_3SnOCOCH=CHC_6H_5$	107–108	41.7	41.8	33.6	33.5	353.0	—	55
$(C_2H_5)_3SnOCOCH_2OH$	106.5–107	26.7	26.8	42.3	42.0	280.9	—	25

[a] Yield upon first crystallization. [b] B.p. (760 mm.) of pentafluoropropionate is 216.5°. [c] B.p. (760 mm.) of heptafluoro-*n*-butyrate is 224°.

EXPERIMENTAL

Starting materials included pure $[(C_2H_5)_3Sn]_2O$[1] and $(C_2H_5)_3SnI$, C_2F_5COOH and *n*-C_3F_7COOH obtained from

(1) G. S. Sasin, *J. Org. Chem.*, **18**, 1142 (1953).
(2) P. Kulmitz, *J. prakt. Chem.*, **80**, 60 (1860).
(3) H. H. Anderson, *J. Org. Chem.*, **19**, 1766 (1954).
(4) H. H. Anderson, *J. Org. Chem.*, **20**, 900 (1955).
(5) H. H. Anderson and G. M. Stanislow, *J. Org. Chem.*, **18**, 1716 (1953).
(6) H. H. Anderson, *J. Am. Chem. Soc.*, **74**, 2371 (1952).
(7) G. S. Sasin and R. Sasin, *J. Org. Chem.*, **20**, 387 (1955).
(8) H. H. Anderson and J. A. Vasta, *J. Org. Chem.*, **19**, 1300 (1954).

Peninsular Chemicals Co., Gainesville, Fla., and redistilled, Eastman Kodak white label haloacids, highly toxic, center-fraction CH_2FCOOH prepared from $NaOCOCH_2F$ and concentrated H_2SO_4, propenoic acid distilled free of inhibiting hydroquinone, methyl methacrylate with inhibitor left present, and $AgOCOCH_2OH$ made from $AgNO_3$, $NaOCOCH_2OH$, and a little excess $HOCH_2COOH$ in aqueous solution.

Analytical methods included determination of tin as SnO_2 after treatment of the organotin compound with mixed fuming nitric and fuming sulfuric acids, determination of molecular weights in camphor solution when the compound had sufficient thermal stability, and direct determination of the OCOR group through titration with ethanolic sodium hydroxide. This last procedure may be part of a future publication upon analytical methods.

Determination of corrected melting points in Table I employed an Anschutz thermometer with the tiny bulb immersed in the melted compound or more frequently employed the customary capillary method without recovery of the compound. Three to five recrystallizations sufficed to produce a compound of constant melting point.

Reactions with acids. Typically, 2.35 g. (11.0 milliequivalents) of $[(C_2H_5)_3Sn]_2O$ and 10.0 milliequivalents of the haloacid were combined and heated for 10 min. at 100° if the haloacid decomposed easily, but up to 60 min. at 100° if the haloacids were relatively stable. Some water formed; pipetting separated most of the water and Na_2SO_4 accepted the rest. The material was crystallized from small volumes of an organic solvent such as n-C_4H_9Cl or petroleum ether (30–60°) until the melting point became constant; often the use of a salt-ice bath was necessary in crystallization. At the melting point or slightly above it $(C_2H_5)_3SnOCOCH{=}CH_2$ decomposed somewhat. Formation of two immiscible layers in the preparation of $(C_2H_5)_3SnOCOCH_2F$ probably was responsible for the low yield of ester.

Reaction with methyl methacrylate. Methacrylic acid alone would probably polymerize too rapidly for use with $[(C_2H_5)_3Sn]_2O$. Three individual runs consisted of heating 2.60 g. of $[(C_2H_5)_3Sn]_2O$ and 1.30 g. of inhibited $CH_3OCOC(CH_3){=}CH_2$ for 1.5 hr. at 100° and then crystallizing from CCl_4 at −10° to get 0.6–1.0 g. of $(C_2H_5)_3SnOCOC(CH_3){=}CH_2$ without isolation of the CH_3OCH_3. In one run excessive viscous polymeric methyl methacrylate prevented recovery of the organotin ester. Later crystallizations employed mixtures of CCl_4 and petroleum ether (30–60°) first and finally petroleum ether alone.

Reaction with $AgOCOCH_2OH$. No reaction occurred between $[(C_2H_5)_3Sn]_2O$ and 70% aqueous $HOCH_2COOH$. However, 1.8 g. of $AgOCOCH_2OH$ and 2.25 g. of $(C_2H_5)_3SnI$ after 15 min. reflux in 15 ml. of CCl_4 and the usual filtration and washing of silver salts[4,8] finally yielded 0.4 g. of $(C_2H_5)_3SnOCOCH_2OH$ upon crystallization from mixed CCl_4 and n-C_4H_9Cl. Two crystallizations from n-C_4H_9Cl followed.

PHILADELPHIA 4, PA.

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

Hydrogenolysis of the Nitrogen—Nitrogen Bond of Acylhydrazines with Raney Nickel

RICHARD L. HINMAN

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The scope of the reductive cleavage of mono- and diacylhydrazines by Raney nickel in the absence of added hydrogen has been explored. Alkyl substituted monoacylhydrazines and unsubstituted 1,2-diacylhydrazines are cleaved readily. 1,2-Diacylhydrazines, which bear substituents other than hydrogen on the nitrogens, are generally reduced with difficulty or not at all. The nitrogen—nitrogen bonds of 1-acyl-2-alkylidenehydrazines undergo smooth hydrogenolysis, yielding the corresponding amides.

In 1954, Ainsworth[1] showed that the nitrogen—nitrogen bond of simple carboxylic acid hydrazides can be reductively cleaved by refluxing an ethanolic solution of the hydrazide with a large quantity of Raney nickel (Equation 1). More recently this

$$RCONHNH_2 \longrightarrow RCONH_2 + NH_3 \qquad (1)$$

reaction has been extended to a variety of other compounds, including 1,2-diacylhydrazines and some heterocycles which contain a nitrogen—nitrogen bond.[2]

The purpose of the present work was to explore more completely the scope and limitations of this useful reaction, as it applies to acylhydrazines bearing various substituent groups on the nitrogens. A number of the acylhydrazines were those prepared in connection with other recently reported work.[3] Raney nickel W-2[4] was used in most of the experiments. However, a commercial catalyst[5] was used in a few of the experiments for comparison purposes. No significant differences in activity were observed. The results are summarized in Table 1.

Although 1,2-dibenzoylhydrazine was cleaved to benzamide in 3 hr., as reported by Ainsworth,[2] only a trace of acetamide was isolated from the reaction of 1,2-diacetylhydrazine which was recovered largely unchanged after 3 hr. Since acetamide was isolated in good yield from the latter reaction after a 15-hr. reaction period, the longer time was used with all 1,2-diacylhydrazines.

As examples 1 to 3 show, the accumulation of

(1) C. Ainsworth, *J. Am. Chem. Soc.*, **76**, 5774 (1954).
(2) C. Ainsworth, *J. Am. Chem. Soc.*, **73**, 1636 (1956).
(3a) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).
(3b) R. L. Hinman, *J. Am. Chem. Soc.* **79**, 414 (1957).
(4) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 181 (1955).
(5) "Raney Catalyst in Water," Raney Catalyst Co., Chattanooga, Tennessee.

TABLE I

SUMMARY OF REDUCTIVE CLEAVAGES OF ACYLHYDRAZINES WITH RANEY NICKEL

Example No.	Compound Reduced	Reference to Preparation	Product Isolated[a]	Reaction Time, Hr.	Yield, %
1	$C_3H_7CONHNHCH_2C_6H_5$	[b]	B	4	45
2	$C_6H_5CONHNHC_2H_5$	[b]	A	4	40
3	$C_6H_5CONHN(CH_3)_2$	[c]	A	4	45
4	$(CH_3CONH—)_2$	[d]	C	15	50
5	$(C_6H_5CONH—)_2$ CH_3	[e]	A	15	60
6	$C_6H_5CONNHCOC_6H_5$ C_6H_5	[f]	A	18	12
7	$CH_3CONNHCOCH_3$	[g]	C + D	20	30
8	$(CH_3CONCH_3)_2$	[e]	[l]	15	—
9	$(C_6H_5CONCH_3)_2$	[e]	[l]	20	—
10	$(C_6H_5CO)_2NN(CH_3)_2$	[c]	A[l]	15	5
11	N,N′-Dimethylphthalhydrazide	[h]	E	15	35
12	Phthalhydrazide	[i]	[l]	20	—
13	$C_3H_7CONHN{=}CHC_6H_5$	[j]	B	4	50
14	$C_6H_5CONHN{=}CHCH_3$	[k]	A	4	40

[a] A = benzamide, B = *n*-butyramide, C = acetamide, D = acetanilide, E = N-methylphthalimide. [b] From reduction of the corresponding 1-acyl-2-alkylidenehydrazine with lithium aluminum hydride Ref. 3b. [c] Ref. 3a. [d] R. Stollé, *Ber.*, **32**, 796 (1899). [e] H. H. Hatt, *Org. Syntheses*, Coll. Vol. II, 208 (1943). [f] G. von Brüning, *Ann.*, **253**, 5 (1889). [g] A. Michaelis and F. Schmidt, *Ann.*, 252, 300 (1888). [h] H. D. K. Drew, H. H. Hatt, and F. A. Hobart, *J. Chem. Soc.*, 33 (1937). [i] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937). [j] R. Stollé and G. Zinsser, *J. prakt. Chem.*, [2] **69**, 486 (1904). [k] R. Stollé and E. Münch, *J. prakt. Chem.*, [2] **70**, 393 (1904). [l] More than 50% of starting material recovered.

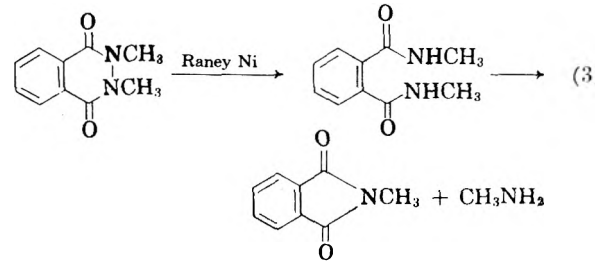
alkyl groups on the nitrogens of a monoacylhydrazine does not hinder the cleavage. Cleavage of a 1,2-diacylhydrazine can be effected if only one nitrogen is substituted by an additional group (Examples 6 and 7). The lower yields, however, seem to be indicative of diminished reactivity. When both nitrogens bear methyl groups, cleavage does not take place (Examples 8 and 9), and most of the starting material is recovered. A similar result was obtained with the tetrasubstituted 1,1-dibenzoyl-2,2-dimethylhydrazine (Example 10). The formation of a small amount of benzamide in this case may be ascribed to the known reaction of dibenzamide, one of the possible cleavage products, with boiling ethanol to produce ethyl benzoate and benzamide.[6] It also seemed possible that 1,1-dibenzoyl-2,2-dimethylhydrazine like dibenzamide might benzoylate ethanol under the conditions of the experiment. Although over 80% of the starting material was recovered from refluxing a solution of 1,1-dibenzoyl-2,2-dimethylhydrazine in ethanol for 15 hr., the wintergreen-like odor of ethyl benzoate was quite strong. If acylation occurred to even a slight extent, the resulting 1-benzoyl-2,2-dimethylhydrazine could give rise to benzamide, as shown in Equation 2.

$$(C_6H_5CO)_2NN(CH_3)_2 \xrightarrow{C_2H_5OH} C_6H_5CONHN(CH_3)_2 + C_6H_5CO_2C_2H_5 \quad (2)$$

$$C_6H_5CONHN(CH_3)_2 \xrightarrow{\text{Raney Ni}} C_6H_5CONH_2$$

(6) F. Krafft, *Ber.*, **23**, 2389 (1890).

Although 1,2-diacetyl-1,2-dimethylhydrazine, 1,2-dibenzoyl-1,2-dimethylhydrazine, and 1,1-dibenzoyl-2,2-dimethylhydrazine are quite unreactive, a related compound, 2,3-dimethylphthalazine-1,4-dione, yields N-methylphthalimide when refluxed with Raney nickel (Example 11). The product is probably formed by hydrogenolysis of the nitrogen—nitrogen bond, followed by ring closure of the resulting N,N′-dimethylphthalamide, as shown in Equation 3. This ring closure has been effected by merely shaking the diamide in water at 25° for 1 hr.[7]



(3)

Since the cleavage reaction undoubtedly occurs at the surface of the nickel catalyst, the failure of the diacylhydrazines 8, 9 and 10 to react may be caused by the bulky groups shielding the nitrogen—nitrogen bond from the surface of the catalyst. The cleavage of 2,3-dimethylphthalazine-1,4-dione is probably made possible by its cyclic form, which would reduce the shielding effect and facilitate the ap-

(7) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 625 (1945).

proach of the functional group to the surface of the catalyst.

In contrast to 2,4-dimethylphthalazine-1,4-dione, phthalhydrazide was not attacked during a 20-hr. reaction (*cf.* Ref. 2). This is in accord with the observation that the former compound resembles a simple diacylhydrazine (*e.g.*, it undergoes hydrolysis easily[8]), whereas the latter seems to be a more highly stabilized aromatic ring system.

The last two examples show that hydrazones also are easily cleaved by refluxing with Raney nickel. Since phenylhydrazine[2] and phenylhydrazides[9] undergo cleavage, there is little question that phenylhydrazones can also be cleaved. This promises to be an important application of the method, and is under investigation in this laboratory.

(8) J. C. E. Simpson, *Condensed Pyridazine and Pyrazine Rings*, Interscience Publishers, Inc., New York, N. Y., 1953, p. 175.

(9) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).

EXPERIMENTAL

The reactions with Raney nickel were carried out by refluxing and stirring vigorously a mixture of 0.5–1.0 g. of the compound to be cleaved with ten times its weight of Raney nickel W-2[4] in 50 ml. of absolute ethanol. When commercial Raney nickel[5] was used, it was slurried several times with absolute ethanol before use. At the end of the reaction the catalyst was removed by filtration and the solvent was distilled under reduced pressure. The product was recrystallized from a suitable solvent and identified by mixed m.p. with an authentic specimen.

The reactions of 1,2-diacetylhydrazine, 1,2-dibenzoylhydrazine, and 1,2-dibenzoyl-1,2-dimethylhydrazine were carried out with Raney nickel W-2 and with commercial Raney nickel. No significant differences in yield were observed.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANNEX C LABORATORIES, EMORY UNIVERSITY]

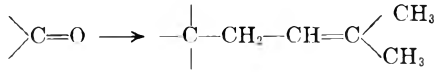
Addition of Isopentenyl[1] Magnesium Chloride to Cyclohexanone

LEON MANDELL

Received July 23, 1956

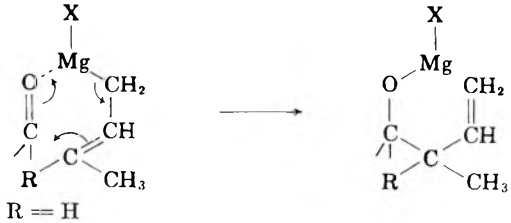
Isopentenyl magnesium chloride has been prepared and added to cyclohexanone. The alcohol produced, on the basis of its infrared spectrum, its ozonization products, and the ultraviolet absorption spectrum of its dehydration product, has been assigned formula III.

In the course of the syntheses of certain sesquiterpenes, being carried out in these laboratories, it became necessary to add to a ketone group an isopentenyl moiety, that is;



As a possible route for this transformation, the addition of the Grignard reagent of 1-chloro-3-methyl butene-2 to cyclohexanone was studied make clear whether this allylic Grignard reagent adds *via* normal addition or with rearrangement.

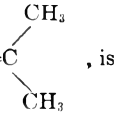
The mode of addition of an unsymmetrical allylic Grignard reagent to ketones has been studied by Young and co-workers[2] who found that butenyl magnesium chloride added to ketones with rearrangement. Their extensive studies led them to postulate that both 3-chloro butene-1 and crotyl chloride give rise to the same Grignard reagent, namely the primary one, and that due to the favorable cyclic transition state possible, Ia, this primary Grignard adds with rearrangement.



Ia. R = H
b. R = CH_3

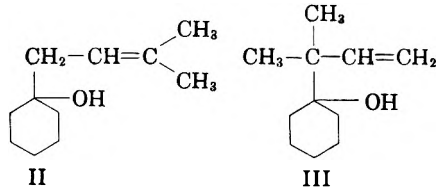
This situation may also obtain with isopentenyl magnesium chloride, the only difference being an extra methyl group substituted at the end of the allylic system. However, one could not predict *a priori* whether the analogy would here be valid, for the extra methyl group could so hinder the formation of the cyclic system, Ib, as to raise its energy over that of the transition state needed for normal addition.

The carbonation of the Grignard reagent of isoprene hydrobromide and hydrochloride has been in-

(1) For the sake of simplicity,  , is referred to as isopentenyl.

(2) W. G. Young, A. N. Prater, and S. Winstein, *J. Am. Chem. Soc.*, **55**, 4805 (1933); W. G. Young, S. Winstein, and A. N. Prater, *J. Am. Chem. Soc.*, **58**, 289 (1936); J. F. Love, J. D. Roberts, and W. G. Young, *J. Am. Chem. Soc.*, **66**, 543 (1944); J. D. Roberts and W. G. Young, *J. Am. Chem. Soc.*, **67**, 148 (1945); W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.*, **67**, 319 (1945); W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.*, **66**, 1472 (1946).

vestigated and although the early workers[3] reported addition without rearrangement, recent work[4] has indicated this finding to be fallacious. Studies carried out[5] on the addition to open chain ketones indicated also a similarly to butenyl Grignard. In order to make more complete these investigations, the product of the reaction between isopentenyl magnesium chloride and cyclohexanone was carefully analyzed by spectral analysis and ozonization to distinguish between the two possible structures, II and III.

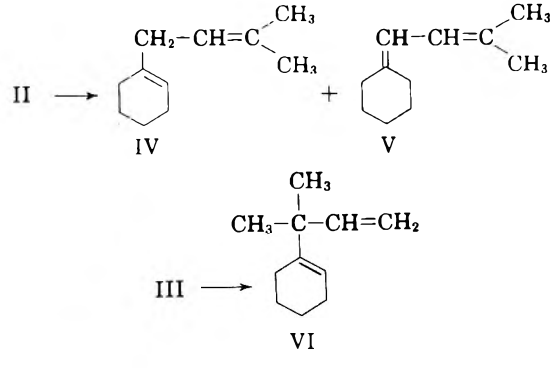


II III

The infrared spectrum of the adduct clearly indicated the presence of a mono substituted olefin[6] and excluded any detectable amount of compound containing a trisubstituted double bond.[6] This would suggest that rearrangement had occurred and the alcohol has structure III.

This spectral evidence that rearrangement similar to the type mentioned above had taken place was confirmed by ozonization, from which formaldehyde (as the dimedone derivative) could readily be isolated whereas no acetone could be detected.

Final confirmation of the structure of the adduct was obtained by dehydration of the alcohol. It is seen that II can give rise to two dienes, IV and V, the latter being a substance which should exhibit



IV V VI

absorption in the ultraviolet. Structure III, on the other hand, can yield only one diene,[7] VI, a non-conjugated one, which therefore, would be transparent toward the ultraviolet. The ultraviolet spectrum of the total crude reaction product from dehydration of the adduct with thionyl chloride and pyridine (which was demonstrated to be dehydrated from its infrared spectrum) showed only end absorption and thus is in accord with the structure deduced from the infrared and ozonization data.

One may therefore conclude that the situation with isopentenyl magnesium chloride is much the same as the case of butenyl Grignard.

EXPERIMENTAL[8]

Grignard reaction of 1-chloro-3-methyl butene-2. With rapid stirring 9.5 g. of 1-chloro-3-methyl-butene-2[9] in 100 ml. dry ether was added to 7 g. magnesium suspended in 20 ml. dry ether. The addition was carried out over 3 hr., and the reaction mixture was stirred 30 min. after the addition was completed.

To the above solution was added 10 g. cyclohexanone in 50 ml. dry ether over a period of 0.75 hr.

The reaction mixture was cooled in an ice bath and decomposed with cold 10% hydrochloric acid and extracted with ether. The ether extract was washed with water to *p*H 6, dried over sodium sulfate, and distilled. A forerun of cyclohexanone was taken and the fraction boiling 93–95°/8 mm. collected. Yield, 6.75 g. (40%).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.5; H, 12.0. Found: C, 78.1; H, 11.9.

The infrared spectrum of the adduct exhibited, besides other absorptions, bands at 3095 cm.$^{-1}$ (m.), 1839 cm.$^{-1}$ (w.), 1642 cm.$^{-1}$ (m.), 1418 cm.$^{-1}$ (s.), 1300 cm.$^{-1}$ (m.), 1009 cm.$^{-1}$ (s.), and 915 cm.$^{-1}$ (s.). These bands are all associated with the monosubstituted ethylene grouping. Of particular interest is the absorption at 1009 cm.$^{-1}$ due to CH out of plane deformation, the higher than usual frequency for this absorption being associated with the vinyl double bond substituting a quaternary carbon atom.[10] The lack of absorption in the 840–790 cm.$^{-1}$ region precluded the presence of any trisubstituted double bond.

Ozonization of adduct. A 5% ozone-oxygen mixture was bubbled through a solution of 0.550 g. adduct dissolved in 20 ml. purified chloroform cooled by a dry-ice acetone bath, for 5 min. past the point where the solution became blue. Fifteen ml. water was then added and the chloroform and water were distilled off. The distillate was divided into two equal portions and one half treated with 0.5 g. dimedone in 10 ml. methanol and the other half added to a solution of 1 g. 2,4-dinitrophenylhydrazine in 100 ml. ethanol and 2 ml. concentrated hydrochloric acid.

The former solution was heated in a steam bath to drive off the chloroform and most of the methanol. Upon cooling fine needles separated which on filtration gave 0.122 g., m.p. 188–189°. Mixture melting point with authentic formaldehyde dimedone derivative showed no depression. This corresponds to 25% yield of formaldehyde.

The latter solution was concentrated so as to remove the chloroform and allowed to evaporate slowly at room temperature. From several fractions of crystals taken over a period of days only unchanged reagent could be isolated.

Dehydration of adduct. To a solution of 2.5 g. adduct in

(3) H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).

(4) H. Kwart and R. K. Miller, *J. Am. Chem. Soc.*, **76**, 5403 (1954); J. M. Rule, Senior Thesis, University of California at Los Angeles, 1944; also reference (5).

(5) B. L. Garner, Ph.D. thesis, University of California at Los Angeles, 1952.

(6) For a discussion of the infrared spectra, see Experimental.

(7) One could envisage a rearrangement involving ring expansion by which III could also give rise to a conjugated diene. However, as the results indicated no conjugated diene to be present at all, this possibility need not be considered.

(8) Melting points are uncorrected. Analyses are by Drs. G. Weiler and F. B. Strauss, Microanalytical Lab., Oxford, Great Britain.

(9) Prepared using the procedure of A. J. Ultee, *Rec. trav. chim.*, **68**, 125 (1949).

(10) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, Chapter 3.

10 ml. anhydrous ether and 3 ml. purified pyridine cooled in an ice bath, was slowly added with shaking, 2 g. thionyl chloride. The reaction mixture was allowed to warm to room temperature and then stand for 16 hr. It was then poured onto cracked ice and the mixture extracted with ether. The ether extract, after having been washed several times with water and then dried over sodium sulfate, was concentrated *in vacuo* to remove the ether.

An infrared spectrum of the total crude product revealed that the hydroxyl group, which appeared in the adduct at 3580 cm.$^{-1}$ as a sharp and intense bond, was completely lacking, thus indicating the completeness of the dehydration reaction.

The ultraviolet spectrum run on an ethanol solution whose concentration was $1.2 \times 10^{-3}M$, showed only end absorption above 220 mμ.

EMORY UNIVERSITY, GA.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE U. S. NAVAL ORDNANCE TEST STATION]

Preparation and Oxidation of 1,2-Diamino-1,2-dimethylguanidine

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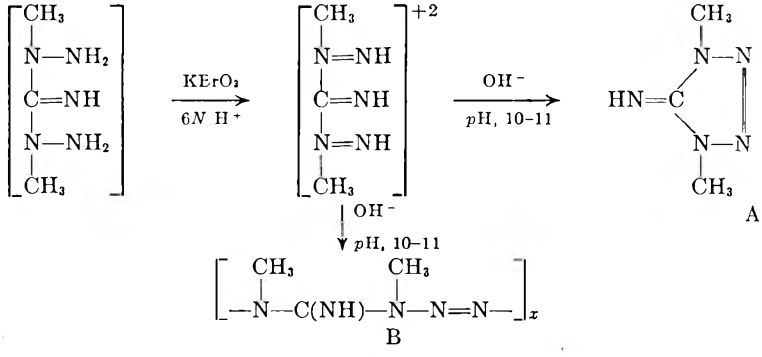
1,2-Diamino-1,2-dimethylguanidine has been synthesized and oxidized with bromate in acidic medium to 1,4-dimethyl-5-iminotetrazole.

It has recently been demonstrated[1] that the oxidation of 1,1-dialkylhydrazines with bromate or iodate in strongly acidic medium involves a two electron change and yields diazo-like intermediates, $[R_2N{=}NH]^+$, of varying stability. These intermediates are irreversibly converted to tetraalkyltetrazenes in basic medium. This sequence of reactions has now been applied to 1,2-diamino-1,2-dimethylguanidine. The coupling of the diazo-like intermediate can occur either intramolecularly to give the known 1,4-dimethyl-5-iminotetrazole[2] or intermolecularly to give a water-soluble polytetrazene.



Experimentally the substituted tetrazole (A) was recovered as its phenylthiourea derivative in 35–37% yield. The synthesis of the 1,4-dimethyl-5-iminotetrazole in this manner is further proof that the previously assigned positions[2] for the methyl groups are correct. In addition, this method offers a new route to this class of tetrazole compounds.

Since the phenylthiourea derivative of the 1,4-dimethyl-5-iminotetrazole is readily formed and is sparingly soluble, the results from this method of isolation should be a good indication of the total amount of tetrazole present in solution. However, a comparison of the molar absorbancy indices (A_M) for 1,4-dimethyl-5-iminotetrazole and the oxidized species from 1,2-diamino-1,2-dimethylguanidinium nitrate (A_M = 1980 and *ca.* 1750, respectively, at 258 mμ in basic aqueous solution) indicates that conversion to tetrazole or compounds with a similar nitrogen resonance system should be about 90%. This spectrophotometric procedure would probably not discriminate between the nitrogen system in the tetrazole and that found either in a polytetrazene (B) or conceivably in a 10-membered ring compound resulting from a dimerization of the diazo-like intermediate. Hence, the difference between the 36% and the 90% is best attributed to polytetrazene although it has not been isolated.

One other product that might result indirectly during the oxidation of 1,2-diamino-1,2-dimethylguanidine is 1,4-dimethyl-5-tetrazolone (from the hydrolysis of the corresponding imino-compound). This possibility is largely excluded, however, by the following: 1,4-Dimethyl-5-tetrazolone in aqueous solution has a maximum absorption at 223 mμ (A_M = 3185), which is similar to that for 1,4-dimethyl-5-iminotetrazole in acidic medium, but which is otherwise essentially independent of *p*H.

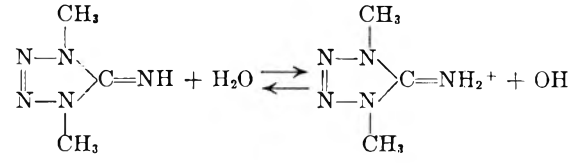
(1) W. R. McBride and H. W. Kruse, Abstracts 129th National Meeting, AMERICAN CHEMICAL SOCIETY, 6Q, Dallas, April 1956. *J. Am. Chem. Soc.*, **79**, 572 (1957).

(2) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

As stated earlier, when the solution arising from the oxidation is made basic, the absorption at 258 mμ corresponds to 90% conversion to 1,4-dimethyl-5-iminotetrazole or compounds with similar resonance systems. Hence, the amount of tetrazolone formed is at best only about 10%. Hattori, *et al.*,[3] previously used the similarity in the characteristic absorptions of 1,3-dimethyl-5-tetrazolone (256 mμ, A_M = 2030) and of 1,3-dimethyl-5-iminotetrazole (256 mμ, A_M = 2670) as indirect evidence to support the former structure.

In contrast to the relative instability of the diazo-like intermediate formed by the oxidation of the 1,1-dialkylhydrazines in acid media,[1] the corresponding intermediate obtained from the 1,2-diamino-1,2-dimethylguanidine was stable and showed no evidence of decomposition, either titrimetrically (a further consumption of iodate as the solution aged) or spectrophotometrically. With the 1,1-dialkylhydrazines the decomposition of the diazo-like intermediate could be followed by both procedures. Furthermore, in contrast to the behavior of the diazo-like intermediate from a 1,1-dialkylhydrazine, the intermediate formed in the oxidation of 1,2-diamino-1,2-dimethylguanidine does not appear to be reduced by stannous chloride in acid medium to the starting hydrazine. 1,4-Dimethyl-5-iminotetrazole is not reduced to the starting diaminoguanidine derivative by stannous chloride in concentrated hydrochloric acid at 60–70° during 1.5 hr. These facts might be interpreted to mean that in the oxidation of 1,2-diamino-1,2-dimethylguanidine the proposed diazo-like compound either is not formed at all or is capable of cyclizing immediately under acidic conditions to the tetrazole derivative. On the other hand, this particular intermediate should be much more stable because of increased resonance than the one from a 1,1-dialkylhydrazine. Furthermore, the equilibrium concentration of the unstable, reactive, unprotonated form in acidic solution should be very much less with the derivative from the 1,2-diamino-1,2-dimethylguanidine. The existence of the diazo-like intermediate from a 1,1-dialkylhydrazine can easily be demonstrated spectrophotometrically. However, since the region in which both the proposed intermediate and the 1,4-dimethyl-5-iminotetrazole should absorb is opaque in the acidic oxidation medium, it is not possible to resolve this problem unambiguously by the spectrophotometric method.

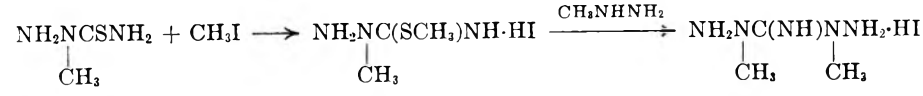
In connection with the spectrophotometric studies, it was noted that the ultraviolet absorption spectrum of 1,4-dimethyl-5-iminotetrazole was dependent on *p*H. A single absorption maximum occurs at 258 mμ (A_M = 1980) in aqueous solutions of *p*H 10 or higher. In aqueous hydrochloric acid solutions with a *p*H of 6 or less the 258 mμ peak disappears and is replaced by an absorption maximum at 220 mμ (A_M = 2194). The hydrochloride salt in absolute ethanol has an absorption at 221 mμ identical to that in the acidic, aqueous solution. Previous workers[2,4] overlooked this effect of *p*H and described only a single absorption maximum; consequently the reported molar absorbancy indices are probably in error since the particular solutions examined would contain an appreciable concentration of each of the two absorbing forms. For example, the molar absorbancy index reported by Murphy and Picard[4] for 1,4-dimethyl-5-iminotetrazole in 95% ethanol (A_M = 1750 at 260 mμ) is probably low since no allowance has been made for the following equilibrium:



Only at high *p*H's (above 10) where the equilibrium lies predominantly on the left, will the absorption spectrum be almost exclusively that due to the free imino form. Although the conclusion of Murphy and Picard that the amino- and imino- forms of substituted 5-aminotetrazoles can be distinguished by the differences in their absorption maxima is correct, in acidic solution 1,4-dimethyl-5-iminotetrazole is distinguished from the other 5-aminotetrazole derivatives only by the intensity of absorption and not by the peak displacement, as these authors suggest.

1,1-Dialkylhydrazines can be oxidized directly to tetrazenes by iodine[1,5] in neutral or slightly basic solution. However, the oxidation of 1,2-diamino-1,2-dimethylguanidine in a solution of sodium bicarbonate with iodine involves a total electron change of about eight rather than the desired four. Considerable gas is evolved with this reaction in contrast to essentially no gas liberated during the oxidation with iodate or bromate in acid solution; and no tetrazole derivative can be recovered. This result appears to be independent of the order of addition.

The 1,2-diamino-1,2-dimethylguanidine used in the oxidation experiments was prepared by the following reaction sequence:



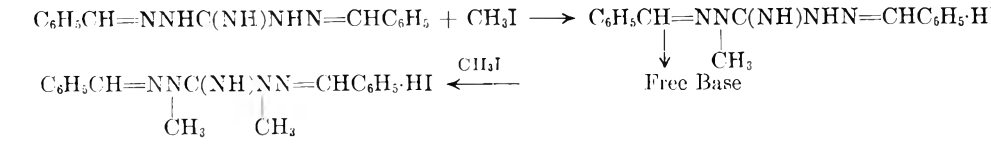
The corresponding dibenzal derivative can be made by a two-step methylation of dibenzaldiami-

(3) K. Hattori, E. Licber, and J. P. Horwitz, *J. Am. Chem. Soc.*, **78**, 411 (1956).

(4) D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1807 1954).

(5) Rowe and Audrieth, *J. Am. Chem. Soc.*, **78**, 563 (1956).

noguanidine in a process analogous to that used for synthesizing benzal 1-amino-1-methylguanidinium iodide:[6]



Since the second methylation appears to be considerably more difficult than the first and since separation of unreacted dibenzal 1,2-diamino-1-methylguanidine from the product is also difficult, this method does not readily or conveniently yield a pure compound.

Attempts to form 1,2-diamino-1,2-dimethylguanidine by the reaction of methylhydrazine and guanidinium nitrate in refluxing aqueous solution led only to low yields of 1-amino-1-methylguanidine; under similar conditions the hydrazinolysis of guanidinium nitrate readily gives triaminoguanidinium nitrate.[7] Similarly, methylhydrazine and aminoguanidinium nitrate reacted very slowly to give small yields of 1,2-diamino-1-methylguanidine, isolated as the picrate of the dibenzal hydrazone. The latter compound was identical with the monomethyl derivative obtained from dibenzaldiaminoguanidine.

The syntheses of several other methylated amino- and diaminoguanidine derivatives are described in the experimental part. Reaction of dimethylamine and S-methylisothiocarbohydrazide hydroiodide in an effort to prepare 1,2-diamino-3,3-dimethylguanidinium iodide yielded triaminoguanidinium iodide as the most easily recoverable product. A similar result was noted when methylhydrazine and S-methylisothiocarbohydrazide hydroiodide were reacted in ethanol.

EXPERIMENTAL[8]

Oxidation of 1,2-diamino-1,2-dimethylguanidine in acid solution. 1,2-Diamino-1,2-dimethylguanidinium nitrate (0.8676 g., 0.00482 mole) was dissolved in 40 ml. of 6*N* hydrochloric acid, cooled to 0–4°, and titrated potentiometrically with a 1.000*N* solution of potassium bromate. The amount of oxidant used corresponded to 0.01900 equivalent, the theoretical requirement was 0.01928 equivalent. The resulting solution was neutralized with a solution of sodium hydroxide to the phenophthalein end point during which time the temperature rose to 15°. The solution was diluted to 100 ml. The molar absorbancy index, A_M, for this solution at 2580 Å was 1727 in units of 1000 cm.²/mol; the pK_b of the oxidation product, as determined spectrophotometrically,[9] was 5.42 at 25°. To 97 ml. of the solution was added 50 ml. of 95% ethanol. The resulting solution was shaken with phenyl isothiocyanate (0.83 g.; 0.0061 mole) and allowed to stand overnight at room temperature; the precipitated solid was removed by filtration, washed several times with pentane, dried, and weighed. The yield was 0.40 g. (34.7%), m.p. 198–202°; a mixed melting point with an authentic sample of the phenylthiourea of 1,4-dimethyl-5-iminotetrazole was 205–207°. The melting point after recrystallization from absolute ethanol was 207–208°.

When the procedure for the initial oxidation with potassium bromate was repeated at room temperature, the yield of the phenylthiourea derivative of 1,4-dimethyl-5-iminotetrazole was 36.7%; the A_M at 2580 Å was 1755.

In the oxidation at 0° an extraneous peak of low intensity which is not accounted for by 1,4-dimethyl-5-iminotetrazole was observed at 277 mμ in a reacidified solution.

1,2-Diamino-1,2-dimethylguanidinium nitrate (0.0686 g. or 0.003807 mole) dissolved in 60 ml. of 6.1*N* hydrochloric acid was rapidly titrated with 0.1000*N* potassium iodate at 25° by the potentiometric procedure. The observed titer was 15.33 ml. (theory 15.23 ml.); after 24 hr. an additional titer of only 0.25 ml. was consumed.

Oxidation of 1,2-diamino-1,2-dimethylguanidine with iodine in neutral solution. A solution of 1 g. of diaminodimethylguanidinium nitrate in 50 ml. of water was added during 2 hr. to 440 ml. of 0.1*N* iodine in potassium iodide (20 g. per l.). Sodium bicarbonate (10 g.) was used to buffer the iodine solution. The reaction mixture was stirred vigorously and the temperature maintained between 0 and 5°. There was a steady evolution of gas. This amount of iodine, which corresponds to twice the theoretical amount required for the desired four electron change, was almost completely reduced. The slight excess of iodine was destroyed with sodium sulfite, the *p*H of the solution was adjusted to 9, and 0.5 ml. of phenyl isothiocyanate in 100 ml. of 95% ethanol added. No thiourea precipitated even after several days at room temperature.

A similar result was observed when the 0.1*N* solution of iodine was added to a buffered solution of the diaminodimethylguanidinium nitrate at 0–3°. Twice the expected quantity of oxidizing agent was required, much gas was evolved, and no phenylthiourea derivative of the 1,4-dimethyl-5-iminotetrazole was recovered.

Ultraviolet absorption data. The ultraviolet absorption spectra were determined with a Cary recording spectrophotometer, model 11MS. The pK_b for 1,4-dimethyl-5-iminotetrazole as determined spectrophotometrically was 5.43 at 25°; the previously reported value determined potentiometrically was 5.32.[2]

The ultraviolet absorption spectrum of 1,3-dimethyl-5-iminotetrazole[2] is also dependent on the *p*H of the solution; for example in an aqueous solution of the hydrochloride at *p*H 1.8 the absorption maximum occurred at 256 mμ (A_M = 2487); at *p*H 12.9, 307 mμ (A_M = 1903). For 1,3-dimethyl-5-iminotetrazole the pK_b was 2.36 at 25° versus a previously reported value[2] of 2.5.

1,2-Diamino-1,2-dimethylguanidine. Methylhydrazine sulfate (72 g.; 0.5 mole) was dissolved in 100 ml. of water and neutralized to a bromophenol blue end point with a 50% solution of sodium hydroxide. Solid sodium thiocyanate (40.5 g.; 0.5 mole) was added and the resulting solution was evaporated to a syrup *in vacuo* on a steam bath. The syrup was extracted three times with 100 ml. portions of boiling 95% ethanol. The ethanol solution of methylhydrazine thiocyanate was evaporated to dryness *in vacuo* on a steam bath and the residue heated to 150° for 30 min. The reaction mixture was then cooled and 100 ml. of ice water added. The precipitated 2-methylthiosemicarbazide was removed by filtration; yield, 37.5 g. Concentration of the filtrate to dry-

(6) Finnegan, Henry, and Smith, *J. Am. Chem. Soc.*, **74**, 2981 (1952).

(7) G. Pellizzari and A. Gaiter, *Gazz. chim. ital.*, **44**, II, 72 (1944).

(8) All melting points are uncorrected.

(9) J. E. DeVries and E. S. Gantz, *J. Am. Chem. Soc.*, **76**, 1008 (1954).

ness, reheating the residue to 150° for 30 min. and dilution with 50 ml. of water yielded an additional 1.1 g. of product. The combined yield of product amounted to 73.5%. One recrystallization from water gave 37.2 g. of product, 166–167.5°, which was adequately pure for the subsequent reactions. Repeated recrystallizations from acetonitrile or from 2-propanol finally gave a material decomposing at 174–176° (very dependent on the rate of heating). The reported[10] melting point of 183–186° was never obtained.

Anal. Calcd. for $C_2H_7N_3S$: N, 39.96. Found: N, 39.86, 39.64.

The benzal thiosemicarbazone after one recrystallization from ethanol melted at 172–174°; reported,[10] 174°.

The 2-methylthiosemicarbazide (37.2 g.; 0.35 mole) was suspended in 150 ml. of absolute ethanol and 60 g. (0.423 mole) of methyl iodide was added. The suspension was kept in a cold water bath for 48 hr., then heated to reflux for 1 hr. The 2-methylthiosemicarbazide gradually dissolved during this time. Removal of the ethanol *in vacuo* left 88 g. of crude 2,S-dimethylisothiosemicarbazide hydroiodide as a thick syrup.

The crude hydroiodide from the preceding reaction was dissolved in 100 ml. of water. To this solution was added 100 ml. of an aqueous solution containing 0.36 mole of methylhydrazine. The reaction mixture was allowed to stand for 48 hr. and then was heated on a steam bath for 4 hr. Methyl mercaptan was evolved copiously. When the solution was concentrated *in vacuo*, 1,2-diamino-1,2-dimethylguanidine hydroiodide (87 g.) was recovered as a syrup. All of the hydroiodide was dissolved in 300 ml. of 60% ethanol, acidified with nitric acid, and converted to the nitrate by reaction with 60 g. (0.353 mole) of silver nitrate in 100 ml. of water. The precipitated silver iodide was removed by filtration and the filtrate was concentrated to dryness under reduced pressure on the steam bath. The residue of 1,2-diamino-1,2-dimethylguanidinium nitrate partially solidified on standing. Crystallization from 100 ml. of boiling acetonitrile yielded 16.23 g. (25.8% based on the methylthiosemicarbazide or 18% over-all) of colorless, coarse crystals, m.p. 82–84°.

Anal. Calcd. for $C_3H_{12}N_6O_3$: C, 20.00; H, 6.72; N, 46.65; mol. wt., 180.19. Found: C, 19.61, 20.25; H, 6.87, 6.94; N, 46.62; mol. wt., 181.1, 179.5.

The *dipicrate* melted at 141–142° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{15}H_{17}N_{11}O_4$; C, 31.31; H, 2.98; N, 26.78; mol. wt., 575.38. Found: C, 31.92; H, 3.19; N, 27.20; mol. wt., 575.1.

The *monobenzal 1,2-diamino-1,2-dimethylguanidinium nitrate* was obtained as prisms from 2-propanol; m.p. 202–203°.

Anal. Calcd. for $C_{10}H_{16}N_6O_3$: C, 44.77; H, 6.01; N, 31.33. Found: C, 44.81; H, 6.18; N, 31.73.

The *dibenzal 1,2-diamino-1,2-dimethylguanidinium nitrate* crystallizes from 2-propanol-diethyl ether as rosettes of fine, white needles; m.p. 128–129°.

Anal. Calcd. for $C_{17}H_{20}N_6O_3$; C, 57.29; H, 5.66; N, 23.59. Found: C, 57.65; H, 6.19; N, 23.54.

The picrate of the dibenzal derivative melted at 192–193° after recrystallization from ethanol; short needles.

Anal. Calcd. for $C_{23}H_{22}N_8O_7$: C, 52.87, H, 4.25; N, 21.45. Found: C, 52.79; H, 4.97; N, 22.16.

The free base of the dibenzal hydrazone crystallized from cyclohexane as white needles, m.p. 135–136° (still impure). Admixture with a pure sample (m.p. 143–144°) of the dibenzal dimethyl derivative prepared in the following experiment was 142°.

Methylation of dibenzal 1,2-diaminoguanidine. Dibenzal 1,2-diaminoguanidine (67 g.; 0.253 mole) was suspended in 200 ml. of absolute ethanol and 37 g. (0.26 mole) of methyl iodide was added. The mixture was allowed to stand 48 hr. at room temperature, then refluxed for 1 hr. On cooling to 5°, 59.8 g. (0.147 mole, 58.1%) of yellow-orange dibenzal 1,2-diamino-1-methylguanidine hydroiodide precipitated; m.p. 225–227° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{18}IN_5$: C, 47.18; H, 4.45; N, 17.20. Found: C, 47.43; H, 4.95; N, 17.17.

The entire quantity of hydroiodide was suspended in 300 ml. of 95% ethanol, and converted to the free base by adding a solution of 6.2 g. of sodium hydroxide in 10 ml. of water. The mixture was heated to boiling and sufficient ethanol was added at the boiling point to dissolve the free base. Cooling yielded the light yellow *dibenzal 1,2-diamino-1-methylguanidine* (26.19 g.; 63.9%), m.p. 137–138° after an additional recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{17}N_5$: C, 68.79; H, 6.14; N, 25.08. Found: C, 68.45; H, 6.03; N, 24.76.

Dibenzal 1,2-diamino-1-methylguanidinium picrate melted at 229–230° after recrystallization from 95% ethanol. A mixed melting point with benzalaminoguanidinium picrate was 215–220°.

Anal. Calcd. for $C_{22}H_{20}N_8O_7$: C, 51.97; H, 3.97; N, 22.04. Found: C, 52.18; H, 4.09; N, 22.12.

Dibenzal 1,2-diamino-1-methylguanidine (30.6 g., 0.11 mole) was methylated with 15.6 g. (0.11 mole) of methyl iodide in a sealed tube at 100° for 18 hr. Recrystallization from 500 ml. of ethanol yielded 32.7 g. (70.5%) of a yellow-orange product melting from 192–197°. Another recrystallization raised the melting point to 209–215° (dec.).

Anal. Calcd. for $C_{17}H_{20}IN_5$: N, 16.63. Found: N, 16.86.

The picrate after two recrystallizations from 95% ethanol melted at 191–192° (dec.). A mixed melting point with an authentic sample of dibenzal 1,2-diamino-1,2-dimethylguanidinium picrate, m.p. 192–193° (dec.), was 191.5–192.5° (dec.). Thus, one of the products formed by methylation is dibenzal 1,2-diamino-1,2-dimethylguanidine.

The free base was obtained as fine colorless needles by treating the hydroiodide in 95% ethanol with concentrated sodium hydroxide. The melting point after two recrystallizations from ligroin was 143–144°.

Anal. Calcd. for $C_{17}H_{19}N_5$: C, 69.95; H, 6.53; N, 23.88. Found: C, 69.87; H, 6.51; N, 23.67.

Reaction of methylhydrazine and guanidinium nitrate. Method A. A solution consisting of 12.2 g. (0.1 mole) of guanidinium nitrate, 9.6 g. (0.2 mole) of methylhydrazine, and 150 ml. of water was refluxed for 6 hr. and then evaporated to dryness under reduced pressure to remove unreacted methylhydrazine. The residue was redissolved in 100 ml. of water, acidified with 1 ml. of concentrated nitric acid, warmed on the steam bath, and shaken with 10 ml. of benzaldehyde. The product, which still contained excess benzaldehyde, was removed by filtration after being chilled to 5°, washed with much cold water, triturated with diethyl ether, and dried. The yield amounted to 5.6 g.; m.p. 170–200°. Recrystallization from absolute ethanol gave 2.8 g. of benzal 1-amino-1-methylguanidinium nitrate melting at 195–196° (dec.); the mother liquor was retained (*A*). A second recrystallization raised the melting point to 199–200° (dec.).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.28. Found: C, 45.33; H, 5.64; N, 29.57.

The purified hydrazone gave a picrate melting at 215–217°; admixture with an authentic sample of benzal 1-amino-1-methylguanidinium picrate[11] was 217–218°.

When the mother liquor (*A*) was treated with an excess of picric acid, 1.4 g. of the benzal methylaminoguanidinium picrate (m.p. 210–213°) was recovered, together with some guanidinium picrate (m.p. above 300°). No diaminodimethylguanidine was detected in these products.

Increasing the reaction time to 24 hr. did not change significantly the yield of benzal 1-amino-1-methylguanidinium nitrate (5.2 g.; m.p. 198–200°). However, from the mother liquors a small quantity of a second compound was

(10) E. Cattelain, *Compt. rend.*, 209, 799 (1939).

(11) A. H. Greer and G. B. L. Smith, *J. Am. Chem. Soc.*, 72, 874 (1950).

recovered as a picrate (0.5 g.). Several recrystallizations from 95% ethanol gave rosettes of thin, yellow needles, 202–203°. Admixture with benzal 1-amino-1-methylguanidinium picrate lowered the melting point to about 180°; with dibenzal 1,2-diamino-1,2-dimethylguanidinium picrate to 160–170°.

Anal. Calcd. for $C_{23}H_{22}N_8O_7$: C, 52.87; H, 4.25; N, 21.45. Found: C, 53.33; H, 4.44; N, 21.21, 21.96.

Method B. Methylhydrazine sulfate (43.2 g.; 0.3 mole) and 11.5 g. of guanidine nitrate (0.094 mole) were dissolved in an ice cold solution of 24 g. of sodium hydroxide (0.6 mole) in 125 ml. of water. This solution was refluxed for 13.5 hr.; ammonia was evolved steadily. After the solution had been evaporated to dryness on the steam bath, the remaining solid was extracted successively with the following portions of boiling 80% ethanol: 100 ml., 50 ml., 50 ml., and 25 ml. The weight of alcohol insoluble residues was 41.5 g. The combined extracts were chilled overnight at 0° to yield 0.55 g. of impure 1-amino-1-methylguanidine sulfate (4.2%). This material was characterized by conversion to the picrate which melted at 230–231° (dec.) after recrystallization from 80% ethanol; a mixed melting point with an authentic sample of 1-amino-1-methylguanidine picrate was the same.

One half of the alcoholic mother liquors was diluted to 125 ml. with 95% ethanol, heated to boiling, and treated with a hot solution of 11 g. of picric acid in 100 ml. of 95% ethanol. An orange microcrystalline salt began to separate almost immediately and was removed by filtration when the temperature of the solution reached 40°; this material (1.7 g.) proved to be guanidine picrate. Further cooling of the filtrate to room temperature yielded 9.0 g. of material, m.p. 165–170°; the filtrate was retained. Fractional crystallization of the 9.0 g. of solid from 110 ml. of 95% ethanol gave 5.3 g. of methylhydrazine picrate, m.p. 166°C (dec.), and 1.2 g. (8.0% on total basis) of 1-amino-1-methylguanidine picrate, m.p. 229–231° (dec.). When the original filtrate was cooled at 0° for 3 weeks, 0.8 g. more of guanidine picrate was recovered. After the guanidine picrate was removed the filtrate was evaporated to 20 ml. and cooled; there was obtained 1.8 g. of material melting at 173–176° (dec.). Recrystallization from 65 ml. of 95% ethanol gave 0,6 g. (4%) of 1-(methylamino)guanidine picrate, m.p. 182–184° (dec.). A mixed melting point with an authentic sample of 1-(methylamino)guanidine picrate[6] was the same; x-ray powder diagrams were also identical. Limited attempts to obtain other pure materials from the mother liquors were not successful.

The other half of the original alcoholic extraction liquors was diluted to 125 ml. with 95% ethanol, heated to boiling, and treated successively with 16 ml. of benzaldehyde and 11.0 g. of picric acid in 100 ml. of hot ethanol. Upon cooling the solution to room temperature fluffy rosettes of yellow needles crystallized. This material was removed and dried; yield 2.6 g. (13.6% on total basis); m.p. 215–217°; a mixed melting point with an authentic sample of benzal 1-amino-1-methylguanidine picrate was 217–218° (dec.). Cooling the mother liquors at 0° for several days gave 9.9 g. of amorphous solid, m.p. 120–130°; the remaining filtrate was discarded. Fractional crystallization from 200 ml. of 95% ethanol gave 2.0 g. of guanidine picrate, 0.1 g. of benzal 1-amino-1-methylguanidine picrate, and the balance essentially monobenzal methylhydrazine picrate. The latter was obtained as orange prisms, m.p. 137.5–138.5° when recrystallized from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_5O_7$: C, 46.28; H, 3.61; N, 19.28. Found: C, 46.42; H, 3.76; N, 19.36.

Reaction of methylhydrazine and aminoguanidine. Aminoguanidinium chloride (11.0 g; 0.1 mole), 4.8 g. (0.1 mole) of methylhydrazine, and 150 ml. of water were heated under reflux for 16 hr. Ammonia was evolved slowly. Concentrated hydrochloric acid was then added until the *p*H was 5. Benzaldehyde (20 ml.) was added with shaking; a precipitate formed immediately and was removed by filtration after the solution had been cooled to 5°. The solid hydrazone was washed several times with cold water, then with diethyl ether. The yield of dried product was 10.8 g. Solution in a minimum volume of hot 95% ethanol and cooling gave 1.0 g. (3.2%) of impure dibenzal 1,2-diamino-1-methylguanidinium chloride, m.p. 190–205°. This salt was converted to the free base, which recrystallized from 95% ethanol as yellow plates, m.p. 139–140°; admixture with the compound made by monomethylating dibenzaldiaminoguanidine did not depress the melting point.

The ethanolic mother liquors were diluted with 100 ml. of ethanol, heated to boiling, and treated with 10 g. of picric acid. Fractional crystallization of the picrates from 95% ethanol finally gave about 4.1 g. (8.0%) of impure dibenzal 1,2-diamino-1-methylguanidinium picrate, m.p. about 220°. Further recrystallizations raised the melting point to 224–227°. A mixed melting point with benzalaminoguanidinium picrate was 215–220°, with dibenzal 1,2-diamino-1-methylguanidinium picrate made by another method was 223–226°. X-ray powder patterns on the two different samples of dibenzal diaminomethylguanidinium picrate were identical. The only other picrate which was recovered in reasonable purity was that from benzalaminoguanidine.

1,2-Diamino-1,3-dimethylguanidine. Twelve grams of 4-methylthiosemicarbazide (m.p. 138–140°) was slurried in 200 ml. of absolute ethanol and treated with 16.5 g. of methyl iodide. The mixture was allowed to stand overnight at room temperature, then refluxed until complete solution was attained, evaporated to one half its volume under reduced pressure, and mixed with 5.3 g. of methylhydrazine in 40 ml. of ethanol. Methyl mercaptan was evolved slowly during several days at room temperature; the solution was refluxed for 1 hr. to complete the reaction before evaporating to dryness. The soft residue was recrystallized from 2-propanol; 17.5 g.; m.p. *ca.* 90°. This once recrystallized product was freed from some triaminoguanidine hydroiodide (0.5 g.; m.p. 225–230°; x-ray powder pattern same as that for an authentic sample) by warming to 60° with 200 ml. of 2-propanol and filtering rapidly. The crystalline hydroiodide obtained by cooling the filtrate was removed and recrystallized another time from 2-propanol; m.p. 91–92°.

Anal. Calcd. for $C_3H_{12}IN_5$: C, 14.70; H, 4.94; N, 28.58. Found: C, 15.12; H, 5.14; N, 28.35.

The dipicrate after two recrystallizations from 95% ethanol and drying at 105° melted at 116.5–118°. The salt obtained directly from the recrystallization and air dried at room temperature is a dihydrate (loss in weight on drying: 6.18%.)

Anal. Calcd. for $C_{15}H_{17}N_{11}O_{14}$ (anhydrous): C, 31.31; H, 2.98; N, 26.78. Found: C, 31.99; H, 3.16; N, 27.11, 26.56.

The picrate of the dibenzal hydrazone separated as rosettes of small, yellow needles after a second recrystallization from ethanol; m.p. 171–172° (dec.).

Anal. Calcd. for $C_{23}H_{22}N_8O_7$: C, 52.87; H, 4.25; N, 21.45. Found: C, 53.30; H, 4.15; N, 21.38, 21.74.

1,2-Diamino-3-methylguanidine. The hydroiodide was obtained in 65% yield by allowing 5.04 g. of S-methylisothiocarbohydrazide hydroiodide[12] and 2.5 g. of 25% aqueous methylamine in 50 ml. of 95% ethanol to stand 1 week at room temperature, then chilling to 5°C. After recrystallization from ethanol the compound decomposed at 238–239°.

Anal. Calcd. for $C_2H_{10}IN_5$: C, 10.40, H, 4.36; I, 54.93; N, 30.31. Found: C, 10.19; H, 4.42; I, 55.31; N, 31.32.

The picrate was obtained as prisms from 95% ethanol; m.p. 167–168°.

Anal. Calcd. for $C_8H_{12}N_8O_7$: C, 28.92; H, 3.64; N, 33.73. Found: C, 29.20; H, 3.51; N, 34.38, 33.59.

1-Amino-1,2,3-trimethylguanidine was formed when methylhydrazine (0.1 mole) and 1,3,S-trimethylisothiourea hydroiodide (0.1 mole) in 80 ml. of water were heated under

(12) E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, 19, 1231 (1954).

reflux until the evolution of methyl mercaptan ceased. The picrate of the benzal hydrazone melted at 156–156.5° (dec.); orange, flat needles from 95% ethanol.

Anal. Calcd. for $C_{17}H_{19}N_7O_7$: C, 47.11; H, 4.42; N, 22.63. Found: C, 47.15; H, 4.69; N, 21.50.

Acknowledgment. We are indebted to Mr. E. M. Bens for many of the microanalyses.

China Lake, Calif.

[Contribution from the Chemistry Department, Faculty of Science, Cairo University]

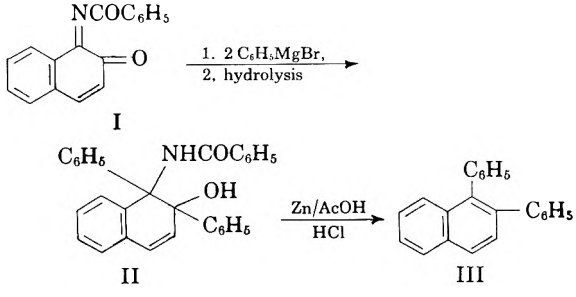
Experiments with Quinone Imides. III. A Novel Synthesis of 1,4-Diphenylnaphthalene

AHMED MUSTAFA and MOHAMED KAMEL

Received July 25, 1956

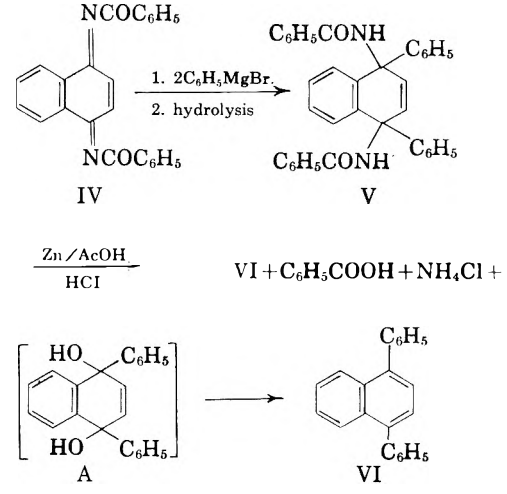
The action of phenylmagnesium bromide on 1,4-naphthoquinone dibenzimide, followed by the treatment of the hydrolyzed Grignard product with zinc dust and acetic and hydrochloric acids establishes a novel synthesis of 1,4-diphenylnaphthalene.

In Part II,[1] Mustafa and Kamel have shown that when 1,2-naphthoquinone-1-benzimide (I) is treated with an excess of phenylmagnesium bromide followed by hydrolysis, 1-benzamido-2-hydroxy-1,2-diphenyl-1,2-dihydronaphthalene (II) is obtained. Compound II, on treatment with zinc dust and acetic and hydrochloric acids gives 1,2-diphenylnaphthalene (III).



We now have investigated the action of phenylmagnesium bromide on a *p*-quinone dibenzimide, namely 1,4-naphthoquinone dibenzimide (IV). Thus, when the pale yellow IV is treated with phenylmagnesium bromide, followed by hydrolysis, a colorless product believed to be 1,4-dibenzamido-1,4-diphenyl-1,4-dihydronaphthalene (V) is obtained.

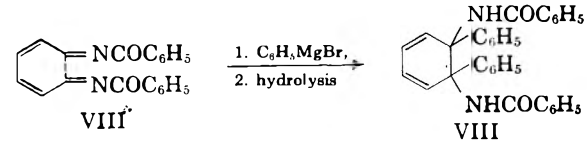
Compound (V) gives correct analytical values: When its solution in glacial acetic acid is treated with a mixture of zinc dust and concentrated hydrochloric acid in the presence of a few drops of platinum chloride, it gives 1,4-diphenylnaphthalene (VI) in good yield, together with ammonium chloride and benzoic acid,[1] probably *via* the intermediate A. The ready transformation of the intermediate (A) to VI may be compared with the ready transformation of 9,10-dihydroxy-9-10-diphenyl-9,10-dihydroanthracene to 9,10-diphenylanthracene



by the action of zinc dust and glacial acetic acid.[2]

The action of phenylmagnesium bromide on IV, followed by the action of Zn/HCl/acetic acid, establishes a novel synthesis of 1,4-diphenylnaphthalene (VI). The new synthesis of VI may be considered as an extension of our previous finding for the synthesis of 1,2-diarynaphthalenes, *e.g.* II.

We also have investigated the action of phenylmagnesium bromide on *o*-quinone dibenzimides, *e.g.*, *o*-benzoquinone dibenzimide (VII). When VII is treated with phenylmagnesium bromide, followed by hydrolysis, a colorless compound, believed to have a structure like VIII and which is under further investigation, is obtained.

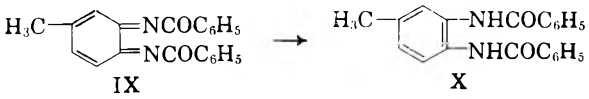


On the other hand, when 4-methyl-*o*-benzoqui-

(1) A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, 77, 5630 (1955).

(2) A. Haller and A. Guyot, *Compt. rend.*, 138, 1251 (1904).

none dibenzimide (IX) is treated with this reagent, only the diamide[3] (X) is obtained.



IX X

The quinone imides used in this investigation have been prepared after the procedure described by Adams and his co-workers. The dibenzimides (IV and IX) now have been prepared by the oxidation of their corresponding diamides with lead tetraacetate in chloroform[4] and in dry benzene,[5] respectively.

EXPERIMENTAL

Preparation of 1,4-naphthoquinone dibenzimide (IV). A suspension of 5.8 g. of 1,4-dibenzamidonaphthalene[6] and 7 g. of lead tetraacetate in 400 ml. of chloroform was refluxed with stirring for 1 hr. The orange suspension was then filtered hot and the lead salt precipitate washed with 50 ml. of chloroform. The filtrate and washings were concentrated in a vacuum to 15 ml. volume (water bath at 40–50°) and 170 ml. of petroleum ether (b.p. 60–80°) was added, whereby a yellow solid came down. This solid was filtered off and crystallized from ethyl acetate, m.p. 216–217°. Yield *ca.* 30%.

Anal. Calcd. for $C_{24}H_{16}N_2O_2$: C, 79.12; H, 4.39; N, 7.69. Found: C, 79.20; H, 4.23; N, 7.63.

IV is readily soluble in benzene, chloroform and ethyl acetate, but sparingly soluble in petroleum ether.

Preparation of 4-methyl-o-benzoquinone dibenzimide (IX). A suspension of 2.8 g. of 4-methyl-1,2-dibenzamidobenzene[7] and 3.7 g. of lead tetraacetate in 100 ml. of dry, thiophene-free benzene was heated under reflux for 10 hr. The reddish solution was filtered to remove the precipitated lead salt and reduced in volume to about 10 ml. Petroleum ether (b.p. 80–100°) was added and the solution was chilled in a Dry-Ice–methanol mixture. The red oil that formed by this treatment did not solidify after standing for 3 hr. The benzene-petroleum ether layer was decanted and left to evaporate slowly, whereby a yellow solid (*ca.* 0.3 g.) came down. This solid was crystallized from ethyl acetate, m.p. 191° and identified as IX.

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.82; H, 4.87; N, 8.53. Found: C, 76.61; H, 4.55; N, 8.68.

When the red oil, obtained as above, was treated with ethyl acetate (10 ml.) a further crop of IX (0.2 g.) was obtained.

Action of phenylmagnesium bromide on 1,4-naphthoquinone dibenzimide. To a solution of phenylmagnesium bromide (prepared from 0.9 g. of magnesium and 9 g. of bromobenzene in 50 ml. of dry ether) was added a solution of 1.5 g. of IV in 50 ml. of dry benzene. The ether was evaporated and the reaction mixture heated for 3 hr. on a steam bath. After the mixture had stood overnight at room temperature, it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution and extracted with ether. The ether-benzene mixture was washed twice with water (100 ml.), dried over sodium sulfate, filtered, and concentrated on a steam bath. The oil that remained was washed several times with light petroleum (*ca.* 40 ml.) until a viscous mass was obtained which was dissolved in alcohol (10 ml.). When to the alcoholic solution ether (*ca.* 30 ml.) was added and the mixture left to evaporate slowly, a colorless solid (*ca.* 0.7 g.) was formed. This material was filtered off and, after recrystallization from alcohol, gave V, m.p. 235° (clear melt).

Anal. Calcd. for $C_{36}H_{28}N_2O_2$: C, 83.07; H, 5.38; N, 5.38. Found: C, 82.82; H, 5.50; N, 5.12.

1,4-Dibenzamido-1,4-diphenyl-1,4-dihydronaphthalene (V) dissolves in alcohol, benzene, and glacial acetic acid, but sparingly in ether and light petroleum. It gives a brownish green color with concentrated sulfuric acid.

Action of phenylmagnesium bromide on o-benzoquinone dibenzimide (VII). A procedure identical to the above was used. On evaporation of the ether-benzene mixture, colorless crystals came down which, after recrystallization from a mixture of dioxane and light petroleum gave VIII, m.p. 248° (yellow-orange melt). Yield *ca.* 60%.

Anal. Calcd. for $C_{32}H_{26}N_2O_2$: C, 81.70; H, 5.53; N, 5.95. Found: C, 81.20; H, 5.28; N, 6.26.

VIII is soluble in glacial acetic acid and dioxane but sparingly soluble in petroleum ether. It gives no color with concentrated sulfuric acid.

Action of phenylmagnesium bromide on 4-methyl-o-benzoquinone dibenzimide (IX). When IX was treated with phenylmagnesium bromide in a manner identical to the above procedure, only the diamide X was obtained (m.p. and mixed m.p.[7]) in an almost quantitative yield.

Preparation of 1,4-Diphenylnaphthalene VI. To a mixture of 1 g. of V, 30 ml. of glacial acetic acid, 5 g. of zinc dust and 2 drops of (0.5%) solution of platinum chloride, was added 15 ml. of concentrated hydrochloric acid at intervals. The reaction mixture was heated on a sand bath for 15 hr. It was then cooled, decanted from the unreacted zinc and poured into 50 ml. of ice-cold water. Both the acidic mixture and the unreacted zinc dust were repeatedly extracted with ether. The combined ether extracts were washed with dilute aqueous sodium hydroxide solution (5%), then with water, and dried. The ether solution on evaporation gave colorless crystals which on repeated crystallization from alcohol gave a m.p. 136°, (undepressed when admixed with a sample of 1,4-diphenylnaphthalene prepared according to Dufraisse and Priou[8]). Yield 80%.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.29; H, 5.71. Found: C, 94.21; H, 5.65.

The alkaline solution was then acidified with hydrochloric acid and repeatedly extracted with ether; on evaporation of the ethereal solution, benzoic acid was identified (m.p. and mixed m.p.). Ammonium chloride was identified in the mother liquor.

GIZA, CAIRO,
EGYPT

(3) Compare the ready reduction of quinone imides, *e.g.* 4-methyl-*o*-benzoquinone dibenzenesulfonimide, by Grignard reagent, A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **75**, 2939 (1953).

(4) R. Adams and J. W. Way, *J. Am. Chem. Soc.*, **76**, 2763 (1954).

(5) R. Adams and J. L. Anderson, *J. Am. Chem. Soc.*, **72**, 5154 (1950).

(6) A. Wohl, *Ber.*, **36**, 4139 (1903).

(7) O. Hinsberg and L. v. Udranszky, *Ann.*, **254**, 252 (1889).

(8) C. Dufraisse and R. Priou, *Bull. soc. chim.* [5] **5**, 502 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Some Schiff Bases of *p*-Dimethylamino- and *p*-Diethylaminobenzaldehyde[1]

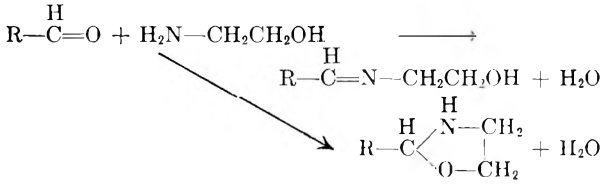
MASUMI NAKAMICHI[2] AND GEORGE L. WEBSTER

Received July 31, 1956

Fifteen new Schiff bases of *p*-dimethylamino- and *p*-diethylaminobenzaldehyde have been prepared. Infrared spectral studies were made on four Schiff bases of *p*-diethylaminobenzaldehyde.

Since the synthesis of Procaine in 1909,[3] its structure has been the prototype upon which the synthesis of hundreds of compounds has been based. In attempts to find an agent with a larger therapeutic index than Procaine, Adams and his group prepared aminophenyl-2-oxazoline,[4] aminophenyl-2-pentoxazoline,[5] and aminophenyl-2-oxazole.[6] The marked activity of these compounds as local anesthetics suggested that other closely related structures might exhibit similar physiological properties. The compounds resulted from the condensation of *p*-dimethylamino and *p*-diethylaminobenzaldehyde with various primary aminoalcohols and aminoethers could be visualized as the N-alkylated analogs of aminophenyl-2-oxazoline and aminophenyl-2-pentoxazoline.

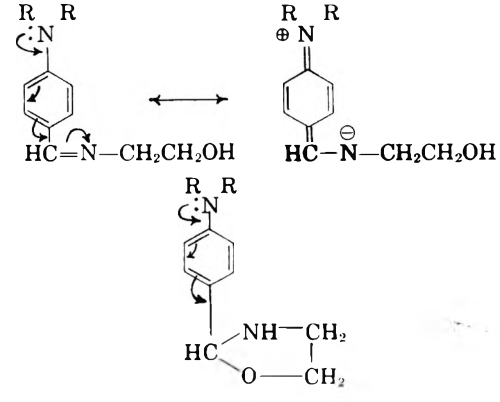
The condensation of an aromatic aldehyde with a primary aliphatic aminoalcohol can result in the formation of either the Schiff base or of the isomeric oxazolidine.[7]



It was necessary to determine whether our condensation products had the open Schiff base or the oxazolidine structure.

The chemical properties of the Schiff bases and of the oxazolidines are so similar that classical chemical methods of distinguishing between them are not successful. Physical methods such as infrared[8] and ultraviolet[9] spectroscopy, and molecular refraction[8,10] are used. Bergmann and his co-workers[7] have shown that aromatic aldehydes, like the *alpha, beta* unsaturated carbonyl compounds, tend to form Schiff bases rather than oxazolidines. They rationalized that *o*-methoxybenzaldehyde reacted with 2-aminoethanol to form the Schiff base, since the Schiff base can form an *ortho*-quinonoid resonance structure not possible in the case of the oxazolidine without cleavage of the hetero ring.

An analogous rationalization of the contribution of a *para*-quinonoid resonance structure might be applied to the condensation products of *p*-dimethylamino- and *p*-diethylaminobenzaldehyde with primary aminoalcohols and aminoethers. Here again, a quinonoid structure is not possible if the oxazolidine moiety is present.



Further evidence for the predominance of the Schiff base structure is demonstrated in the infrared spectra of the condensation products of *p*-diethylaminobenzaldehyde with 2-aminoethanol, 3-aminopropanol, 1-amino-2-propanol, and 2-amino-1-butanol. (The infrared spectral results for these compounds are listed in Table II.) The infrared spectra of oxazolidines may be expected to show the following:

1. The characteristic absorption due to the O—C—N system, a triplet of bands in the 1080–1200 cm.$^{-1}$ region (1149–1185, 1116–1139, 1080–1200 cm.$^{-1}$).[7]

(1) Abstracted from a thesis submitted by Masumi Nakamichi to the Graduate College of the Chicago Professional Colleges of the University of Illinois in partial fulfillment of the requirements of the degree of Master of Science in Pharmaceutical Chemistry.

(2) Graduate Fellow in the Chicago Professional Colleges of the University of Illinois.

(3) A. Einhorn and E. Uhlfelder, *Ann.* **371**, 131 (1909).

(4) M. T. Leffler, and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1937).

(5) A. Novelli, and R. Adams, *J. Am. Chem. Soc.*, **59**, 2259 (1937).

(6) B. S. Friedman, M. Sparks, and R. Adams, *J. Am. Chem. Soc.*, **59**, 2262 (1937).

(7) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).

(8) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).

(9) E. D. Bergmann, Y. Hirschberg, S. Pinchas, and E. Zimkin, *Rec. trav. chim.*, **71**, 192 (1952).

(10) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, 358 (1953).

TABLE I

SCHIFF BASES

Comp. No.	Primary Amine Used	Method Used	Yield, %	M.P. or B.P.	n_D^{20}	d^{27a}	Molecular Formula	N Analysis[b] Calcd.	Found
	N-(*p*-dimethylaminobenzylidene) derivatives of:								
I	2-aminoethanol[c]	A	57	103–104°			$C_{11}H_{16}N_2O$	14.57	14.33
II	3-aminopropanol	B	62	72–74°			$C_{12}H_{16}N_2O$	13.58	13.55
III	1-amino-2-propanol	A	67	98–99°			$C_{12}H_{16}N_2O$	13.58	13.55
IV	2-amino-1-butanol	A	25	70–71°			$C_{13}H_{20}N_2O$	12.72	12.72
V	2-methoxyethylamine	B	63	132–140° at 0.3 mm.	1.6052	1.049	$C_{12}H_{18}N_2O$	13.58	13.47
VI	3-methoxypropylamine	B	33	147–150° at 0.4 mm.	1.5892	1.016	$C_{13}H_{20}N_2O$	12.72	12.42
VII	3-isopropoxypropylamine	B	48	142–144° at 0.4 mm.	1.5680	1.076	$C_{15}H_{24}N_2O$	11.28	11.04
VIII	3-dimethylaminopropylamine	B	65	134–140° at 0.2 mm.	1.5870	1.073	$C_{14}H_{23}N_3$	18.01	17.62
	N-(*p*-diethylaminobenzylidene) derivatives of:								
IX	2-aminoethanol[d]	B	58	137–142° at 0.4 mm.	1.6253		$C_{13}H_{20}N_2O$	12.72	12.51
X	3-aminopropanol[d]	B	47	156–160° at 0.4 mm.	1.6120		$C_{14}H_{22}N_2O$	11.96	11.71
XI	1-amino-2-propanol[d]	B	39	56–57°			$C_{14}H_{22}N_2O$	11.96	12.06
XII	2-amino-1-butanol[d]	B	30	67–68°			$C_{15}H_{24}N_2O$	11.28	11.33
XIII	2-methoxyethylamine	B	70	132–138° at 0.3 mm.	1.5910	1.049	$C_{14}H_{22}N_2O$	11.96	11.75
XIV	3-methoxypropylamine	B	36	142–146° at 0.5 mm.	1.5818	1.036	$C_{15}H_{24}N_2O$	11.28	11.09
XV	3-isopropoxypropylamine	B	67	152–156° at 0.6 mm.	1.5600	0.975	$C_{17}H_{26}N_2O$	10.14	10.31
XVI	3-dimethylaminopropylamine	B	56	140–144° at 0.2 mm.	1.5755	0.976	$C_{16}H_{27}N_3$	16.08	15.94

[a] Density determination on a Fisher-Davidson Gravitometer. [b] Nitrogen analysis by a semi-micro Kjeldahl method. [c] This compound was listed in a table in reference (7) as an unpublished result of the work of E. D. Bergmann, E. Gil-Av, and S. Pinchas. [d] IR studies made.

TABLE II

INFRARED SPECTRAL RESULTS

Comp. No.	O—C—N System	Aromatic C=N System	Alcoholic System
IX	Absent No. 1116–1139 cm.$^{-1}$ band	C=N (STR)[a] 1641 cm.$^{-1}$	Primary alcohol OH (STR) 3240 and 3350 cm.$^{-1}$ Two maxima due to high intermolecular bonding with C=N C—O (STR) 1080 cm.$^{-1}$ region
X	Absent No. 1116–1139 cm.$^{-1}$ band	C=N (STR) 1639 cm.$^{-1}$	Primary alcohol OH (STR) 3300 cm.$^{-1}$ region C—O (STR) 1075 cm.$^{-1}$ region
XI	Absent No. 1116–1139 cm.$^{-1}$ band	C=N (STR) 1643 cm.$^{-1}$	Secondary alcohol OH (STR) 3540 cm.$^{-1}$ (unbonded) and 3230 cm.$^{-1}$ region (bonded) C—O (STR) 1080 cm.$^{-1}$ region
XII	Absent No. 1116–1139 cm.$^{-1}$ band	C=N (STR) 1639 cm.$^{-1}$	Primary alcohol OH (STR) 3590 cm.$^{-1}$ (unbonded) and 3220 cm.$^{-1}$ region (bonded) C—O (STR) 1080 cm.$^{-1}$ region

[a] STR = Stretching frequency.

2. Absence of the absorption due to the alcoholic hydroxyl group.

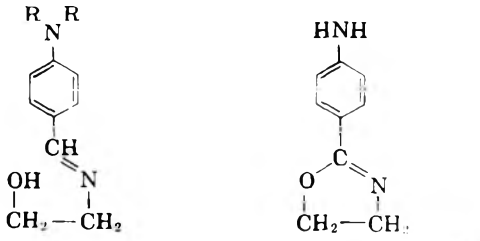
In contrast to this, the Schiff base would be expected to show:

1. Absorption due to the C=N system (1650 cm.$^{-1}$).[7,11]

2. Absorption due to the alcoholic hydroxyl group (3300 cm.$^{-1}$).[7,11]

The infrared spectra of our compounds showed excellent correlation with the spectra of Schiff bases and they differed markedly from those of oxazolidines. These Schiff bases might be considered to be the N-alkylated analogs of an open chain model of aminophenyl-2-oxazoline and aminophenyl-2-pentoxazoline.

(11) G. F. McCasland, and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951).



Aminophenyl-2-oxazoline

EXPERIMENTAL[12]

Materials. *p*-Dimethylaminobenzaldehyde (m.p. 72–73°) and *p*-diethylaminobenzaldehyde (m.p. 38–39°) were prepared by the method of Duff.[13] All of the following reagents were used without further purification: 2-Aminoethanol was Eastman Reagent Grade. 1-Amino-2-propanol and 2-methoxyethylamine were Eastman Practical Grade. 3-Aminopropanol, 3-methoxypropylamine, 3-isopropoxypropylamine, and 3-dimethylaminopropylamine were furnished to us by the American Cyanamid Co. 2-Amino-1-butanol was furnished by the Commercial Solvents Corp.

Preparation of the Schiff base. A mixture of 0.1 mole of the *p*-dialkylaminobenzaldehyde, 0.12 mole of the primary amino compound, and 50 ml. of dry benzene contained in a Dean-Stark moisture determination apparatus was heated under reflux in an oil bath until the volume of water collected in the trap remained constant (2–3 hr.). The benzene was removed by distillation under reduced pressure, and the residual oil was poured onto an ice water mixture. If the organic layer solidified, Process A was used; if it did not, Process B was used.

Process A. The solid crystalline mass was triturated with cold water, collected on a suction filter, and washed on the filter with several portions of cold water. After drying the crystals on the filter by use of a rubber dam followed by air drying, the crude material was dissolved in boiling petroleum ether (b.p. 30–60°), treated with Norite A for 15 min., filtered, and the filtrate was cooled in an ice-water bath to induce crystallization. The crystals were collected on a suction filter and washed with several small portions of cold petroleum ether.

Process B. The organic layer was extracted with ether, and the ethereal solution was washed several times with cold water, the washings being discarded. After drying over anhydrous magnesium sulfate and filtering, the ether was removed on a steam bath. In some instances, the residual liquid solidified after standing at room temperature for several days, and the solid product was recrystallized from boiling petroleum ether as in Process A. If the liquid did not solidify, it was purified by distillation under reduced pressure.

Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 21, using a NaCl prism. A smear was used for the liquids and a 5% solution in CCl_4 was used for the solids.

Acknowledgment. The authors wish to express their thanks to the American Cyanamid Co. and the Commercial Solvents Corp. for their generous gifts of reagents, to Dr. James J. Brader of the Noyes Laboratory for the determination and interpretation of the infrared spectra, and to Mr. Joseph G. Cannon for his many helpful suggestions and criticisms.

CHICAGO 12, ILL.

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

(13) J. C. Duff, *J. Chem. Soc.*, 1945, 276 (1945).

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

Syntheses and Ultraviolet Spectra of 1-(5- and 8-Methyl-1-naphthyl)-1-cyclopentenes and 1-Cyclohexenes[1–3]

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Syntheses of the four 1-(5- and 8-methyl-1-naphthyl)cyclopentenes and cyclohexenes from 1-nitronaphthalene are described. The ultraviolet absorption spectral characteristics of these alkenes and of several 1,5- and 1,8-disubstituted naphthalene intermediates are presented and discussed.

In previous papers[4–6] we reported syntheses and ultraviolet absorption spectra of I, II, and their 2-naphthyl isomers as well as five derivatives (bearing methyl groups on the cycloalkenyl moiety) of these four parent naphthylcycloalkenes. The present paper extends these studies to four additional derivatives III–VI (bearing methyl groups on the naphthyl moiety).

The synthetic scheme for the 1,8-disubstituted naphthalenes III and IV is outlined herewith.

1-Nitronaphthalene was first nitrated *via* mixed acid to a mixture of 1,5- and 1,8-dinitronaphthalenes, resolved into its components by fractional crystallization. The latter isomer was reduced read-

(1) Presented at the Northwest Regional Meeting of the AMERICAN CHEMICAL SOCIETY, Seattle, Wash., June, 1956. Paper VIII in the series on "Chemical Reactivities of Arylcycloalkenes." For preceding papers see L. H. Klemm and H. Ziffer, *J. Org. Chem.*, 21, 274 (1956) and ref. (18).

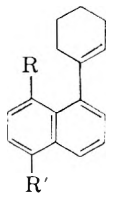
(2) Performed under the sponsorship of the Office of Ordnance Research, U.S. Army Contract No. DA-04-200-ORD-176.

(3) Abstracted largely from the M.A. and Ph.D. dissertations of J. W. Sprague, University of Oregon, 1954 and 1955, respectively.

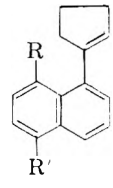
(4) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, 73, 5181 (1951).

(5) L. H. Klemm and H. Ziffer, *J. Org. Chem.*, 20, 182 (1955).

(6) L. H. Klemm, H. Ziffer, J. W. Sprague, and H. Hodes, *J. Org. Chem.*, 20, 190 (1955).

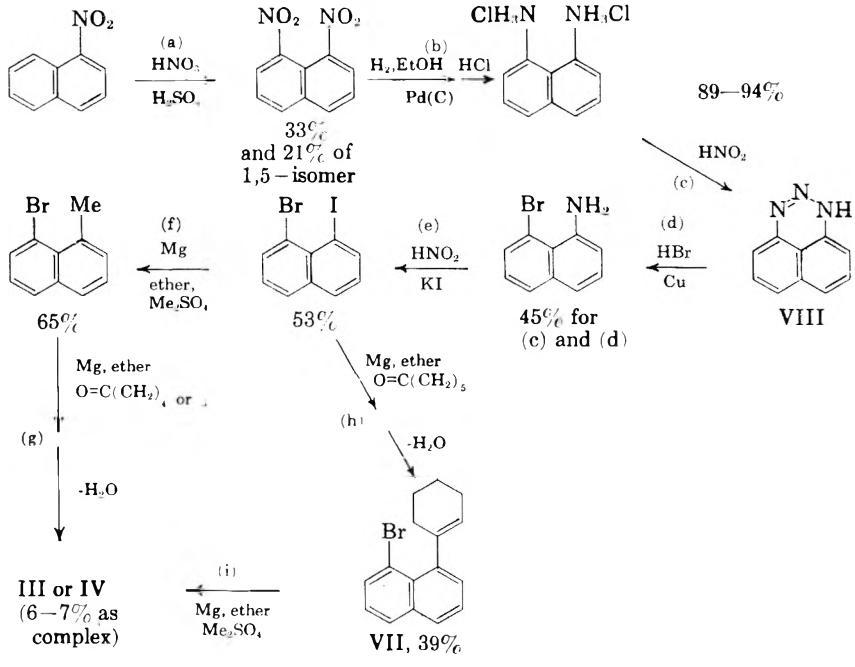


I: R, R′ = H
III: R = CH_3; R′ = H
V: R = H; R′ = CH_3



II: R, R′ = H
IV: R = CH_3; R′ = H
VI: R = H; R′ = CH_3

gent produced better yields of addition products with *o*-chlorobenzaldehyde (44%) and phthalic anhydride (66%), where no α-hydrogens are present, than with the enolizable *o*-chloroacetophenone (20% after dehydration). In an effort to circumvent reduction of this Grignard reagent we investigated the alternate route involving steps (h) and (i). Though a fair yield of crystalline 1-(8-bromo-1-naphthyl)cyclohexene (VII) (plus 16% of 1-bromonaphthalene) was obtainable in the former step, the



ily, by means of low-pressure catalytic hydrogenation using 30% palladium-charcoal as catalyst and 95% ethanol as solvent, to 1,8-diaminonaphthalene, isolated as the crystalline dihydrochloride in excellent yield. Steps (c) to (f) followed closely the procedure of Fieser and Seligman[7] except that use of activated copper in step (d) gave inconsistent results in our hands. Meanwhile it was noted that copper turnings dissolved in refluxing 48% hydrobromic acid to give a solution which readily effected the desired transformation. Reaction of the Grignard reagent from 1-bromo-8-methylnaphthalene with cyclohexanone (or cyclopentanone), dehydration of the intermediate carbinol, and fractional distillation of the crude product gave an unusually large amount of forerun and only a very small yield of purified III or IV, isolated from the alkene fraction *via* the crystalline polynitroaromatic molecular compound. Examination of the forerun indicated that the main product formed was 1-methylnaphthalene, probably produced through preferential abstraction of hydrogen from the cycloalkanone by the sterically hindered Grignard reagent. Consistent with this interpretation are the findings of Fieser and Seligman[7] that this same Grignard reagent subsequent methylation proceeded poorly. A pure intermediate was not obtained when cyclopentanone was used in step (h).

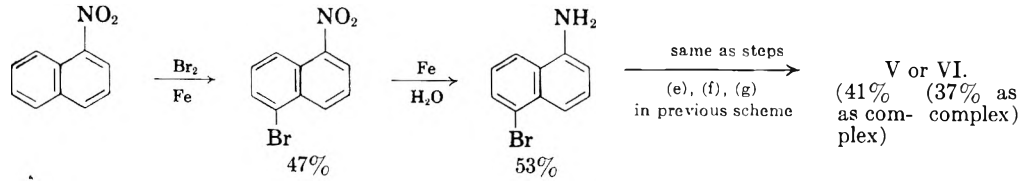
Much better success was attained in syntheses of the sterically less hindered 1,5-disubstituted naphthalenes V and VI, *via* the scheme.[8]

The product from bromination of molten 1-nitronaphthalene was reduced with iron (theoretical quantity) and acidulated water to 5-bromo-1-naphthylamine, transformed first to 1-bromo-5-iodonaphthalene (72% yield, by diazotization in a mixture of glacial acetic and concentrated sulfuric acids and rapid addition of the resultant mixture to excess aqueous potassium iodide) and then to 1-bromo-5-methylnaphthalene (35–49% yield) by the procedure used for the analogous conversion in the 1,8- series. Step (g) yielded about 40% of purified complexes of V and VI.

Pertinent data on the ultraviolet absorption maxima of III–VII and of nine intermediates prepared

(7) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **61**, 136 (1939).

(8) Despite the availability of 1,5-dinitronaphthalene as a by-product from nitration of 1-nitronaphthalene, a synthetic scheme for V and VI exactly analogous to that used for the 1,8-isomers is precluded on the basis that a 1,5-aziminonaphthalene intermediate is sterically impossible. Such an intermediate (VIII) effectively controls stepwise diazotization and replacement of the two amino groups in the 1,8-series.



in their syntheses are given in Table I, where comparison may be made with corresponding data for 1,5- and 1,8-dimethylnaphthalenes. The absorption curves for the five compounds bearing amino or nitro groups exhibit the typical smoothness associated with conjugation[9,10] and resemble in general shape the spectra recorded for 1-nitronaphthalene [λ_{max} 243 mμ (log ϵ 4.02); 342 (3.59); solvent, absolute ethanol][11] and 1-naphthylamine[λ_{max} 240 mμ (log ϵ 4.36), 322 (3.71); solvent ethanol].[12] Variation in solvent used (especially in these cases where hydrogen-bonding may be large) interferes with a complete and meaningful comparison of results. One observes, however, that substitution of a bromine atom in the 8-position of 1-naphthylamine produces an anticipated bathochromic shift in the spectrum (7 and 20 mμ in the respective positions of the absorption maxima). Also it appears that substitution of a second nitro group into the 5- or 8- position of 1-nitronaphthalene effects a hypsochromic shift in the spectrum, *i.e.* makes the corresponding transitions more difficult—perhaps due to counteraction between the strongly electron-withdrawing nitro groups. This shift is more pronounced in the 1,8- isomer, where the nitro groups are in closer proximity than in its 1,5- counterpart.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA FOR SOME DISUBSTITUTED NAPHTHALENES[a]

Substituents in 1,5- Positions

1-C_6H_9, CH_3[b]		1-C_5H_7, CH_3[b]		CH_3, CH_3[d]		Br, CH_3[g]		Br, I[g]		Br, NH_2[b]		Br, NO_2[b]		NO_2, NO_2[g]	
λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ
										218	4.82	220	4.59	—[h]	—
229	4.86	229	4.79	227	5.13	227	4.90	230	4.78						
										245–8	4.19	245	4.35	233	4.32
(279)	3.89	(280)[c]	3.79	276	3.85	280	3.83	(288)	3.91						
287	3.99	289	3.92	286	3.95[e]	290	3.93	297	4.01						
(296)	3.90	(294–8)	3.90	298	3.80[f]	301	3.78	307	3.88						
										331	3.76	326	3.84	327	3.81

Substituents in 1,8- Positions

1-C_6H_9, CH_3[b]		1-C_5H_7, CH_3[b]		CH_3, CH_3[d]		Br, CH_3[b]		Br, I[b]		Br, NH_2[g]		Br, 1-C_6H_9[b]		NO_2, NO_2[g]	
λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mμ	log ϵ	λ_{max} mη	log ϵ
										—[h]	—			—[h]	—
229	4.82	229	4.81	228	5.04	230	4.84	234	4.75			228–9	4.82		
		(260)	3.39							247	4.34			231	4.44
(277)	3.81	(278)	3.79	275	3.80	(280)	3.71	(296)	3.93			(285–6)	3.86		
287	3.91	288	3.91	285	3.86[e]	293	3.85	306–8	4.00			293–4	3.94		
(296)	3.83	(296–8)	3.83	293	3.74[f]	(303)	3.76	(321)	3.88			(302–3)	3.88		
(321)	2.90									342	3.83			313	3.81

[a] Determined by means of a Beckman DU spectrophotometer using analytically pure samples. Parenthesized values of λ_{max} represent shoulders rather than true maxima. [b] Solvent, cyclohexane. [c] Shoulder barely discernible. [d] See reference 10, spectra 202 and 205; solvent, isooctane. [e] Some barely perceptible shoulders in the region 250–270 mμ have been omitted. [f] Fine structure beyond this maximum has not been included in this table. [g] Solvent, ethanol. [h] From the curve it is apparent that a maximum is present at <214 mμ.

All of the other spectra investigated (Table I) have the same general shape as that of a dimethylnaphthalene (but devoid of some minor fine structure), where the substituents produce mainly a bathochromic shift in the spectrum of naphthalene in the general order of effectiveness I >> Br > cycloalkenyl $\cong$ Me > H.[10] It is particularly noteworthy that the spectra of III–VI are nearly identical and differ from those of their parent hydrocarbons I and II[6] essentially only in being shifted bathochromically by about 4 mμ (equal to the shift observed in going from 1-methylnaphthalene[13] to the 1,5- and 1,8-dimethylnaphthalenes). The θ'-distributions[6] (sterically unrestricted angles of twist between the planes of the naphthalene ring and the

(9) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(10) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951, pp. 19–21.

(11) H. H. Hodgson and D. E. Hathway, *Trans. Faraday Soc.*, **41**, 115 (1945).

(12) Y. Hirshberg and R. N. Jones, *Can. J. Research*, **27B**, 437 (1949).

(13) Ref. (10), spectrum 196.

cycloalkenyl double bond) for I and II should not be altered by insertion of a methyl group in the 5-position of the naphthalene ring but will be decreased in extent ($\theta' = 80–128°$ for I, $\theta' = 90°$ for III) by methylation in the 8- position. The insensitivity of the spectra to such variation in θ' is consistent with our previous suggestions[6] that from the point of view of ultraviolet spectroscopy the alkenyl double bonds in I and II [as well as in III–VI] are effectively unconjugated with the naphthalene nucleus (θ- distribution $= 90° \pm \beta$).

EXPERIMENTAL[14]

1-Nitronaphthalene. Technical grade 1-nitronaphthalene was recrystallized from ethanol (2 ml. per g. of nitronaphthalene), m.p. 58–60°.

Nitration of 1-nitronaphthalene. To the dark red solution of 500 g. of purified 1-nitronaphthalene in 4.1 kg. of technical grade sulfuric acid (66° Baumé) contained in a 16-l. borosilicate jar immersed in a stirred ice-salt bath was added, dropwise (over 1.5–2 hr.) with efficient stirring[15] at a reaction temperature maintained at 0–5°, 1 l. of mixed acid (prepared from 200 ml. of technical grade 36° Baumé nitric acid and 800 ml. of technical grade sulfuric acid). An additional 100–200 ml. of mixed acid was then added portionwise (over 15–30 min.) until no further red coloration was apparent on extended stirring. The mixture was poured slowly, with stirring, onto 16 l. of powdered ice and the reaction vessel was rinsed with ice-cold water. Several hours later the precipitate was collected by suction filtration, washed with 6–8 l. of hot water, and dissolved in 14 l. of hot acetone. The filtered (with a cheesecloth mat) acetone solution deposited yellow needles on cooling to room temperature. The washed (with 200 ml. of acetone) needles were recrystallized from pyridine (5 ml. per g. of crystals), yield 113–120 g. of 1,5-dinitronaphthalene, m.p. 215–216°; reported[16a] m.p. 219°.

The acetone mother liquor was concentrated to crystallization, cooled to 5°, and filtered. The collected precipitate was washed with 1 l. of ethanol, dried, and dissolved in 3 l. of hot benzene. The crystals which formed on cooling the filtered benzene solution to room temperature were recrystallized two or three times from benzene and once from glacial acetic acid (Norit A), washed with water (first cold, then hot), and dried at 110°, yield 175–190 g. of 1,8-dinitronaphthalene as pale yellow rhombs, m.p. 171–172°; reported[16b] m.p. 172°.

Processing (*via* the entire preceding crystallization scheme) of the precipitate obtained from concentrating and cooling the benzene and acetic acid mother liquors gave additional yields of 13 g. of 1,5- isomer and 25 g. of 1,8- isomer (21% and 33%, av. over-all yields, respectively).

1,8-Diaminonaphthalene dihydrochloride. A mixture of 100 g. of finely powdered 1,8-dinitronaphthalene, 2 g. of 30% palladium-charcoal, and 1 l. of ethanol, contained in a 2-l borosilicate aspirator bottle (tightly stoppered *via* a collar screw assembly and strapped horizontally into a metal can partially filled with water at 15°), was shaken mechanically in the presence of hydrogen (introduced from a reservoir *via* the side connector of the aspirator bottle) at a pressure of 1.7–4.0 atm. until the theoretical amount (6 molar quantity) of hydrogen had been absorbed. The nearly colorless solution resulting from filtration (Celite) of the reaction mixture was treated with 250 ml. of concentrated hydrochloric acid and 250 ml. of ether, chilled, and filtered. The solid was washed with ether and dried, yield 94–100 g. (89–94%) of creamy white powder, m.p. 290° (dec.); reported[16c] m.p. *ca.* 280°.

Use of Adams' platinum catalyst instead of palladium-charcoal gave a red solution and a blue-gray product. Attempts to use Raney nickel catalysts of various types and under a variety of conditions were uniformly unsuccessful.

8-Bromo-1-naphthylamine. To the solution prepared by refluxing a mixture of 60 g. (0.94 g.-atom) of copper turnings with 900 ml. of reagent grade 48% hydrobromic acid and maintained at 100–110° was added portionwise the pulverized crude aziminonaphthalene[7] obtained from a total of 198 g. (0.86 mole) of 1,8-diaminonaphthalene dihydrochloride. The mixture was then refluxed for 30 min. and processed further according to the directions of Fieser and Seligman,[7] yield 82–88 g. (43–46%), b.p. 140–150° (2 mm.), m.p. 86–88°.

1-Bromo-8-iodonaphthalene was prepared according to published directions,[7] m.p. 97–99°.

1-Bromo-8-methylnaphthalene was prepared according to Fieser and Seligman[7] except that the magnesium was added portionwise to aid in moderation of the reaction and the final product was crystallized from methanol, m.p. 74–76°, yield 65%; reported m.p. 76–78°, yield 74%.

1-(8-Bromo-1-naphthyl)cyclohexene (VII). To the Grignard reagent (prepared by initiation *via* iodine and subsequent moderation by cooling) from 33.3 g. (0.01 mole) of 1-bromo-8-iodonaphthalene, 2.4 g. (0.10 mole) of magnesium, and 100 ml. of ether was added slowly a solution of 11 ml. (0.11 mole) of cyclohexanone in 20 ml. of benzene. The mixture was stirred for 10 hr. at room temperature and then poured into excess dilute acetic acid. The nonaqueous phase, combined with ethereal extracts of the aqueous phase, was washed with water, dried, and evaporated. The residue was heated at 200° (nitrogen atmosphere) until evolution of water had ceased and then fractionally distilled to yield 12.3 g. of yellow liquid, b.p. 172–178° (2.4 mm.), which crystallized on standing. Recrystallization from methanol produced 11.1 g. (39%) of flakes, m.p. 51–53°, elevated to 55–56° on repeated crystallization of a small sample from the same solvent.

Anal. Calcd. for $C_{16}H_{15}Br$: C, 66.91; H, 5.27. Found: C, 66.28; H, 5.51.

The product decolorized bromine in carbon tetrachloride. It failed to yield a crystalline complex with either picric acid in ethanol or trinitrofluorenone in glacial acetic acid.

1-(8-Methyl-1-naphthyl)cyclohexene (III). (*a*) *From VII.* To a refluxing mixture of 30 ml. of ether, 1.4 g. (0.058 g.-atom) of magnesium, and an iodine crystal was added (over a period of 6 hr.) a solution of 15 g. (0.052 mole) of VII in 30 ml. of ether. After 15 hr. further refluxing, a solution of 15 ml. (0.16 mole) of purified[17] dimethyl sulfate in 60 ml. of benzene was added slowly. About half of the solvent was removed by distillation. The residue was refluxed 18 hr. longer and processed as per directions for 1-bromo-8-methylnaphthalene, crude yield 5.8 g. (50%) of liquid, b.p. 128–137° (0.35 mm.).

Further purification of the alkene was effected *via* the

(14) Melting points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(15) A Lightnin Model 1 stirrer, equipped with a 2-inch stainless steel propeller with the blades inverted so as to force the liquid from top to bottom, was used. The stirrer and dropping funnel were positioned so as to prevent clotting of the reaction mixture and the excessive pastiness eventually resultant therefrom.

(16) F. Radt, *Elsevier's Encyclopaedia of Organic Chemistry*, Elsevier Publishing Company, Inc., New York, 1948, **12B**, (a) p. 388, (b) p. 390, (c) p. 831, (d) p. 372, (e) p. 293.

(17) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., Boston, 1941, p. 373.

TNF molecular compound[18] (m.p. 105–135°), chromatographic dissociation thereof (using 1:1 by volume Celite-activated alumina as adsorbent and 30–60° petroleum ether as eluent), vacuum distillation, and conversion to the picrate, formed in methanol, recrystallized to constant m.p. (119–120°) from ethanol, obtained as orange-yellow needles (over-all yield 1.4 g., 6%).

Anal. Calcd. for $C_{23}H_{21}N_3O_7$: N, 9.31. Found: N, 9.43.

Chromatographic dissociation of the picrate by the preceding method gave colorless III, b.p. 108–109° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 92.04; H, 8.30.

(*b*) *From 1-bromo-8-methylnaphthalene.* To the ice-cold Grignard reagent[7] prepared from 11.0 g. (0.050 mole) of 1-bromo-8-methylnaphthalene, 1.3 g. (0.054 g.-atom) of magnesium, 7 ml. of benzene, and 30 ml. of ether was added dropwise a solution of 5.4 g. (0.055 mole) of cyclohexanone in 8 ml. of benzene. Further processing followed the general directions of Bachmann and Kloetzel,[19] yield 3.4 g. (36%) of crude III, b.p. 148–155° (1 mm.). Treatment of this product with an equimolar quantity of TNF in glacial acetic acid and repeated crystallization (with occasional mechanical separation of some brown, high-melting by-product) from the same solvent gave red, silky needles of III.TNF molecular compound, m.p. 119–121° (over-all yield 7%).

1-(8-Methyl-1-naphthyl)cyclopentene (IV). To the Grignard reagent (at 10°) from 5.5 g. (0.23 g.-atom) of magnesium, 50 g. (0.23 mole) of 1-bromo-8-methylnaphthalene, 300 ml. of benzene, and 100 ml. of ether was slowly added a solution of 38 g. (0.45 mole) of cyclopentanone in 60 ml. of benzene. Further processing was conducted essentially as in the preparation of III, but with dehydration of the crude intermediate carbinol effected thermally (by heating at 200° in an atmosphere of nitrogen for 30 min.) instead of *via* anhydrous formic acid, yield 14.6 g. (30%) of yellow liquid, b.p. 130–140° (0.35 mm.). The product decolorized bromine in carbon tetrachloride and gave a positive Baeyer test.

For further purification a sample of the liquid was redistilled *in vacuo* from sodium (using a nitrogen bubbler) and converted to the picrate in absolute ethanol. Recrystallization thereof to constant m.p. (99–100°) from the same solvent produced orange needles.

Anal. Calcd. for $C_{22}H_{19}N_3O_7$: N, 9.61. Found: N, 9.68.

The purified alkene, recovered from the picrate by the method of Klemm and Hodes,[4] was obtained as a pale yellow liquid, b.p. 128–129° (0.6 mm.).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 91.84; H, 7.87.

5-Bromo-1-nitronaphthalene. To a stirred mixture of 500 g. (2.89 moles) of 1-nitronaphthalene and 5–6 g. of reduced (by hydrogen) iron powder, maintained at a temperature of 80–85°, was added dropwise over a period of 2–3 hr. 450 g. (2.81 moles) of bromine. About an hour later when gas evolution had ceased the reaction mixture was crystallized directly, once from ethanol and then once from acetone using Norit A both times, average yield 300 g. of fine yellow needles, m.p. 121–122°, plus 30 g. from processing of the mother liquors, m.p. 120–121° (47%, total); reported[16d] m.p. 122.5°.

5-Bromo-1-naphthylamine. To a vigorously stirred suspension of 168 g. (3 moles) of reduced (by hydrogen) iron powder in 1.25 l. of hot water was added 5 ml. of glacial acetic acid and then (cautiously in 20-g. portions and at such a rate as to maintain gentle reflux) 252 g. (1 mole) of 5-bromo-1-nitronaphthalene.

After an additional hour of heating and stirring, the mixture was cooled and the two phases were separated by decantation. The liquid phase was extracted once with ether; the solid phase, three times with hot acetone (filtered). Combined organic extracts were washed with excess 40% aqueous sodium hydroxide, dried (magnesium sulfate), concentrated *in vacuo* to a dark liquid, and extracted with 3.3 l. of boiling 0.33*N* hydrochloric acid. The gray-white needles of the amine hydrochloride which separated on cooling the extract were washed with 6*N* hydrochloric acid and air-dried. A sample of the hydrochloride was obtained almost pure white by recrystallization from dilute hydrochloric acid and then sublimation at 0.5–1.0 mm. pressure, m.p. > 225° (dec.).

The main part of the hydrochloride was suspended in ethanol and treated with an equivalent quantity of saturated aqueous potassium hydroxide. The precipitate which formed was removed by filtration and washed with ethanol. Combined filtrates were fractionally distilled, yield 117 g. (53%) of nearly white solid, b.p. 156–158° (1.4 mm. of nitrogen), m.p. 69–72°. A sample was recrystallized twice from 9:1 carbon tetrachloride-petroleum ether (60–90°), m.p. 69.5–71°; reported[20] m.p. 69°.

1-Bromo-5-iodonaphthalene. To a cooled, stirred solution of 155 g. (0.69 mole) of 5-bromo-1-naphthylamine in 1.4 l. of glacial acetic acid were added, at such a rate that the temperature did not exceed 20°, 37 ml. of concentrated sulfuric acid and then a solution of 55 g. (0.77 mole) of sodium nitrite in 550 ml. of concentrated sulfuric acid. When the intermediately formed precipitate had redissolved, 15 g. of urea was added. On cessation of evolution of gas the mixture was poured rapidly into a vigorously stirred solution of 170 g. (1.02 moles) of potassium iodide in 340 ml. of water. Again after evolution of gas had ceased, the mixture was heated to 90° for 30 min. and then poured slowly into a stirred solution of 120 g. of sodium bisulfite in 6 l. of water. The precipitate was collected from the cooled solution, dried, and distilled at 1.5 mm. pressure. The distillate boiling up to 175° was crystallized first from glacial acetic acid and then from acetone, yield 165 g. (72%) of needles, m.p. 118.5–120°; reported[21] yield 28%, m.p. 118°. Recrystallization of a sample from acetone (Norit A) gave m.p. 119–120°.

1-Bromo-5-methylnaphthalene. Following almost the exact procedure of Fieser and Seligman[7] for the preparation of the isomeric 1-bromo-8-methylnaphthalene there was obtained 15–21 g. (35–49%) of platelets (from methanol), m.p. 59.5–62°. Two recrystallizations from methanol raised the m.p. to 61–63°; reported[16e] m.p. 63–64°.

1-(5-Methyl-1-naphthyl)cyclohexene (V). The product, prepared as for III but in ether only, from interaction of the Grignard reagent of 1-bromo-5-methylnaphthalene (50 g.) and cyclohexanone (22 g.) was hydrolyzed and dehydrated (with anhydrous formic acid) by the procedure of Bachmann and Kloetzel.[19] Fractional distillation of the resultant alkene gave a crude yield of 28 g. (56%) of light yellow liquid, b.p. 137–142° (0.75 mm.). Treatment of a methanolic solution of the liquid with an equimolar amount of picric acid precipitated V-picrate, recrystallized from methanol to constant melting range 96–111°, yield 41 g. (41% over-all) of orange rods.

Anal. Calcd. for $C_{17}H_{18}{\cdot}C_6H_3N_3O_7$: picric acid, 50.8. Found:[22] picric acid, 51.2.

The picrate was dissociated chromatographically according to the method of Klemm and Ziffer[5] for TNB and TNF molecular compounds. Distillation of the effluent yielded colorless V, b.p. 153–154° (1.8 mm.).

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.36; H, 8.30.

1-(5-Methyl-1-naphthyl)cyclopentene (VI). In a fashion analogous to the preparation of V, 100 g. of 1-bromo-5-methylnaphthalene yielded 52 g. (55%) of crude alkene, obtained as a yellow liquid, b.p. 135–145° (1 mm.) converted to VI.TNF[18] and recrystallized from glacial acetic acid to

(18) L. H. Klemm, J. W. Sprague, and H. Ziffer, *J. Org. Chem.*, 20, 200 (1955).

(19) W. E. Bachmann and M. C. Kloetzel, *J. Am. Chem. Soc.*, 60, 2204 (1938).

(20) F. Ullmann and F. Consonno, *Ber.*, 35, 2802 (1902).

(21) G. Lock, *Monatsh.*, 81, 850 (1950).

constant melting range 103–119°, yield 87 g. (37% over-all) of red needles.

Anal. Calcd. for $C_{16}H_{16}\cdot C_{13}H_5N_3O_7$: TNF, 60.2. Found:[22] TNF, 59.5.

(22) Determined spectrophotometrically by a procedure to be described elsewhere.

Chromatographic dissociation of the molecular compound by the preceding method produced nearly colorless VI, b.p. 139–140° (1.4 mm.).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 91.83; H, 7.89.

EUGENE, ORE.

[CONTRIBUTION FROM THE POLYCHEMICALS RESEARCH DEPARTMENT, DOW CHEMICAL CO.]

Reaction of Ethylene Oxide with Urea

W. F. TOUSIGNANT AND A. W. BAKER

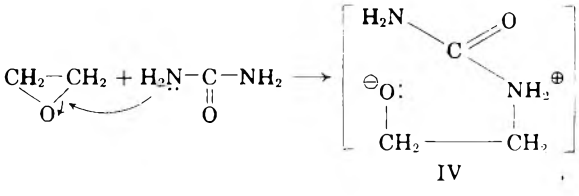
Received August 17, 1956

The reaction of equimolar amounts of ethylene oxide and urea gives as a main product β-aminoethylcarbamate, rather than the expected β-hydroxyethylurea. The reaction mechanism can be compared with an N → O acyl migration.

Pacquin[1] reported that a high molecular weight, water soluble product is obtained by reaction of ethylene oxide with urea at temperatures above 90°. However, the intermediates and the final product were ill defined.

The purpose of this paper is to present a study of the reaction products obtained by passing ethylene oxide into molten urea. It was shown that small amounts of β-hydroxyethylurea (I) and 2-oxazolidinone (II) were produced along with the main reaction product, β-aminoethylcarbamate (III).

The various products isolated and characterized in the experimental section are in conformity with a mechanism involving as a first step a nucleophilic attack by urea on ethylene oxide. This would give the transient intermediate (IV):

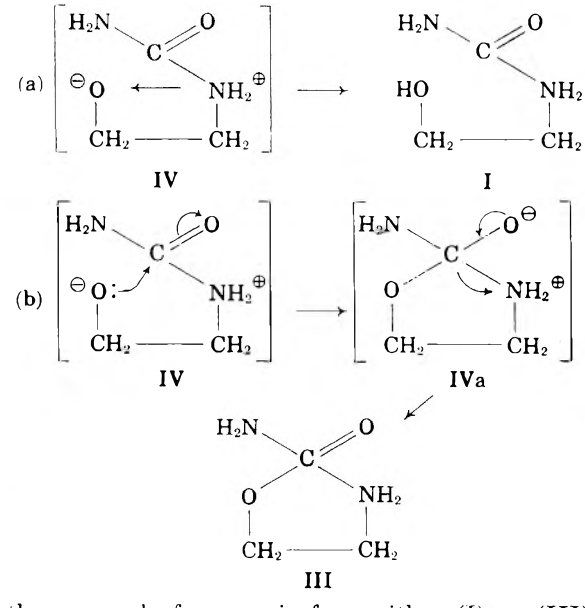


IV

The intermediate could be stabilized by a proton transfer from nitrogen to oxygen to form β-hydroxyethylurea (I). An alternative method of stabilization could be an intramolecular nucleophilic attack of the negatively charged oxygen on the carbonyl carbon to form the cyclic intermediate (IVa), which subsequently dissociates into β-aminoethylcarbamate (III).

The latter mechanism is similar to that proposed by Van Tamelen[2,3] for the formation of *cis*-2-aminocyclopentyl (*p*-nitrobenzoate) by the action of hydrogen chloride on *cis* or *trans*-*N*-(*p*-nitrobenzoyl)-2-aminocyclopentanol.

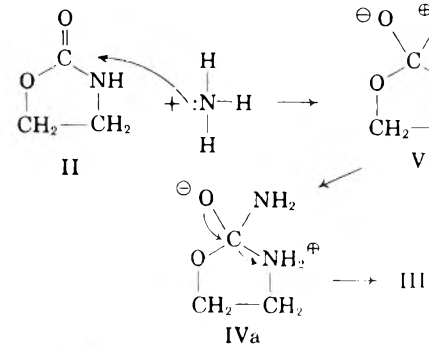
The formation of 2-oxazolidinone (II) conceivably occurs by an elimination reaction involving



IV I IV IVa III

the removal of ammonia from either (I) or (III). Close,[4,5] for example, converted β-hydroxyethylurea into 2-oxazolidinone by heating at 190–200°. By analogous treatment we were able to transform β-aminoethylcarbamate (III) into 2-oxazolidinone (II).

Finally it is of interest that 2-oxazolidinone (II) may be converted into β-aminoethylcarbamate



II V IVa III

(1) A. Pacquin, *Kunststoffe*, **37**, 165 (1947).
(2) Van Tamelen, *J. Am. Chem. Soc.* **73**, 5773 (1951).
(3) Van Tamelen, Tousignant, Peckham, *J. Am. Chem. Soc.* **75**, 1297 (1953).
(4) Close, *J. Am. Chem. Soc.* **73**, 95 (1951).
(5) Close, *J. Org. Chem.* **15**, 1131 (1951).

(III) by reaction with aqueous ammonia. This probably proceeds by a nucleophilic attack of ammonia on the 2-oxazolidinone (II) to form the cyclic intermediate (V) which isomerizes into (IVa).

EXPERIMENTAL

Ethylene-oxide-urea reaction. A 10-gal. water-jacketed stainless steel reaction vessel was charged with 13.6 kg. (227 moles) of urea. The system was rapidly heated to about 136° under a nitrogen atmosphere. At this temperature, urea was molten. Nine and nine-tenths kg. (227 moles) of ethylene oxide was added with stirring over an 8-hr. period. The addition was at such a rate as to maintain a pressure of 50–70 p.s.i.g. The container was then cooled to 65°, evacuated gradually to approximately 10 mm., and, while under vacuum, reheated to 100°. This technique served to remove ammonia and residual amounts of ethylene oxide. The reaction residue was a viscous, water-soluble liquid, which changed into a semicrystalline solid on standing. Attempted vacuum distillation of this material resulted in decomposition and evolution of ammonia.

Isolation of the reaction products was therefore effected by the following treatment: A 2-kg. sample of the residue was diluted with 400 ml. of water to which was added gradually, with stirring, 2 kg. of Dowex 50 (acid form). Stirring was continued for 24 hr. to insure complete liberation of carbon dioxide. The Dowex 50 resin was removed by filtration and the filtrate treated with Norite and refiltered. The 400 ml. of water was removed by vacuum distillation at 2–5 mm. at room temperature.

After this treatment, 800 g. of the above residue was allowed to stand until partial solidification had occurred. The sample was then centrifuged and the solid residue containing 80 gr. (10%) of crude β-hydroxyethylurea (I) was collected and purified by recrystallization from 95% ethanol. The recrystallized product melted at 94–95°. Morgan reported a melting point of 95°.[6] This compound, when mixed with an authentic sample, prepared by the procedure of Morgan,[6] failed to depress the melting point. The compound was further identified by an infrared analysis which compared identically with the known sample of β-hydroxyethylurea.

One hundred grams of the viscous liquid remaining after centrifuging was extracted with 52 100-ml. portions of hot chloroform. The chloroform was evaporated on a steam bath. The residual oil (23.5 g.) was allowed to stand approximately a week, whereupon crystals settled out and were filtered. Recrystallization from chloroform gave 10 g. of a product melting at 87–89°. This compound was identified as 2-oxazolidinone (II) by a mixed melting point with an authentic sample prepared by the method of Homeyer[7] and by an infrared comparison with an authentic sample.

The chloroform insoluble fraction constituted the major portion of the reaction product, which amounted to 76.0 g. This residue decomposed upon attempted distillation. It was identified without further purification by the following means: The infrared spectrum indicated a carbamate linkage. A likely structure that corresponds to these facts would be β-aminoethylcarbamate (III). Since this compound had not been previously characterized in the literature it was prepared by treatment of β-chloroethylcarbamate with ammonium hydroxide as described below. A comparison of the infrared spectra of this compound and the residue remaining after chloroform extraction indicated that they were identical.

Two molecular weight determinations, by boiling point elevation in methanol, gave 105 and 89 (theoretical 104).

Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.61; H, 7.69; N, 26.29. Found: C, 35.12; H, 7.74; N, 26.20.

A potentiometric titration was carried out on this material. The resulting titration curve gave a *p*H end point at 4.45. This corresponded to an equivalent weight of 99.0 (theoretical eq. wt. 104).

Hydrolysis of β-aminoethylcarbamate (III) with a 10% solution of sodium hydroxide, by refluxing for a period of 18 hr. gave the expected degradation products. Ammonia was collected in an acetone dry ice trap, carbon dioxide was obtained as sodium carbonate, and the corresponding alcohol, namely, 2-aminoethanol, was obtained in 45% yield. The identification of 2-aminoethanol was made by preparation of the dibenzoate derivative melting at 88–89° (lit. m.p. 88–89°[8]).

β-Chloroethylcarbamate. One hundred g. (0.7 mole) of β-chloroethylchloroformate was added dropwise with cooling and stirring, to 43.0 g. of 28% aqueous ammonia. The addition required 2.5 hr. and stirring was continued for an additional 0.5 hr. The white precipitate that formed was filtered and amounted to 75 g. (87%) of β-chloroethylcarbamate. The carbamate was recrystallized from hot water to the constant m.p. 73–75° (lit. m.p. 76°.[9]).

β-Aminoethylcarbamate (III). A mixture of 24.6 g. (0.2 mole) of β-chloroethylcarbamate and 360.0 g. of 28% aqueous ammonia (6.0 mole ammonia) was kept at 50–60° with continuous stirring for 24 hr. The course of the reaction was followed by Volhard titrations until the conversion of organic chloride to ionic chloride was 93%.

After cooling, ammonia and water were evaporated from the reaction product by placing in an open dish at room temperature. A viscous oil resulted which contained crystals of ammonium chloride. The latter was removed by filtration, and the oil became semicrystalline. Infrared spectrum of this semisolid exhibited $-O-\overset{O}{\overset{\|}{C}}-NH_2$ absorption at 6.0 μ and N—H stretching band at 3.0 μ.

Anal. Calcd. for $C_3H_8N_2O_2$: N, 26.92. Found: N, 26.46.

2-Oxazolidinone (II) conversion into β-aminoethylcarbamate (III). Into a 1.5-l. stainless steel rocking autoclave were placed 21.7 g. (0.25 mole) of 2-oxazolidinone and 250 g. of 28% aqueous ammonia (4.1 mole ammonia). This mixture was held at 130–135° for 1 hr. under 150 p.s.i.g. Ammonia and water were removed under vacuum from the resulting solution. This gave an oil which became semisolid upon standing for an extended period of time. The infrared spectrum was similar to the previously obtained spectrum of β-aminoethylcarbamate (III).

Acknowledgment. The authors gratefully acknowledge the assistance of Prof. Harold W. Heine of Bucknell University for reading the manuscript and making suggestions to improve it.

MIDLAND, MICH.

(6) Morgan, U.S. Patent 2,501,788.
(7) Homeyer, U.S. Patent 2,399,118.
(8) Gabriel, *Ber.* 38, 2412 (1905).
(9) Gattermann, *Ann.* 244, 41 (1888).

[CONTRIBUTION NO. 995 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Alkylation of 3-Picoline[1,2]

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3-Picoline has been alkylated with a number of alkyl halides in liquid ammonia solution using a 2:2:1 molar ratio of 3-picoline:potassium amide:alkyl halide. Observations have been made which appear to indicate that the order of metalation of 3-picoline by the alkali amides is $LiNH_2 < NaNH_2 < KNH_2$.

The hydrogen atoms of the methyl groups in 2-picoline and its vinylogue, 4-picoline, are labile because they may participate in resonance with the azomethine linkage of the pyridine ring. Thus, it has been possible to effect the side chain metalation of these tar bases by treating them with alkali amides and certain organolithium compounds under appropriate reaction conditions. These alkali metal derivatives have been alkylated[3,4] and acylated[5–8] with a large variety of alkyl halides and esters to give compounds of the types 2- and 4-$C_5H_4NCH_2R$ and 2- and 4-$C_5H_4NCH_2COR$.

In 1951, Brown and Murphey[9] elegantly demonstrated that 3-picoline also shows prototropic activity[10] when they found that the interaction of 3-picoline, sodium amide, and methyl chloride in liquid ammonia solution gives 3-ethylpyridine, which may be further methylated to give 3-isopropyl- and 3-*t*-butylpyridine. We have recently shown[11] that 3-picoline may be acylated with aromatic and heterocyclic esters using potassium amide in liquid ammonia[12] as the condensing agent and, thus, a series of the previously unknown ketones containing the 3-pyridyl radical has been made available. The structure of one of these ketones, 3-phenacylpyridine, was established by reducing it to 3-(2-phenylethyl)-pyridine and showing that the properties of the reduction product are identical with those of an authentic sample which was prepared in very low yield (7.7%)[13] by the reaction of 3-picoline, potassium amide, and benzyl chloride.

Because Brown and Murphey[9] had obtained a good yield of product on methylating 3-picoline and we obtained a poor yield on its benzylation, it was of interest to determine what yields of alkylated products would be obtained with a variety of alkyl halides.[14]

For purposes of arriving at the best reaction conditions for effecting the alkylation of 3-picoline, a study was made of its reaction with *n*-butyl bromide. The results obtained are summarized in Table I. It may be seen that the best yield of 3-*n*-amylpyridine (72%) is obtained by the interaction of a 2:2:1 molar ratio of potassium amide, 3-picoline and *n*-butyl bromide for 3 hr. These conditions are superior to both the use of a 2:2:1 molar ratio of reactants for a 35-min. reaction time and a 1:1:1 molar ratio of reactants for a 3-hr. reaction time. Furthermore, when the optimum reaction conditions with potassium amide were used with lithium amide and sodium amide, considerably lower yields of product, *i.e.*, 33.6% and 58.8%, were obtained. These results appear to indicate that the order of metalation of 3-picoline by the alkali amides is lithium amide < sodium amide < potassium amide.[15]

The alkylations, summarized in Table II, were then effected using a 2:1 molar ratio of 3-picolylpotassium to alkyl halide. It should be noted that

(1) Presented before the Organic Division of the 129th National AMERICAN CHEMICAL SOCIETY Meeting, Dallas, Tex., April 8 to 13, 1956.

(2) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(3) For leading references, see "The Chemistry of the Alkali Amides. III," by R. Levine and W. C. Fernelius, *Chem. Revs.* **54**, 540 (1954).

(4) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

(5) M. S. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

(6) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(7) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(8) J. W. Hey and J. P. Wibaut, *Rec. trav. chim.*, **72**, 522 (1953).

(9) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).

(10) This activity is apparently due to the operation of a powerful inductive effect.

(11) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

(12) The use of sodium amide gives considerably lower yields.

(13) An 18.3% yield of the dibenzylated product, dibenzyl-3-pyridylmethane was also obtained in this reaction.

(14) While our work was in progress, H. L. Lochte and E. N. Wheeler [*J. Am. Chem. Soc.*, **76**, 5548 (1954)] reported a 16% yield of 3-(cyclopentylmethyl)-pyridine from the interaction of a 1.2:1:1 molar ratio of 3-picoline, sodium amide, and cyclopentyl chloride. After our study had been completed, a paper appeared by E. Hardegger and E. Nikles [*Helv. Chim. Acta*, **39**, 505 (1956)] which reported the alkylation of 3-picoline with four alkyl halides, but only the yield of 3-*n*-butylpyridine (67%) was reported.

(15) In this connection, M. Hamell and R. Levine [*J. Org. Chem.*, **15**, 162 (1950)] have observed that ethyl phenylacetate is self-condensed in considerably lower yield by lithium amide than by sodium amide. Also, H. Gilman, M. W. Van Ess, H. B. Willis, and C. G. Stuckwisch [*J. Am. Chem. Soc.*, **62**, 2606 (1941)] have found that ethyllithium, ethylsodium, and ethylpotassium metalate benzofuran with increasing ease.

TABLE I

USE OF ALKALI AMIDES TO EFFECT ALKYLATION OF 3-PICOLINE WITH *n*-BUTYL BROMIDE

Amide	Moles of Reactants: 3-Picoline	Amide	*n*-Butyl bromide	Reaction Time	% Yield of 3-$C_5H_4NC_5H_{11}$-*n*
Lithium	2	2	1	3 hr.[a]	33.6
Sodium	2	2	1	3 hr.[a]	58.8
Potassium	2	2	1	3 hr.[a]	72.0
	2	2	1	35 min.[b]	60.8
	1	1	1	3 hr.[a]	44.3

[a] The alkali amide and 3-picoline were stirred for 2 hr. The *n*-butyl bromide was then added and stirring was continued for 1 more hr. [b] Anion formation time was 15 min. and stirring time after addition of the halide was 20 min.

TABLE II

3-ALKYLPYRIDINES, 3-$C_5H_4NCH_2R$, BY ALKYLATING 3-PICOLINE WITH ALKYL HALIDES IN THE PRESENCE OF POTASSIUM AMIDE

R	Alkyl Bromide	Yield, %	b.p. or m.p.[a] °C	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	Ethyl	49.6	182–184	753	$C_8H_{11}N$	79.29	78.72	9.15	9.17
		Picrate	99.8–100.4[d]		$C_{14}H_{14}N_4O_7$	48.00	48.16	4.03	3.83
C_3H_5	Allyl[b]	13.7	99–102	25	$C_9H_{11}N$	81.15	80.36	8.33	8.36
		Picrate	90.6–91		$C_{15}H_{14}N_4O_7$	49.72	49.90	3.89	3.59
C_3H_7	*n*-Propyl	60.3	75–76	7.5	$C_9H_{13}N$				
		Picrate	88–89[e]		$C_{15}H_{16}N_4O_7$				
C_3H_7	Isopropyl	61.1	85.5–87.5	19	$C_9H_{13}N$	79.95	79.81	9.69	9.70
		Picrate	111.6–112		$C_{15}H_{16}N_4O_7$	49.44	49.84	4.43	4.07
C_4H_9	*n*-Butyl	72.0	110–112	20	$C_{10}H_{15}N$	80.48	80.54	10.13	10.66
		Picrate	78.8–79.2[f]		$C_{16}H_{18}N_4O_7$	50.79	51.14	4.79	4.57
C_4H_9	Isobutyl	46.0	107–108	20	$C_{10}H_{15}N$	80.48	80.19	10.13	10.28
		Picrate	105–105.8		$C_{16}H_{18}N_4O_7$	50.79	50.98	4.79	4.31
$C_4H_{10}N$	β-Dimethylaminoethyl[c]	34.2	101–103	4	$C_{10}H_{16}N_2$	73.06	73.17	9.74	10.08
		Dipicrate	161.6–162.2		$C_{22}H_{22}N_8O_{14}$[g]	42.44	42.21	3.54	3.33
C_5H_9	Cyclopentyl	38.8	149–151	35	$C_{11}H_{15}N$				
		Picrate[h]	120.5–121.5		$C_{17}H_{18}N_4O_7$				
C_5H_{11}	*n*-Amyl	69.6	128–129	20	$C_{11}H_{17}N$	80.92	80.76	10.50	10.24
		Picrate	72.4–73.0[i]		$C_{17}H_{20}N_4O_7$	52.03	52.54	5.14	4.80
$C_6H_{14}N$	β-Diethylaminoethyl[c]	56.3	111–112	3	$C_{12}H_{20}N_2$	74.94	74.87	10.48	10.58
		Dipicrate	141.6–142		$C_{24}H_{26}N_8O_{14}$	44.30	44.75	4.03	3.97

[a] All boiling points and melting points are uncorrected. [b] Chloride was used. [c] Aminochloride hydrochloride was used. In order to free the amine from its hydrochloride, a 3:1 molar ratio of 3-picolylpotassium to hydrochloride was used. In all the other reactions a 2:1 molar ratio of reactants was employed. [d] Hardegger and Nikles (see ref. 14) report 99–100°; [e] a value of 90–90.5° is reported in ref. 17 and a value of 88–89° is given by Hardegger and Nikles (see footnote *d*). [f] Reported value (see footnote *d*) is 77–78°; [g] *N*, calcd.: 18.00; found: 18.04. [h] The styphnate, m.p. 147.5–148.2°, and the trinitro-*m*-cresolate, m.p. 137.8–138.3°, were also prepared. The melting points of all three derivatives agree with those previously reported by Lochte and Wheeler (see ref. 14). [i] Reported value (see footnote *d*) is 71–72°.

by the present method a 38.8% yield of 3-(cyclopentylmethyl)pyridine was obtained as contrasted with the previously reported[14] yield of 16%. Furthermore, while, by the present procedure, 3-picoline is alkylated with *n*-butyl bromide to give a 72% yield of 3-*n*-amylpyridine IV, this compound was previously obtained by Harris *et al.*[16] in an over-all yield of 13.6% by the following multistage synthesis: $CH_3CO_2C_2H_5$ + 3-$C_5H_4NCO_2C_2H_5$ (Claisen) → 3-$C_5H_4NCOCH_2CO_2C_2H_5$(I); I + *n*-C_3H_7Br → 3-$C_5H_4NCOCH(n\text{-}C_3H_7)CO_2C_2H_5$ (II). II (cleavage) → 3-$C_5H_4NCOC_4H_9$-*n*(III); III (Wolff-Kishner) → 3-$C_5H_4NC_5H_{11}$-*n*(IV). In addition, while we have prepared 3-*n*-butylpyridine in 60.3% yield, this compound has been obtained previously[17] in an over-all yield of 24% by the Wolff–Kishner reduction of *n*-propyl 3-pyridyl ketone, which in turn was synthesized from *n*-propylmagnesium bromide and the difficultly accessible 3-cyanopyridine.

EXPERIMENTAL[18]

In this section one typical alkylation is described in detail. *Synthesis of 3-n-Amylpyridine.* 3-Picoline (0.4 mole, 37.2 g.) was added over a 15-min. period to a solution of potas-

(16) G. H. Harris, R. S. Shelton, M. G. VanCampen, E. R. Andrews, and E. L. Schumann, *J. Am. Chem. Soc.*, **73**, 3959 (1951).

(17) R. L. Frank and C. Weatherbee, *J. Am. Chem. Soc.*, **70**, 3482 (1948).

(18) The 3-picoline used in this study was supplied through the courtesy of Dr. F. E. Ciskak, Reilly Tar and Chemical Corp.

sium amide, which was prepared from potassium (0.4 mole, 15.6 g.) and 350–400 ml. of anhydrous liquid ammonia. The resulting blood-red mixture was stirred for 2 hr. and then *n*-butyl bromide (0.2 mole, 27.4 g.), diluted with an equal volume of anhydrous ether, was added over a 20-min. period. After the halide was added, the mixture was stirred for an additional hour and then the reaction was quenched by the addition of solid ammonium chloride (0.41 mole, 22.0 g.). The mixture was then processed as described previously for the acylation of 3-picoline[11] to give 1.8 g. of *n*-butyl bromide, 15.5 g. of recovered 3-picoline, b.p. 135–143°, and 21.5 g. (72%) of 3-*n*-amylpyridine, b.p. 110–112° at 20 mm.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Conjugate Additions of Grignard Reagents to α,β-Unsaturated Esters

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The reactions of *sec*-butyl esters of certain α,β-unsaturated acids with Grignard reagents have been studied. In the presence of catalytic amounts of cuprous chloride, Grignard reagents from a number of primary bromides (as well as bromobenzene) add in high yields to the double bond of *sec*-butyl crotonate. This provides a practical route to 3-methylalkanoic acids. The Grignard reagents from isopropyl bromide and *tert*-butyl chloride give lower yields under the same conditions. When no catalyst is used the yield is low, and a higher-boiling condensation-addition product is formed. Condensation products are the only isolated compounds from the cuprous chloride catalyzed reaction with *sec*-butyl methacrylate and tiglate. With *sec*-butyl cinnamate a fair yield of 3-phenylheptanoic ester is obtained with *n*-butylmagnesium bromide, while methylmagnesium bromide gives 4-phenylpentanone-2 as a result of both 1,2- and 1,4-addition. When ferric chloride is used as a catalyst very little 1,4-addition takes place and a dimer of the crotonic ester is formed in varying yields.

The addition of Grignard reagents to carbon-carbon double bonds conjugated with polar double bonds has been the subject of many investigations. Although the 1,4- addition products are generally obtained in moderate to good yields from α,β-unsaturated esters which carry strongly electron-withdrawing groups such as carbalkoxy and cyano groups at the α-carbon,[2–6,23] the yields with other α,β-unsaturated esters have varied widely. Kohler and Heritage[7] have reported that ethyl cinnamate gives exclusively 1,2- addition (dimethylcinnamylcarbinol) with methylmagnesium iodide, but predominantly 1,4- addition (ethyl β,β-diphenylpropionate) with phenylmagnesium bromide. They also found that with increasing size of the alcohol moiety in the cinnamic ester, the rate of 1,4- to 1,2-addition of phenylmagnesium bromide increased, and Hauser *et al.*[8] have reported that with *tert*-butyl cinnamate only the 1,4- addition product is formed. Ethyl α-methylcinnamate[9] and ethyl α-methyl-β-phenylcinnamate[10] give predominantly 1,2- addition with phenylmagnesium bromide, while ethyl α-phenylcinnamate gives exclusively 1,4-addition.[11] Methylmagnesium halides appear to give 1,2-addition in all cases except with the alkylidenemalonic and -cyanoacetic esters. Ethyl crotonate is likewise reported[12] to give crotyldimethylcarbinol with methylmagnesium bromide. It is reported[13] that the Grignard reagent from 2-bromothiophene with ethyl crotonate gives 1,3-di-(2-thenyl)butanone-1 as a result of both 1,2- and 1,4- addition, and the reaction between ethyl methacrylate and methylmagnesium iodide is likewise reported[14] to give both 1,2- and 1,4- addition.

Recently Wotiz *et al.*[15] reported 1,4- addition in up to 40% yield of ethyl-, *tert*-butyl- and phenylmagnesium halides to free crotonic and cinnamic acids. Although we have been able to verify the result reported for the addition of phenylmagnesium bromide to crotonic acid, we have obtained only a low yield (10% or less) of 3-methylheptanoic acid from *n*-butylmagnesium bromide and crotonic acid; large amounts of unidentified nonacidic and high-boiling acidic products are produced.

Since it may be considered established [*e.g.* in

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(2) Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905) [*Chem. Zentr.*, I, 1389 (1905)]; Kohler, *Am. Chem. J.*, **34**, 132 (1905) [*Chem. Zentr.*, II, 1021 (1905)].

(3) Alexander, McCollum, and Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

(4) Wideqvist, *Arkiv Kemi, Mineral. Geol.*, B **23**, No. 4 (1946); *Arkiv Kemi*, **2**, 321 (1950).

(5) Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

(6) Bush and Beauchamp, *J. Am. Chem. Soc.*, **75**, 2949 (1953); van Heyningen, *J. Am. Chem. Soc.*, **76**, 2241 (1954).

(7) Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905) [*Chem. Zentr.*, I, 521 (1905)].

(8) Hauser, Yost and Ringler, *J. Org. Chem.*, 14, 261 (1949).

(9) Kohler, *Am. Chem. J.*, **36**, 529 (1906) [*Chem. Zentr.*, I, 559 (1907)].

(10) Bergmann and Weiss, *Ann.*, **480**, 64 (1930).

(11) Kohler and Heritage, *Am. Chem. J.*, **33**, 153 (1905) [*Chem. Zentr.*, I, 824 (1905)].

(12) Keersblick, *Bull. soc. chim. Belg.*, **38**, 205 (1929) [*Chem. Zentr.*, II, 2036 (1929)].

(13) Hirao, *J. Pharm. Soc. Japan*, **73**, 1024 (1953) [*Chem. Abstr.*, **48**, 10724a (1954)].

(14) Blaise and Courtot, *Compt. rend.*, **140**, 370 (1905) [*Chem. Zentr.*, I, 726 (1905)]; cf. also ref. 9.

(15) Wotiz, Matthews, and Greenfield, *J. Am. Chem. Soc.*, **75**, 6342 (1953); cf. Wotiz and Matthews, *J. Am. Chem. Soc.*, 74, 2559 (1952).

ref. (7)] that large groups at the carbonyl carbon decrease the extent to which 1,2- addition (to the carbonyl group) takes place, it was thought worth while to investigate the addition of Grignard reagents to *sec*-butyl esters of α,β-unsaturated acids as a way of preparing 3-substituted fatty acids, *e.g.*:

$$\underset{\text{I}}{\text{CH}_3\text{—CH=CH—COO-}sec\text{-Bu}} \xrightarrow{\text{RMgX}} \text{CH}_3\text{—}\underset{\text{R}}{\text{CH}}\text{—CH}_2\text{—COO-}sec\text{-Bu}$$

Although such acids could be prepared by malonic ester syntheses, *e.g.* 3-methylheptanoic acid[16,17] and 3-methylstearic acid[18] from the corresponding secondary halides, these halides are often difficult to obtain entirely free of isomers[19] and, unless the corresponding alcohol is commercially available, the route *via* the malonic acid would consist of many steps. Another pathway for 3-methyl-substituted fatty acids is the electrolysis[20] of the mixture of β-methylglutaric acid mono-methyl ester and a fatty acid, but the yields are rather low and the procedure laborious.

In the reaction between *sec*-butyl crotonate and *n*-butylmagnesium bromide, the 1,4- addition product (II) was obtained in only 25% yield. A rather large quantity of a higher-boiling substance (described below) was formed.

Attention was drawn to the report by Kharasch and Tawny,[21] that the presence of catalytic amounts of cuprous chloride changes the direction of addition of methylmagnesium bromide to isophorone from predominantly 1,2- to almost exclusively 1,4-addition. This effect of cuprous halides on the addition of methyl magnesium halides to cyclic 2-en-1-ones has more recently been reported also by other workers.[22] Cuprous chloride has also been found effective in promoting addition in competition with reduction at the carbon-carbon double bond of alkylidenemalonic and -cyanoacetic esters.[23] Finally, Cook and Percival[24] have reported the cuprous chloride catalyzed formation of hexamethylacetone (that is addition to the carbonyl group) instead of reduction product from trimethylacetyl chloride and *tert*-butylmagnesium chloride.

It has now been found that, in the reaction between *n*-butylmagnesium bromide and *sec*-butyl crotonate, the presence of one mole per cent of cuprous chloride results in an increase in the yield of 1,4- addition product (II) from 25 to 60%, a yield which could be further improved to 85% by increasing the ratio of Grignard reagent.

The higher-boiling product mentioned above is only found in minor amounts when cuprous chloride is present. This compound, however, is not a 1,2- addition product, and such a product has never been obtained with *sec*-butyl crotonate, not even in the reaction with methylmagnesium bromide. The higher-boiling products are believed to be α,β-dialkylglutaric esters (IV)[25] formed by dimerization of the crotonic ester[26,27] by a Michael condensation, followed by a 1,4- addition of the Grignard reagent:

$$\underset{\text{I}}{\text{CH}_3\text{—CH=CH—COO-}sec\text{-Bu}} + \underset{\text{I}}{\text{CH}_3\text{—CH=CH—COO-}sec\text{-Bu}} \longrightarrow \underset{\text{III}}{\begin{matrix}\text{CH}_3\text{—CH=C—COO-}sec\text{-Bu}\\ \quad\quad\quad\quad\text{|}\\ \quad\quad\quad\quad\text{CH}_3\text{—CH—CH}_2\text{—COO-}sec\text{-Bu}\end{matrix}}$$

$$\xrightarrow{\text{RMgX}} \underset{\text{IV}}{\begin{matrix}\quad\quad\quad\quad\text{R}\\ \quad\quad\quad\quad\text{|}\\ \text{CH}_3\text{—CH—CH—COO-}sec\text{-Bu}\\ \quad\quad\quad\quad\text{|}\\ \quad\quad\quad\quad\text{CH}_3\text{—CH—CH}_2\text{—COO-}sec\text{-Bu}\end{matrix}}$$

The structure (III) shown above for the dimer is given by Pechman[26] and by Hurd and Kelso[27] for the corresponding ethyl ester. The product (IV) was first thought to be formed by a Michael condensation between the 1,4-addition product (II) and unreacted crotonic ester (I), but an attempt to prepare IV from these reactants, using sodium *sec*-butoxide as the condensing agent, failed; the 1,4-addition product (II) was recovered and the crotonic ester (I) was converted to its dimer (III). Products of type IV are reported in the literature, *e.g.* by Hauser *et al.*[8] from the reaction between *tert*-butyl cinnamate and diethylaminomagnesium bro-

(16) Linstead, Shephard, Weedon, and Lunt, *J. Chem. Soc.*, 1538 (1953).

(17) Levene and Marker, *J. Biol. Chem.*, 91, 77 (1931).

(18) Kuhn, Köhler, and Köhler, *Zeit. Physiol. Chem.*, 242, 182 (1936).

(19) Cason and Mills, *J. Am. Chem. Soc.*, 73, 1354 (1951).

(20) Ställberg-Stenhagen, *Arkiv Kemi*, 2, 95 (1950).

(21) Kharasch and Tawny, *J. Am. Chem. Soc.*, 63, 2308 (1941).

(22) Birch and Robinson, *J. Chem. Soc.*, 501 (1943); Büchi, Jeger and Ruzicka, *Helv. Chim. Acta*, 31, 241 (1948); Stoll and Commarmont, *Helv. Chim. Acta*, 31, 554 (1948).

(23) Hook and Robinson, *J. Chem. Soc.*, 152 (1944); Brändström and Forsblad, *Arkiv Kemi*, 6, 561 (1953).

(24) Cook and Percival, *J. Am. Chem. Soc.*, 71, 4141 (1949).

(25) The products give the correct elementary analyses, but give by alkaline hydrolyses (in methanolic potassium hydroxide for up to 48 hr.) equivalent weights equal to the molecular weights. This latter fact is probably due to the high degree of steric hindrance. The product from *sec*-butyl tiglate and *n*-butylmagnesium bromide is not hydrolyzed at all in alcoholic potassium hydroxide. By more vigorous saponification of the product from *sec*-butyl crotonate and *n*-butylmagnesium bromide, and treatment of the acid with acetyl chloride, a product was obtained which gave the correct analysis for α-(2-hexyl)-β-methylglutaric anhydride.

(26) von Pechmann, *Ber.*, 33, 3323 (1900).

(27) Hurd and Kelso, *J. Am. Chem. Soc.*, 62, 2187 (1940).

mide, and by Kohler and Peterson[28] and Wittig *et al.*[29] from the reaction between benzalacetophenone and a number of arylmetallic compounds.

In the case of the noncatalyzed reaction between *sec*-butyl crotonate and 1.2 equivalents of *n*-butylmagnesium bromide, the product IV was obtained in 44% yield but when cuprous chloride was present in only about 25% yield. Since the formation of IV is believed to be the result of initial reaction of crotonic ester with itself, it should be suppressed by increasing the excess of Grignard reagent. It was found that, in the cases of *n*-butyl- and *n*-octylmagnesium bromides, an increase in the amount of Grignard reagent from 1.2 to 1.5 equivalents (as measured by the amount of magnesium, in relation to which an excess of bromide was used), did indeed result in an increase in the yield of 1,4-addition product (II) from 60% to 85%, while the yield of by-product dropped to practically zero. A further increase to 2 equivalents did not result in increased yield in these cases. In the case of *n*-tetradecylmagnesium bromide an increase from 1.2 to 2.0 equivalents of Grignard reagent, similarly, resulted in an increase in the yield of 1,4- addition product (II) from 10% to 86%. It was also found that the ratio of higher-boiling product (IV) is increased if more concentrated solution of crotonic ester and a shorter time of ester addition are used.

The results are shown in Table I, while the names of the products and their properties are given in Table II.

It has been suggested[30] that the effect of cuprous halides should be due to a facilitation of the addition to the carbon-carbon double bond, which has been labilized by complex formation with the metallic halide. This theory is consistent with the fact that cuprous chloride not only facilitates 1,4- addition in preference to 1,2- addition, but also favors addition to the carbon-carbon double bond in situations when 1,2- addition (to the carbonyl group) is hindered, but then some other reaction, such as reduction of the double bond,[22] competes with the addition process. In the case here reported, the increased reactivity of the double bond should make the ester react more rapidly; as the Grignard reagent is in large excess during the entire, very slow addition of the ester, the increased reactivity of the double bond makes the ester more likely to react with a molecule of Grignard reagent than with another ester molecule. This is consistent with the great sensitivity of the yield to any excess of crotonic ester; the increase in yield with the increase in the excess of Grignard reagent; and the decrease in yield with the increase of the concentration of crotonic ester solution as well as of the rate of addition of the crotonic ester.

The role of cuprous chloride in effecting ketone synthesis (addition) rather than reduction in the reaction between trimethylacetyl chloride and *tert*-butylmagnesium chloride, for which earlier a free-radical mechanism was suggested,[24] is now also thought[31,32] to be one of a Lewis acid, in this case forming a complex with the acid chloride. However, as the effect does not always increase with increasing Lewis acid strength, other factors must be involved. It was found that ferric chloride was superior to cuprous chloride, also to aluminum chloride in effecting ketone synthesis in certain cases,[31] but in other cases[32] that cuprous, ferric, and manganous chlorides had the same effects superior to those of aluminum chloride, boron trifluoride, and others.

In the reaction here considered the presence of ferric chloride resulted in formation of a mixture of compounds, among which only a dimerization product (different from the crotonic ester dimer obtained under the influence of basic reagents) of the crotonic ester was isolated. The results are the same when the addition procedure is that used with cuprous chloride or when the Grignard reagent is added to the crotonic ester containing the ferric chloride. It should, however, be pointed out that these metallic halides may react with or promote coupling reactions of the Grignard reagent.[33,34] In the reaction here under consideration, this type of reaction must be avoided, since the effect of the catalyst is thereby eliminated. This is accomplished by cooling of the Grignard reagent before adding the cuprous chloride. In the case of ferric chloride a vigorous reaction took place when the catalyst was added to the Grignard reagent, even when this had been precooled in an ice-salt mixture to about −20°. This reaction of ferric chloride with a Grignard solution is mentioned by Kharasch and Tawny,[21] but apparently not considered as being of any significance.

It was further found that the presence of cuprous chloride does not change the reaction between free crotonic acid and *n*-butylmagnesium bromide to give any simple 1,4-addition product; only high-boiling acidic products are obtained.

Finally the reaction of *sec*-butyl crotonate with di-*n*-butylcadmium was tried. Riegel, Siegel, and Lilienfeld[35] state that the yields of 1,4- addition to alkylidenemalonic esters were somewhat higher with α-naphthylmethylcadmium reagent than with the corresponding Grignard compound. In the re-

(28) Kohler and Peterson, *J. Am. Chem. Soc.*, **55**, 1073 (1933).

(29) Wittig, Meyer and Lange, *Ann.*, **571**, 167 (1951).

(30) Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 221.

(31) Percival, Wagner and Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

(32) Morrison and Wishman, *J. Am. Chem. Soc.*, **76**, 1059 (1954).

(33) Gilman and Lichtenwalter, *J. Am. Chem. Soc.*, **61**, 957 (1939).

(34) Kharasch and Fields, *J. Am. Chem. Soc.*, **63**, 2316 (1941).

(35) Riegel, Siegel, and Lilienfeld, *J. Am. Chem. Soc.*, **68**, 984 (1946).

α,β-Unsaturated Acid		RMgX				Products %		
Derivative	Moles	R	Mg g.-atoms	RX moles	Catalyst, 1 Mole %	II 1,4- add.	IV cond. + 1,4- add.	Other products; comments
Crotonic acid	0.5	*n*-C_4H_9	1.24	1.24	None	10		High-boiling acidic and unidentified nonacidic products
	0.25	*n*-C_4H_9	0.62	0.62	CuCl	0		
	0.25	C_6H_5	0.62	0.62	None	40		Not identified crystalline nonacidic product
sec-Butyl crotonate	0.20	*n*-C_4H_9	0.24	0.24	None	25	44	
	0.20	*n*-C_4H_9	0.24	0.30	CuCl	59.3	24.5	
	0.30	*n*-C_4H_9	0.36	0.40	None	21.4	44	
	0.20	*n*-C_4H_9	0.30	0.35	CuCl	85	0	
	0.50	*n*-C_4H_9	0.75	0.93	CuCl	47	31	Ester dissolved in only 240 ml. of ether and added during only 1.5 hr.
	0.40	*n*-C_4H_9	0.60	0.75	CuCl	84	0	25-cm. Vigreux column used for distillation of ester; with Podbielniak column the yield is 86%
	0.20	*n*-C_4H_9	0.30	0.35	$FeCl_3$	3		Dimerization product of crotonic ester in 12% yield.[a] Cooling of Grignard reagent in ice water for 5 min. before adding catalyst
	0.20	*n*-C_4H_9	0.30	0.35	$FeCl_3$	3		Dimerization product of crotonic ester in 44% yield.[a] Cooling of Grignard reagent in ice water for 15 min. before adding catalyst
	0.20	*n*-C_4H_9	0.30	0.37	$FeCl_3$	0		Dimerization product of crotonic ester in 20% yield.[a] Cooling of Grignard reagent in ice salt for 15 min. before adding catalyst
	0.20	*n*-C_4H_9	0.40	0.50	$FeCl_3$	5		Dimerization product of crotonic ester in 28% yield.[a] Filtered Grignard reagent added to ester solution containing suspended catalyst, while cooling in ice water
	0.3	CH_3	0.45	0.69	CuCl	44.5	35	Cooling in ice salt of Grignard reagent before adding catalyst
	0.2	C_2H_5	0.30	0.37	CuCl	0	47	Cooling of Grignard reagent in ice water only, before adding catalyst
	0.2	C_2H_5	0.30	0.37	CuCl	56	22	Cooling of Grignard reagent in ice salt before adding catalyst
	0.2	*iso*-C_3H_7	0.30	0.37	CuCl	39		High-boiling, resinous residue. Isopropyl bromide, *tert*-butyl chloride used
	0.2	*tert*.-C_4H_9	0.30	0.38	CuCl	14		
	0.3	*n*-C_8H_{17}	0.36	0.40	CuCl	56	40	*n*-Octane, *n*-octanol, *n*-hexadecane. Higher-boiling product contaminated with *n*-hexadecane
	0.2	*n*-C_8H_{17}	0.30	0.35	CuCl	75	16	
	0.2	*n*-C_8H_{17}	0.40	0.50	CuCl	70	17	
	0.1	*n*-$C_{14}H_{29}$	0.12	0.13	CuCl	25	(40–50)	*n*-Tetradecane, 1-tetradecanol, *n*-octacosane. Higher-boiling product not pure
	0.1	*n*-$C_{14}H_{29}$	0.12	0.14	CuCl	12	(60)	
	0.1	*n*-$C_{14}H_{29}$	0.20	0.25	CuCl	86	0	
	0.2	C_6H_5	0.30	0.35	CuCl	67		Ether solution of ester should be washed with sodium hydroxide to remove phenol. Product contaminated with small amounts of biphenyl. Saponification as described for 3-methylheptanoic acid gives pure acid in 90% yield
	0.2	C_6H_5	0.30	0.35	CuCl	67		
Methyl crotonate	0.2	*n*-C_4H_9	0.30	0.37	CuCl	4.4		Self-condensation product of 1,4-addition product: Methyl 2-(2′-hexyl)-3-keto-5-methylnonanoate obtained in 66% yield
sec-Butyl methacrylate	0.2	*n*-C_4H_9	0.30	0.40	CuCl	0	30	Small amounts of unidentified solid passed over with first part of distillate. In the first experiment the ester contained 0.1% hydroquinone; in the two latter pure ester was used
	0.2	*n*-C_4H_9	0.30	0.35	CuCl	0	41	
	0.2	*n*-C_4H_9	0.60	0.75	CuCl	0	52	
sec-Butyl tiglate	0.2	*n*-C_4H_9	0.24	0.30	CuCl	0	25	Mixture of unidentified low- and high-boiling products
sec-Butyl cinnamate	0.1	*n*-C_4H_9	0.15	0.20	CuCl	0	0	Grignard solution not cooled before adding catalyst. Unreacted ester and high-boiling residue obtained
	0.1	*n*-C_4H_9	0.15	0.20	CuCl	46	0	High-boiling residue
	0.2	CH_3	0.3	0.7	CuCl			4-Phenylpentanone-2 (1,2 and 1,4-addition) in 40% yield. 20% unreacted ester recovered. Residue

[a] Calcd. for $C_{16}H_{28}O_4$ (284.4): C, 67.57, H, 9.92. Found C, 67.43; H, 9.92. Sap. equiv. found 281. I.R. spectrum shows one very sharp carbonyl band at 5.80 μ (1725 cm^{-1}), but no absorption in the 6.0–6.20 μ region (conjug. C=C).

TABLE II—Products Isolated from Reactions of Grignard Reagents with α,β-Unsaturated Esters

α,β-Unsaturated Ester	RMgX	Products
sec-Butyl crotonate	*n*-C_4H_9MgBr (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylheptanoate, b.p. 110–111°/19 mm., 116–116.5°/25 mm., 102–103°/13.5 mm., 71°/2 mm., n_D^{25} 1.4190. Calcd. for $C_{12}H_{24}O_2$ (200.3) C, 71.95; H, 12.08. Found C, 71.59; H, 11.77. Sap. equiv. found 200.
		2. (Cond. + 1,4- add.): di-*sec*-butyl α-(2-hexyl)-β-methylglutarate, b.p. 136°/0.8 mm., 140–141°/1.2 mm., 143–145°/1.5 mm., n_D^{25} 1.4400. Calcd. for $C_{20}H_{38}O_4$ (342.5) C, 70.13; H, 11.18. Found C, 70.50; H, 10.88. Sap. equiv. found 342.
sec-Butyl crotonate	*n*-C_4H_9MgBr ($FeCl_3$)	Dimer of *sec*-butyl crotonate, b.p. 99°/0.3 mm., n_D^{25} 1.4322. Calcd. for $C_{16}H_{28}O_4$ (284.4) C, 67.57; H, 9.92. Found C, 67.43; H, 9.91. Sap. equiv. found 281.
sec-Butyl crotonate	CH_3MgBr (CuCl)	1. (1,4- add.): *sec*-butyl isovalerate, b.p. 100°/98 mm. (rep. 163–164°/752 mm.,[a] n_D^{25} 1.4075. Calcd. for $C_9H_{18}O_2$ (158.2) C, 68.31; H, 11.46. Found C, 68.50; H, 11.49. Sap. equiv. found 157.
		2. (Cond. + 1,4- add.): di-*sec*-butyl α-isopropyl-β-methylglutarate, b.p. 124°/2 mm., n_D^{25} 1.4341. Calcd. for $C_{17}H_{32}O_4$ (300.4) C, 67.96; H, 10.74. Found C, 68.06; H, 10.52. Sap. equiv. found 302.
sec-Butyl crotonate crotonate	C_2H_5MgBr (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylvalerate, b.p. 79–81°/19 mm., n_D^{25} 1.4103. Calcd. for $C_{10}H_{20}O_2$ (172.3) C, 69.72; H, 11.70. Found C, 69.94; H, 11.58. Sap. equiv., found 174.
		2. (Cond. + 1,4- add.): di-*sec*-butyl α-*sec*-butyl-β-methylglutarate, b.p. 130°/1.4 mm., n_D^{25} 1.4367. Calcd. for $C_{18}H_{34}O_4$ (314.5) C, 68.75; H, 10.90. Found C, 68.84; H, 10.73. Sap. equiv. found 312.5.
sec-Butyl crotonate	*iso*-C_3H_7MgBr (CuCl)	(1,4- add.): *sec*-butyl 3,4-dimethylvalerate, b.p. 93°/20 mm., n_D^{25} 1.4173. Calcd. for $C_{11}H_{22}O_2$ (186.3) C, 70.91; H, 11.91. Found C, 71.18; H, 11.90. Sap. equiv. found 186.0.
sec-Butyl crotonate	*tert*-C_4H_9MgCl (CuCl)	(1,4- add.): *sec*-butyl 3,4,4-trimethylvalerate, b.p. 95°/12 mm., n_D^{25} 1.4231. Calcd. for $C_{12}H_{24}O_2$ (200.3) C, 71.95; H, 12.08. Found C, 71.89; H, 12.18. Sap. equiv. found 202.2.
sec-Butyl crotonate	*n*-$C_8H_{17}MgBr$ (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylhendecanoate, b.p. 115°/1.5 mm., n_D^{25} 1.4305. Calcd. for $C_{16}H_{32}O_2$ (256.4) C, 74.94; H, 12.58. Found C, 75.13; H, 12.43. Sap. equiv. found 260.
		2. (Cond. + 1,4- add.): di-*sec*-butyl α-(2-decyl)-β-methylglutarate, b.p. 186°/1.5 mm., n_D^{25} 1.4447. Calcd. for $C_{24}H_{46}O_4$ (398.6) C, 72.31; H, 11.63. Found C, 72.47; H, 11.46. Sap. equiv. found 420.
sec-Butyl crotonate	*n*-$C_{14}H_{29}MgBr$ (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylheptadecanoate, b.p. 196°/3.5 mm., n_D^{25} 1.4405. Calcd. for $C_{22}H_{44}O_2$ (340.6) C, 77.58; H, 13.02. Found C, 77.61; H, 13.01. Sap. equiv. found 338.
		2. (Cond. + 1,4-add.): di-*sec*-butyl α-(2-hexadecyl)-β-methylglutarate, b.p. 225°/1.7 mm., n_D^{25} 1.4498. Calcd. for $C_{30}H_{58}O_4$ (482.7) C, 74.63; H, 12.11. Found C, 74.57; H, 11.94. Sap. equiv. found 486.
sec-Butyl crotonate	C_6H_5MgBr (CuCl)	1a. (1,4- add.): *sec*-butyl 3-phenylbutyrate, b.p. 105.5°/2 mm., n_D^{25} 1.4811. Calcd. for $C_{14}H_{20}O_2$ (220.3) C, 76.32; H, 9.15. Found C, 76.53; H, 8.99. Sap. equiv. found 220.9.
		1b. (Saponification of 1a): 3-phenylbutyric acid, b.p. 104.5–105°/0.5 mm. (rep.[b] 112–113°/2 mm.), n_D^{25} 1.5147, m. p. 35–36° (rep. 35–36°). Calcd. for $C_{10}H_{12}O_2$ (164.2) C, 73.14; H, 7.37. Found C, 73.37; H, 7.46. Neut. equiv. found 164.4.
Methyl crotonate	*n*-C_4H_9MgBr (CuCl)	1. (1,4- add.): methyl 3-methylheptanoate, b.p. 70°/13.5 mm. (rep.[c] 90.2°/30 mm.), n_D^{25} 1.4144. Calcd. for $C_9H_{18}O_2$ (158.2) C, 68.31; H, 11.46. Found C, 68.33; H, 11.43. Sap. equiv. found 159.2.
		2a. (Self-condensation of 1): methyl 2-(2′-hexyl)-3-keto-5-methylnonanoate, b.p. 135°/2.5 mm., n_D^{25} 1.4419. Calcd. for $C_{17}H_{33}O_3$ (284.4) C, 71.79; H, 11.34. Found C, 72.03; H, 11.02. Sap. equiv. found 277.
		2b. (Saponification and decarboxylation of 2a): 5,9-dimethyltridecanone-7, b.p. 93.5°/1 mm., n_D^{25} 1.4354. Calcd. for $C_{15}H_{30}O$ (226.4) C, 79.57; H, 13.36. Found C, 79.74; H, 13.53.
sec-Butyl methacrylate	*n*-C_4H_9MgBr (CuCl)	(Cond. + 1,4- add.): di-*sec*-butyl α-*n*-amyl-α,γ-dimethylglutarate, b.p. 142°/1.7 mm., n_D^{27} 1.4371. Calcd. for $C_{20}H_{38}O_4$ (342.5) C, 70.13; H, 11.18. Found C, 70.19; H, 11.13. Sap. equiv. found 344.
sec-Butyl tiglate	*n*-C_4H_9MgBr	(Cond. + 1,4- add.): di-*sec*-butyl α-(2-hexyl)-α,β,γ-trimethylglutarate, b.p. 158°/1.5 mm., n_D^{25} 1.4520. Calcd. for $C_{22}H_{42}O_4$ (370.6) C, 71.30; H, 11.43. Found C, 71.58; H, 11.36. Sap. equiv. found 4800 (!).
sec-Butyl cinnamate	*n*-C_4H_9MgBr (CuCl)	(1,4- add.): *sec*-butyl 3-phenylheptanoate, b.p. 115°/0.8 mm., n_D^{25} 1.4792. Calcd. for $C_{17}H_{26}O_2$ (262.4) C, 77.81; H, 9.99. Found C, 77.99; H, 10.00. Sap. equiv. found 262.6.
sec-Butyl cinnamate	CH_3MgBr (CuCl)	(1,2- + 1,4- add.): 4-phenylpentanone-2, b.p. 88.5°/1.7 mm., n_D^{25} 1.5102 (rep. b.p. 113–115°/13 mm., n_D^{20} 1.5124[d]; b.p. 109°/11 mm., n_D^{15} 1.5090[e]). Intensive rhubarb-like odor. I.R. spectrum shows strong carbonyl-band. Calcd. for $C_{11}H_{14}O$ (162.2) C, 81.44; H, 8.70. Found C, 81.46; H, 8.87. Sap. equiv. found 2500.

[a] Norris and Green, *Am. Chem. J.*, 26, 311 (1901) [*Chem. Zentr.*, II, 1113 (1901)]. [b] Reference (14). [c] Reference (19). [d] Nenitzescu and Gavat, *Ann.*, 519, 260 (1935); (*e*) Cologne and Pichat, *Bull. soc. chim.*, 177 (1949).

action here reported very little, if any, 1,4- addition took place when the cadmium reagent was used. Even after heating under reflux in ether-benzene solution, the crotonic ester was recovered.

It should be noted that, in the presence of cuprous chloride, *n*-butylmagnesium bromide also adds only to the carbon-carbon double bond of methyl crotonate. However, in this case only traces of the simple 1,4- addition product (corresponding to II) are obtained; this initial product apparently self-condenses to the corresponding acetoacetic ester [methyl α,γ-di-(2-hexyl)acetoacetate]. This compound (obtained in 67% yield), on saponification, spontaneously decarboxylates into the corresponding ketone in 75% yield.

It is further remarkable that even methylmagnesium bromide does not add to the carbonyl group of *sec*-butyl crotonate when cuprous chloride is present; however, in the cases of methyl- and ethylmagnesium bromides, the proportion of simple 1,4-addition product (II) to condensation addition product (IV) is somewhat smaller than in the cases of the larger primary Grignard reagents. The explanation for this should probably be sought in the above-mentioned possibility of competitive reaction of the cuprous chloride with the Grignard reagent before the crotonic ester is added, to which reaction the Grignard solutions from methyl and ethyl bromide were considerably more sensitive than the higher Grignard reagents.

Isopropylmagnesium bromide and *tert*-butylmagnesium chloride give only rather poor yields (39% and 14%, respectively) of the simple 1,4- addition products (II), and large amounts of resinous material are formed. Secondary and tertiary Grignard reagents have been reported to give poor yields also in the reaction with alkylidenecyanoacetic esters.[3,5]

The introduction of a methyl group in the α-position of an α,β-unsaturated ester (*e.g.*, methacrylic and tiglic esters) results in the exclusive formation of the condensation addition product (IV), even in the presence of a large excess of Grignard reagent. The yields, however, are rather small.

To *sec*-butyl cinnamate, *n*-butylmagnesium bromide adds 1,4- to give a fair yield of *sec*-butyl 3-phenylheptanoate, but methyl-magnesium bromide adds at both 1,2- and 1,4- positions to give a 40% yield of 4-phenylpentanone-2; the yield of this product could probably be improved by using a greater excess of Grignard reagent, since a considerable amount of unreacted *sec*-butyl cinnamate was recovered.

The usual by-products are formed from the Grignard reagents, RMgX: the hydrocarbons RH and R—R, and traces of the hydroxyl compounds ROH. As mentioned in Table I, these products sometimes contaminate the main products, but mostly they can be separated.

EXPERIMENTAL[36]

Preparation of sec-butyl esters (Table III). A mixture of 258 g. (3 moles) of crotonic acid (Eastman, pract.), 370 g. (5 moles) of 2-butanol in which were dissolved 6–7 ml. of concentrated sulfuric acid, and 300 ml. of thiophene-free benzene was heated under reflux overnight, as water (65 ml.) was removed from the reaction mixture by means of a Wideqvist water separator.[38] The cooled reaction mixture was diluted with 200 ml. of ether, then washed with sodium bicarbonate solution and with water, and finally dried over anhydrous sodium sulfate. After distillation of the solvents the ester was fractionated through a 25-cm. Vigreux column.

TABLE III

sec-BUTYL ESTERS

sec-Butyl	B.p. °C./mm.	n_D^{25}	Moles	Yield, %	Analyses for	Calcd. C	Calcd. H	Calcd. S.E.	Found C	Found H	Found S.E.
Crotonate	74–75/30 83–84/45	1.4261	1–3	85–90	$C_8H_{14}O_2$	67.57	9.92	142.2	67.56	9.87	142.6
Methacrylate	59–62/34	1.4161	2	85	$C_8H_{14}O_2$	67.57	9.92	142.2	67.64	10.12	143.2
Tiglate	84.5/27	1.4332	0.5	60	$C_9H_{16}O_2$			156.6			156.0
Cinnamate	122/2	1.5382	1	92	$C_{13}H_{16}O_2$	76.43	7.90	204.3	76.31	7.92	204

The other esters were prepared similarly. The methacrylic ester was stabilized with 1% hydroquinone during the preparation and with 0.1% hydroquinone for storage after distillation. Glacial methacrylic acid was purchased from Monomer-Polymer, Inc., Leominster, Mass. Tiglic acid was prepared as described in the literature.[39]

Reactions of α,β-unsaturated esters with Grignard reagents (Tables I and II). Reaction of *sec*-butyl crotonate with *n*-butylmagnesium bromide is illustrative. A solution of *n*-butylmagnesium bromide was prepared from 7.2 g. (0.3 g.-atom) of magnesium turnings and 50 g. (0.37 mole) of *n*-butyl bromide in 120 ml. of ether. This solution was cooled for about 10 min. in ice water, after which 0.3 g. (1 mole %)

(36) All melting and boiling points are uncorrected; pressures above 5 mm. were measured with a Zimmerli gage, those below 5 mm. with a tilting McLeod gage. Unless otherwise specified, all distillations were through a 45-cm. Podbielniak-type column with simple tantalum wire spiral, heated jacket, and partial reflux head.[37] Microanalyses were by the Microanalytical Division, Department of Chemistry and Chemical Engineering, University of California, Berkeley. Infrared spectra were recorded on a Baird double-beam spectrophotometer.

(37) Cason and Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, New York, 1950, p. 237 ff.

(38) Wideqvist, *Acta Chem. Scand.*, **3**, 303 (1949).

(39) Buckles and Mock, *J. Org. Chem.*, 15, 680 (1950).

of cuprous chloride[40] was added in one portion. While stirring in the ice bath, a solution of 28.4 g. (0.2 mole) of *sec*-butyl crotonate in 125 ml. of ether was added dropwise during 1–1.5 hr. (With runs on a larger scale, it was found necessary to increase the amount of ether as solvent, as well as the addition time, proportionally, in order to obtain the maximum yield.) After the addition of the ester had been completed, the reaction mixture was stirred in the ice bath for an additional 10–15 min. and then at room temperature for 1–1.5 hr. It was then poured, under vigorous shaking or swirling, onto ice to which 35 ml. of concentrated hydrochloric acid and 50 ml. of ether had been added. The two clear layers were separated and the water layer was extracted with ether. Then the combined ether layers were washed with sodium bicarbonate solution and with water, and dried over anhydrous sodium sulfate. The ether was distilled and the residue fractionated. The products obtained are given in Tables I and II; in the last column of Table I is given certain additional experimental information.

Saponification of sec-butyl 3-methylheptanoate. This ester (40 g., 0.2 mole) was saponified by heating under reflux in a solution of potassium hydroxide (35 g., 0.6 mole) in 95% ethanol (250 ml.) for 6–8 hr., after which time about half of the alcohol was distilled. The corresponding amount of water was added, and the distillation repeated in order to remove any volatile compounds. After pouring into water, acidifying, and extracting with ether, distillation produced 3-methylheptanoic acid in 94% yield, b.p. 116.5–117°/10 mm., n_D^{25} 1.4242 [lit. 121°/15 mm., n_D^{16} 1.4276[16]].

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18; neut. equiv., 144.2. Found: C, 66.64; H, 11.05; neut. equiv., 144.4.

The amide, crystallized from heptane, melted at 81.5–82°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 67.16; H, 11.88; N, 9.62.

Attempted preparation of product IV. A mixture of 14.2 g. (0.1 mole) of *sec*-butyl crotonate and 20 g. (0.1 mole) of *sec*-butyl 3-methylheptanoate, dissolved in 100 ml. of ether, was added to a stirred suspension of sodium *sec*-butoxide in 100 ml. of ether, prepared from 1.2 g. (0.05 g.-atom) of sodium and 7.4 g. (0.1 mole) of 2-butanol. The mixture was stirred at room temperature for 9 hr., then for 3 hr. under reflux, after which it was worked up in the conventional way. Fractionation gave 17.5 g. (87%) of recovered *sec*-butyl 3-methylheptanoate, b.p. 98–99°/10 mm., n_D^{25} 1.4191, and 9.3 g. (65%) of the dimer of *sec*-butyl crotonate (III), b.p. 120–121°/1.5 mm., n_D^{25} 1.4443.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; sap. equiv., 142.2. Found: C, 67.70; H, 10.09; sap. equiv., 253.

The infrared spectrum showed two carbonyl bands at 5.78 μ (1730 cm.$^{-1}$), 5.86 μ (1708 cm.$^{-1}$) and one conjugated carbon-carbon double bond band at 6.10 μ (1640 cm.$^{-1}$). These data show that this compound is different from the isomeric dimer obtained in the attempted ferric chloride catalyzed 1,4- addition of *n*-butylmagnesium bromide to *sec*-butyl crotonate.

Preparation of the anhydride corresponding to product IV from sec-butyl crotonate and n-butylmagnesium bromide [*α-(2-hexyl)-β-methylglutaric anhydride*]. A 10-g. (0.03-mole) sample of IV was saponified under reflux with a solution of 12 g. (0.2 mole) of potassium hydroxide in 95 ml. of ethylene glycol for 72 hr. After dilution with water, washing with ether and boiling to expel volatile compounds, the solution was acidified and the acid extracted with ether. After removal of the ether, the crude liquid acid (7.6 g.) was heated under reflux with acetyl chloride (20 ml.) for 4 hr. The excess of acetyl chloride was removed and the residue distilled to give 3 g. of a colorless oil, b.p. 116°/0.5 mm., n_D^{25} 1.4635.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; sap. equiv., 106.2. Found: C, 68.00; H, 9.41; sap. equiv. 107.3.

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(40) Cuprous chloride was prepared by heating under reflux with copper-metal a solution of commercial cuprous chloride in hydrochloric acid, isolation of the cuprous chloride in the conventional way, drying and storing *in vacuo* over phosphorus pentoxide and sodium hydroxide, applying dry nitrogen whenever the vacuum was released.

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

Some Reactions Effected by Means of Bromomagnesium *t*-Alkoxides[1]

J. L. GUTHRIE[2] AND NORMAN RABJOHN

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It has been found that tribenzoylmethane results in about 10% yield when methyl ketones are caused to react with benzoyl chloride in the presence of bromomagnesium *t*-alkoxides. Bromomagnesium *t*-butoxide has been shown to be effective in bringing about some carbonyl condensations with methyl ketones.

In an attempt to prepare benzoates directly by the action of benzoyl chloride on the reaction mixtures obtained from methyl ketones and Grignard reagents, it was observed[3] that a small amount of a high-melting aromatic compound was formed in several cases. In the present investigation this material has been shown to be tribenzoylmethane.

A detailed study of the reaction product obtained from the treatment of the complex from *n*-dodecylmagnesium bromide and methyl *n*-hexyl ketone with benzoyl chloride afforded 7–18% of tribenzoylmethane, an olefin which might have been produced by the dehydration of methyl-*n*-hexyl-*n*-

(1) Presented, in part, at the 128th Meeting of the AMERICAN CHEMICAL SOCIETY, Minneapolis, Minn., Sept. 11–16, 1955.

(2) Abstracted from the Ph.D. thesis of J. L. Guthrie, 1956.

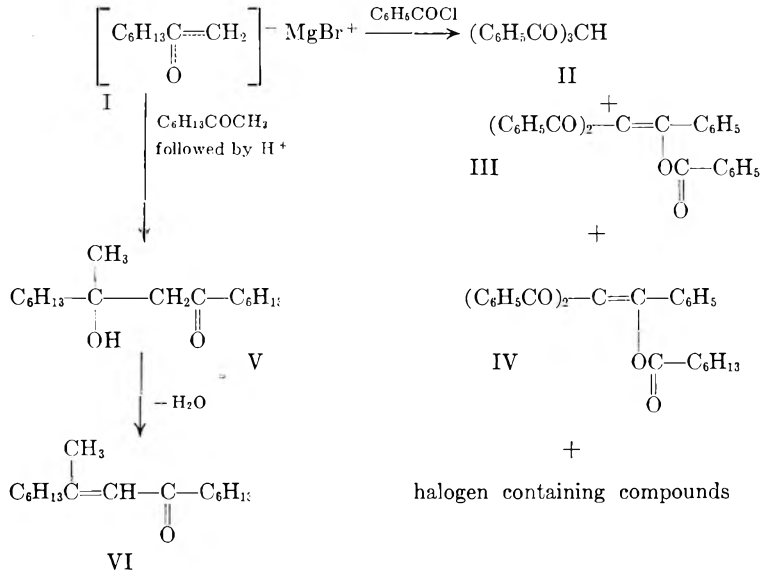
(3) These experiments were carried out by G. R. Collins.

dodecylcarbinol, the enol enanthate of tribenzoylmethane and unidentified halogen-containing compounds. In addition, there were isolated unchanged methyl *n*-hexyl ketone, benzoic acid, *n*-tetracosane and much tarry material which could neither be distilled nor induced to crystallize.

These results suggested that the bromomagnesium alkoxide had served as the condensing agent which had brought about the benzoylation of the methyl *n*-hexyl ketone. Accordingly, the latter ketone was treated then with the simpler alkoxide, bromomagnesium *t*-butoxide, and the resulting enolate (I) was caused to react with benzoyl chloride. The reaction mixture was separated to give tribenzoylmethane (II) in 7–15% yields, the enol benzoate of tribenzoylmethane (III), the enol enanthate of tribenzoylmethane (IV), a 16-carbon α,β-unsaturated ketone (VI), which apparently came from the ketol (V), and unidentified halogen-containing compounds.

Although the mechanism for the formation of tribenzoylmethane from methyl ketones was not determined, it seems reasonable to believe that the bromomagnesium enolates of the methyl ketones suffer benzoylation. Kohler, Tishler, and Potter[4] have benzoylated the magnesium bromide derivatives of a series of selected ketones and observed the formation of diketones in varying yields, with the remainder of the product being composed mainly of benzoates representing O-acylation. Also, Freer and Lachman[5] have reported the mono- and dibenzoylation of acetophenone and methyl *n*-propyl ketone in the presence of sodium ethoxide. However, neither of these groups of investigators apparently observed the formation of tribenzoylmethane.

The formation of the α,β-unsaturated ketone (VI), presumably through an aldol type condensation similar to those first reported by Grignard[6] as being effected by halomagnesium alcoholates and



In order to test the generality of the benzoylation reaction, a number of other methyl ketones were treated with bromomagnesium *t*-butoxide, followed by benzoyl chloride. Acetone, methyl ethyl ketone, and methyl β-phenethyl ketone were converted to tribenzoylmethane in yields of 9.8%, 1.2%, and 9.7%, respectively. Under similar conditions, ethyl *n*-butyl ketone failed to produce any tribenzoylmethane. Acetophenone gave 6.7% of tribenzoylmethane together with 24% of tribenzoylmethane enol benzoate and 2.7% of dibenzoylmethane.

The low yields of tribenzoylmethane obtained from the methyl ketones were due in part, at least, to the decomposition of the ketone enolates by the acid liberated during the course of the benzoylation reaction. However, the addition of basic reagents to the reaction mixtures produced no improvements, and substances such as triethylamine, magnesium carbonate, and powdered magnesium caused the reaction to fail.

Grignard reagents, suggested that the bromomagnesium enolates, such as I, might be capable of undergoing other reactions like those described by Fuson, Fugate,, and Fisher[7] for the bromomagnesium enolates of hindered carbonyl compounds.

It was found that the enolates of several methyl ketones, prepared by treating the latter with bromomagnesium *t*-butoxide, reacted readily with carbonyl compounds, but poorly or not at all with acetyl chloride, carbon dioxide, ethyl carbonate, or ethyl benzoate, under the conditions employed. The results of the successful carbonyl reactions, the

(4) Kohler, Tishler, and Potter, *J. Am. Chem. Soc.*, **57**, 2517 (1935).

(5) Freer and Lachman, *Am. Chem. J.*, **19**, 881 (1897).

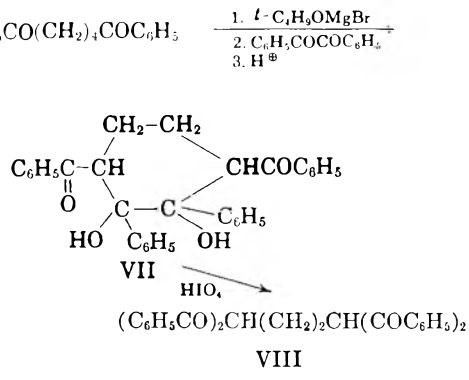
(6) Grignard, *Ann. chim. et phys.* [7], **24**, 433 (1901); see also, Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 176.

(7) Fuson, Fugate, and Fisher, *J. Am. Chem. Soc.*, **61**, 2362 (1939).

products of which were isolated as α,β-unsaturated ketones, are tabulated below.

Enolate	Addendum	Yield of α,β-Unsaturated Ketone, %
Methyl *n*-hexyl ketone	Methyl *n*-hexyl ketone	65
Acetophenone	Benzaldehyde	60
Acetophenone	Acetophenone	72
Acetomesitylene	Benzaldehyde	75

More recently, Fuson and Hill[8] have reported that the dienolate of 1,4-dimesitoylbutane undergoes condensation with benzil to form 1,4-dimesitoyl-2,3-dihydroxy-2,3-diphenylcyclohexane. In the present work it has been found that a similar type of reaction can be effected between the unhindered diketone, 1,4-dibenzoylbutane, and benzil by means of bromomagnesium *t*-butoxide. The cyclohexane derivative (VII) was cleaved with periodic acid to produce 1,1,4,4-tetrabenzoylbutane (VIII).



EXPERIMENTAL[9]

Preparation of the enolate of methyl n-hexyl ketone (I). A solution of ethylmagnesium bromide was prepared from 48.6 g. (2 gram-atoms) of magnesium, 240 g. (2.2 moles) of ethyl bromide, and 500 ml. of anhydrous ether. This was stirred while 149 g. (2 moles) of *t*-butyl alcohol, in an equal volume of anhydrous ether, was added slowly. After all of the alcohol had been added, the alkoxide suspension was stirred vigorously for about 30 min., and 257 g. (2 moles) of methyl *n*-hexyl ketone, in an equal volume of dry ether, was introduced quite rapidly. The precipitate of alkoxide disappeared and a slightly yellowish brown enolate solution resulted. It was allowed to stand for 1 hr. before being used.

Benzoylation of enolate I. A solution of 844 g. (6 moles) of benzoyl chloride, in 500 ml. of absolute ether, was added quite rapidly with stirring to a solution of 2 moles of the enolate. The reaction mixture warmed spontaneously so that the solvent refluxed at a steady rate and a precipitate formed gradually. Stirring was continued for 14 hr. and the mixture was allowed to stand for an additional 16 hr. at which time it was poured into 6 l. of water. It was allowed to stand for 4 hr. with occasional stirring and the precipitate was removed by filtration. There was obtained 30.3 g. of a white solid which melted at 226–231° after one crystallization from benzene. It was shown to be tribenzoylmethane on the basis of its physical and chemical properties and it caused no depression of the melting point of an authentic sample of tribenzoylmethane which had been prepared by the method of Claisen.[10] The filtrate was separated and the water layer was extracted several times with ether. The water layer was distilled until the temperature of the vapor reached 110°, and the distillate was examined but contained no organic compounds. The residue from the distillation was evaporated to dryness and 417 g. of magnesium salts resulted.

The ether layer and extracts were combined and the ether was removed. The residue was distilled at 15 mm. and a fraction was collected to 115°. This was refluxed for 4 hr. with 500 ml. of 3% sodium hydroxide solution and worked up to give 104 g. of methyl *n*-hexyl ketone, n_D^{20} 1.4135, and 3.3 g. of benzoic acid.

The residue from the distillation was stirred for 24 hr. with 2 l. of 12% sodium hydroxide solution, filtered, and 9 g. of tribenzoylmethane was recovered. The filtrate was diluted with ether, separated, and the alkaline solution was acidified with concentrated hydrochloric acid. It was made basic with sodium carbonate and an additional 32.6 g. of tribenzoylmethane precipitated. The basic solution was acidified, the precipitated benzoic acid was removed, and the filtrate was examined but no other compounds could be found.

The organic layer was concentrated and then distilled at 3 mm. to yield 142 g. of material, b.p. 72–155°, and 60 g. of residue. The distillate contained halogen which was removed by boiling with 10% sodium hydroxide solution and finally with 5% alcoholic silver nitrate solution. It was separated into a number of ill-defined fractions which were not identified, but were thought to contain the benzoate of the ketol (V).

The residue (60 g.) was dissolved in a mixture of acetone and petroleum ether (b.p. 60–68°) and after 4 days in a refrigerator, 4 g. of a tan solid precipitated; m.p., 114–116°. After three recrystallizations from aqueous alcohol it melted at 118–120° and did not depress the melting point of an authentic sample of the enol enanthate of tribenzoylmethane (IV). The filtrate was concentrated and distilled at 1 mm. to give a number of wide boiling fractions. The only identifiable materials were benzoic acid and a further 1.3 g. of tribenzoylmethane.

Several experiments similar to the above were performed, but with slight modifications. In general, the results were the same with two exceptions. In the first, a liquid was isolated in three instances which appeared to be a mixture of the ketol (V) and the unsaturated ketone (VI). A sample of this material was distilled from solid sodium carbonate to give 9-methyl-8-pentadecene-7-one (VI); b.p., 118–120°/1 mm., n_D^{20} 1.4562. The ultraviolet absorption spectrum of this material in absolute alcohol showed a maximum at 233 mμ which is in agreement with the findings of Woodward[11] in regard to the spectra of α,β-unsaturated ketones.

In another experiment, there was obtained a 7.3% yield of tribenzoylmethane enol benzoate (III), (m.p. 120–121°) along with 13.8% of tribenzoylmethane. This benzoate was identified by a mixed melting point determination with an authentic sample which was prepared by the benzoylation of tribenzoylmethane with benzoyl chloride in pyridine solution.[10]

Benzoylation of the enolates of other ketones. The enolates were prepared, in the manner indicated previously, from the ketones and bromomagnesium *t*-butoxide, and were benzoylated on a much smaller scale than that of the previous experiment. In most cases the experiments were performed in a cursory fashion and the products of the reactions, other than tribenzoylmethane, were not examined in any detail. The yields of tribenzoylmethane isolated, based on ketone, were: acetone, 9.8%; methyl ethyl ketone, 1.2%;

(8) Fuson and Hill, *J. Org. Chem.*, 19, 1575 (1954).

(9) All melting points are uncorrected. The authors are indebted to R. E. Bolin and R. E. Elliott for the semimicro carbon and hydrogen analytical data.

(10) Claisen, *Ann.*, 291, 90 (1896).

(11) Woodward, *J. Am. Chem. Soc.*, 63, 1123 (1941).

and methyl β-phenethyl ketone, 9.7%. Acetophenone gave 6.7% of tribenzoylmethane, 24.6% of tribenzoylmethane enol benzoate, and 2.7% of dibenzoylmethane.

A compound, b.p. 185–187°/1 mm., n_D^{20} 1.5638, was isolated from the benozylation of methyl β-phenylethyl ketone and appeared to be an α,β-unsaturated ketone formed by dimerization and subsequent dehydration.

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.47; H, 8.14.

Preparation of tribenzoylmethane enol enanthate (IV). To a solution of 20 g. (0.06 mole) of tribenzoylmethane in 100 ml. of dry pyridine was added 18 g. (0.12 mole) of enanthyl chloride. The mixture was allowed to stand for 2 days, was diluted with an equal volume of ether, and filtered. The filtrate was washed with 10% hydrochloric acid, 10% sodium carbonate solution, and water and was dried over anhydrous sodium sulfate. After removing the ether, the oil was distilled until 11 g. of material was collected at 115–160°/2 mm. The residue (21 g.) was dissolved in cyclohexane, and after standing for several days in a refrigerator, there was precipitated 3.4 g. of a tan solid; m.p. 114–116°. It was recrystallized several times from aqueous alcohol and melted at 118–120°.

Anal. Calcd. for $C_{29}H_{28}O_4$: C, 79.07; H, 6.41. Found: C, 79.15; H, 6.70.

The infrared absorption spectrum indicated that O-acylation had occurred.

Reaction of enolate I with methyl n-hexyl ketone. To a solution of 0.5 mole of the enolate in about 300 ml. of ether was added 64.2 g. (0.5 mole) of methyl *n*-hexyl ketone and the mixture was refluxed for 1 hr. After standing overnight, it was decomposed by pouring onto ice and hydrochloric acid. The ether layer was worked up in the usual fashion to give 42.6 g. of unreacted methyl *n*-hexyl ketone and 75 g. of a liquid which boiled at 118–125°/1 mm. A portion (37 g.) of this product was heated for 6 hr. with 1.5 g. of 50% sulfuric acid. It was diluted with ether, washed, dried, concentrated, and distilled to produce 9-methyl-8-pentadecene-7-one (VI) in good yield; b.p. 118–119°/1 mm., n_D^{20} 1.4563.

Anal. Calcd. for $C_{16}H_{30}O$: C, 80.60; H, 12.68. Found: C, 80.38; H, 12.71.

Reaction of the bromomagnesium enolate of acetophenone with benzaldehyde. To a 0.1-molar suspension of magnesium *t*-butoxide in ether was added at once 12 g. (0.1 mole) of acetophenone. The enolate, which appeared as a dense, yellow insoluble oil, was stirred for 1 hr. before 10.6 g. (0.1 mole) of freshly distilled benzaldehyde was added. The reaction mixture was heated at reflux for 13 hr., hydrolyzed with dilute acid, washed, dried, and distilled. There was obtained 12.1 g. (58%) of benzalacetophenone, b.p. 165–170°/2 mm., which melted at 53–55° after one crystallization from ethanol; lit.[12] m.p. 55–57°.

Preparation of dypnone. The bromomagnesium enolate of acetophenone was prepared on a 0.1-molar scale and, after being stirred for 1 hr., an additional 12 g. (0.1 mole) of acetophenone was added. The mixture was stirred for 30 min., 100 ml. of xylene was added, and the ether was removed by distillation until the temperature of the vapors reached 45°. The residue was heated at reflux for 11 hr., hydrolyzed, and purified in the usual way. There was obtained 16.1 g. (72%) of dypnone which boiled at 175–180°/1 mm.; n_D^{20} 1.6312; lit.[13], b.p. 225°/22 mm.

Reaction of the bromomagnesium enolate of acetomesitylene with benzaldehyde. The bromomagnesium enolate was prepared on a 0.1-molar scale and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde was added. The mixture was stirred at room temperature for 3 hr. and then heated at reflux for 3 hr. After hydrolysis, there was obtained 19 g. (75%) of benzalacetomesitylene; b.p. 177–180°/2 mm.; lit.[7], b.p. 215–221°/16 mm.

Preparation of 1,4-dibenzoyl-2,3-dihydroxy-2,3-diphenylcyclohexane (VII). The dienolate was prepared from 0.1 mole of bromomagnesium *t*-butoxide and a solution of 13.3 g. (0.05 mole) of 1,4-dibenzoylbutane in 200 ml. of dry benzene. The mixture was distilled until the ether from the butoxide solution had been removed and the residue was heated at reflux for 1 hr. A solution of 10.5 g. (0.05 mole) of benzil, dissolved in the minimum amount of benzene, was added at once and the mixture was caused to reflux for 5 hr. It was hydrolyzed by means of dilute hydrochloric acid and the organic layer was concentrated to give 12.9 g. of a solid which melted at 220–230°. Several recrystallizations of this material from 95% alcohol gave 7.4 g. (31%) of a white solid; m.p. 231–232°.

Anal. Calcd. for $C_{32}H_{28}O_4$: C, 80.64; H, 5.92. Found: C, 80.58; H, 5.91.

Preparation of 1,1,4,4-tetrabenzoylbutane (VIII). To a solution of 0.5 g. of VII in 50 ml. of purified dioxane was added a solution of 0.55 g. of periodic acid dihydrate in 20 ml. of dioxane and 6 ml. of water. The mixture was heated at reflux for 7 hr., concentrated to about one-half volume, cooled, and filtered. The filtrate was diluted with ether and washed with water, 10% sodium carbonate solution, and water and was dried over anhydrous sodium sulfate. The ether solution was concentrated and there was obtained 0.5 g. of a white solid; m.p., 175–180°. This was recrystallized three times from 95% alcohol and the product melted at 184–185°.

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 80.70; H, 5.56.

COLUMBIA, MO.

(12) Kohler and Chadwell, *Org. Syntheses*, Coll. Vol. I, 78 (1941).

(13) Heilbron, *Dictionary of Organic Compounds*, Eyre and Spottiswoode, London, 1934, Vol. I, p. 668.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE]

A Series of ω-Trimethylammoniumalkylphosphonic Acids and Their Diethyl Ester Iodides[1]

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A series of ω-trimethylammoniumalkylphosphonic acids, $(CH_3)_3N^+(CH_2)_nPO(OH)O^-$ (n = 1, 2, and 3), and of the iodides of their diethyl esters $I^-(CH_3)_3N^+(CH_2)_nPO(OEt)_2$ have been prepared. These compounds are analogs of naturally occurring choline esters and trimethylammoniumalkylcarboxylic acids. As such they may serve as alternate substrates or as inhibitors involving the natural metabolites.

A number of substituted trimethylammonium compounds play important metabolic roles in the living organism. Prominent among these substances are certain betaines of trimethylammoniumalkylcarboxylic acids, choline, and certain of its esters. The structures of some well known illustrative members of these classes of compounds are given in Table I together with a brief statement as to their physiological function.

TABLE I

BETAINES OF TRIMETHYLAMMONIUMALKYLCARBOXYLIC ACIDS

Common Name	Structure	Physiological Function
Betaine	$(CH_3)_3N^+CH_2COO^-$	Transmethylation in the living organism[2]
Carnitine (Vitamin B_T)	$(CH_3)_3N^+CH_2CHOHCH_2COO^-$	A growth factor for certain lower organisms.[3] Present in higher animals but metabolic function not established
	ESTERS OF CHOLINE	
Acetylcholine	$(CH_3)_3N^+CH_2CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3$	Functions in transmission of nerve impulse in the living organism[2]
Phosphorylcholine	$(CH_3)_3N^+CH_2CH_2OPO(OH)_2$	An intermediate in the biosynthesis of lecithin in the living organism[4]

A great many trialkylammonium derivatives, which may be viewed as analogs of compounds of this type, have been shown to possess physiological and pharmacological activity. Trialkylammonium analogs of acetylcholine have been therapeutically useful in *myasthemia gravis*, as miotics and as ganglionic blocking agents.[5] The sulfonic acid analog and the triethylammonium analog of carnitine have weak carnitine-like activity while the deoxy analog is an antagonist of the parent metabolite.[3]

The present paper describes the preparation of a series of ω-trimethylammoniumalkylphosphonic

$$\underset{\text{I}}{(CH_3)_3N^+(CH_2)_nPO(OH)O^-} \qquad \underset{\text{II}}{I^-(CH_3)_3N^+(CH_2)_nPO(OEt)_2}$$

acid betaines (I, n = 1, 2, and 3) and of the iodides of their diethyl esters (II, n = 1, 2 and 3).[7,8] The betaines are designed as phosphonic acid analogs of the natural trimethylammoniumalkylcarboxylic acid betaines and of the natural phosphoric acid esters of choline. The series of esters

(1) Supported by a grant from the Graduate Research Committee, University of Illinois Professional Colleges.

(2) M. R. Everett, *Medical Biochemistry*, Paul B. Hoeber, Inc., New York, N. Y., 1948.

(3) P. K. Bhattacharyya, S. Friedman, and G. Fraenkel, *Arch. Biochem. and Biophys.*, **54**, 424 (1955).

(4) E. P. Kennedy and S. B. Weiss, *J. Am. Chem. Soc.*, **77**, 250 (1955).

(5) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The Macmillan Co., New York, N. Y., 1955.

(6) Phosphonic acids have been suggested as analogs of naturally occurring phosphates [G. M. Kosolapoff, *Organophosphorous Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 145–146; S. Preis, T. C. Myers and E. V. Jensen, Abstracts of papers, 123rd meeting, AMERICAN CHEMICAL SOCIETY, (1953)]. Recently B. S. Griffen and A. Burger [*J. Am. Chem. Soc.*, **78**, 2336 (1956)] have prepared D-glucopyranose 6-deoxy-6-phosphonic acid as an analog of the metabolite glucose-6-phosphoric acid.

(7) A single trialkylammoniumphosphonic acid betaine (trimethylammoniumethylphosphonic acid) has been described in the literature [T. Ya. Medved and M. I. Kabachnik, *Bull. acad. sci. U.R.S.S. Classe sci. chim.*, 999–1001, (1953)] and the methiodide of diethyl β-diethylaminoethylphosphonate has been prepared as a derivative of the free amine [G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948)].

represents a new type of analog of acetyl choline.[8,9]

The ester methiodides were prepared from the corresponding amines by the action of methyl iodide in ether solution and were converted to the betaines by hydrolysis with concentrated hydrochloric acid followed by treatment with silver oxide and then with hydrogen sulfide.

The free amines were synthesized as follows: diethyl β-dimethylaminoethylphosphonate and diethyl γ-dimethylaminopropylphosphonate were produced by the action of aqueous dimethylamine on the halides, diethyl β-bromoethylphosphonate[10] and diethyl γ-chloropropylphosphonate (following the general procedure of Kosolapoff for the preparation of diethyl β-diethylaminoethylphosphonate[12]); diethyl dimethylaminomethylphosphonate was obtained from dimethylamine, formaldehyde, and diethyl phosphite by a modification of the method of Fields.[13]

The ester iodides were obtained as hygroscopic, water soluble, crystalline solids; the betaines as crystalline, high melting, hygroscopic solids which titrated as monobasic acids with approximate *p*K's of 5.0, 6.4, and 6.8 for the series in order of increasing molecular weight.

Studies relating to the biological properties of these compounds are in progress.

EXPERIMENTAL[14]

Diethyl dimethylaminomethylphosphonate. To liquid dimethylamine (22.5 g., 0.5 mole) in a flask cooled to 0° in an ice bath, and fitted with a stirrer, a dropping funnel, and an efficient condenser cooled to 0°, there was rapidly added, with stirring, freshly distilled diethyl phosphite (60.0 g., 0.5 mole). No rise in temperature was noted during this addition. To the resulting solution, still in the ice bath, there was added with stirring, 36% formaldehyde (41.5 g., 0.5 mole) at such a rate that controlled spontaneous refluxing occurred. After addition was complete, stirring was continued for an additional 30 min. in the ice bath and then at room temperature for 1 hr. The resulting solution was concentrated at reduced pressure to a viscous yellow liquid which was distilled from a modified Claisen flask with a low take-off arm, at a bath temperature of 200°, and the fraction distilling between 43°/2mm. and 120°/15 mm. was collected. Considerable decomposition occurred during this distillation and considerable high boiling, highly viscous residue remained in the flask. On redistillation, after a low boiling forerun, the product was collected at 72–77°/0.4 mm. (reported,[13] 88°/3.0 mm.) as a water white liquid; $n_D^{24.5}$ 1.4280; yield 18.1 g. (18.5%). This product was redistilled and the fraction of b.p. 70°/0.25 mm. and $n_D^{24.5}$ 1.4281 was analyzed.

Anal. Calcd. for $C_7H_{18}NO_3P$: N, 7.17. Found: N, 7.35.

Diethyl trimethylammoniummethylphosphonate iodide (II, $n = 1$). To a solution of 1.1 g. of diethyl dimethylaminomethylphosphonate in 7 ml. of anhydrous ether, there was added 2.3 g. of methyl iodide in 8 ml. of anhydrous ether, drop by drop, with efficient stirring and careful exclusion of moisture, at 0°. A white solid began to appear after 4 ml. of solution had been added and the mixture, after complete addition, was a thick white slurry. Stirring was continued at room temperature for 1.5 hr. The solid was filtered with careful protection from moisture, washed with anhydrous ether, and dried under vacuum to yield 1.5 g. (70%) of product, m.p. 126–128°; m.p. 128–129° after recrystallization from methanol-ether.

Anal. Calcd. for $C_8H_{21}IN_3OP$: C, 28.49; H, 6.27; I, 37.64; N, 4.15; P, 9.18. Found: C, 28.78; H, 6.27; I, 37.5; N, 4.16; P, 9.13.

Trimethylammoniummethylphosphonic acid betaine (I, ($n = 1$). A solution of 4.0 g. of diethyl trimethylammoniummethylphosphonate iodide (crude) in 20 ml. of concentrated hydrochloric acid was refluxed for 12 hr. and the resulting solution was concentrated at reduced pressure to a yellow solid. Following the procedure of Medved and Kabachnik[7] an excess of freshly prepared silver oxide suspension was added to a solution of the solid in 50 ml. of distilled water and the mixture was allowed to stand at room temperature for 3 hr. with intermittent shaking. The mixture was filtered with suction (Super Cel filter aid), refiltered until clear, and the filtrate was treated with excess hydrogen sulfide. The resulting suspension was concentrated to one third volume on the steam bath at reduced pressure and filtered to give a clear colorless filtrate which was concentrated to a colorless solid, 1.4 g. (76.5%); m.p., after recrystallization from ethanol, 270–272° (reported[4] 267°).

Anal. Calcd. for $C_4H_{12}NO_3P$: Neut. equiv., 153. Found: Neut. equiv., 154 (*p*K *ca.* 5.0).

Diethyl β-dimethylaminoethylphosphonate. A solution of 8.2 g. of diethyl β-bromoethylphosphonate[10] and 32 g. of 25% aqueous dimethylamine was refluxed for 2 hr. and allowed to stand overnight at room temperature. The colorless solution was treated with 20 ml. of 25% aqueous sodium hydroxide and extracted with 100 ml. of benzene. The benzene was dried over sodium sulfate and concentrated at reduced pressure to a yellow oil which on distillation gave 4.1 g. (58.6%) of the ester with almost no forerun or residue; b.p. 75–77°/0.6 mm.; n_D^{25} 1.4331 (reported,[10] b.p. 108–109°/6.0 mm.; n_D^{20} 1.4340).

Anal. Calcd. for $C_8H_{20}NO_3P$: N, 6.69. Found N, 6.87.

Diethyl β-trimethylammoniumethylphosphonate iodide (II, $n = 2$). The free amine (1.8 g.) and methyl iodide (4.0 g.) were allowed to react in ether solution in a manner similar to that described for the preparation of II, $n = 1$. The yield was 2.5 g. (80.6%); m.p. 155–156°, raised to 156–157° on recrystallization from methanol–ethyl acetate.

Anal. Calcd. for $C_9H_{23}INO_3P$: C, 30.77; H, 6.60; I, 36.14; N, 3.98; P, 8.82. Found: C, 30.77; H, 6.74; I, 36.05; N, 3.82; P, 8.5.

β-Trimethylammoniumethylphosphonic acid betaine (I, $n = 2$). Two grams of the ester was hydrolyzed with concentrated hydrochloric acid and the product was isolated in a manner described for the preparation of I, $n = 1$.

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(8) B. E. Smith and A. Burger [*J. Am. Chem. Soc.*, **75**, 5891 (1953)] have prepared a number of dialkylaminoalkyl esters of some phosphonic and phosphinic acids and have demonstrated parasympatholytic activity by the methiodide of β-dimethylaminoethyl diphenylphosphinate.

(9) The phosphonic acid esters (II, $n = 1, 2$, and 3) bear a strong structural resemblance to the "reversed carboxyl" analog of acetylcholine $(CH_3)_3N^+CH_2CH_2C(=O)OCH_3$ of W. B. Bass, F. W. Schuler, R. M. Festherstone, and E. H. Gross [*J. Pharmacol. Exptl. Therap.*, **100**, 465 (1950)] which possesses a high order of muscarinic activity.

(10) A reaction reported by A. N. Pudovic and G. M. Denisova, *Zhur. Obschei. Khim.*, **23**, 263 (1953).

(11) Prepared by the action of sodium diethyl phosphite on trimethylene chlorobromide; with R. Harvey, H. Jacobson, and E. V. Jensen, to be published.

(12) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

(13) E. K. Fields, U. S. Patent **2,635,112** (1953).

(14) Analyses of the free amines were conducted by The Microtech Laboratories of Skokie, Ill.; of the betaines and ester iodides by G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England, and by William Saschek of Chicago, Ill.

Recrystallization from ethanol gave 800 mg. (80%) of the product, which analyzed as the hemihydrate, m.p. 250–252°.

Anal. Calcd. for $C_5H_{14}NO_3P \cdot 1/2\ H_2O$: C, 34.09; H, 8.58; N, 7.95; P, 17.58; Neut. equiv., 176. Found: C, 33.7; H, 8.8; N, 8.19; P, 17.6; Neut. equiv., 174 (*p*K, *ca.* 6.4).

Diethyl γ-trimethylammoniumpropylphosphonate. This compound was prepared as described for the analog II, $n = 2$. The yield from 6.5 g. of diethyl γ-chloropropylphosphonate[11] and 50 ml. of 25% aqueous dimethylamine was 2.2 g. (33%); b.p. 82–84°/0.25 mm., with almost no forerun or residue; $n_D^{25.5}$ 1.4327–1.4325. The product was redistilled and the fraction of b.p. 83°/0.16 mm., and n_D^{26} 1.4340 was analyzed.

Anal. Calcd. for $C_9H_{22}NO_3P$: N, 6.27. Found: N, 6.27.

Diethyl γ-trimethylammoniumpropylphosphonate iodide (II, $n = 3$). This compound was prepared by the procedure described for the analogs II, $n = 1$ and 2, except that special techniques were employed for its isolation because of its extremely hygroscopic nature.

After the reaction (1.8 g. of the free amine and 4.0 g. of methyl iodide in ether solution), the reaction mixture was concentrated under vacuum to a white solid which was washed in the flask by decantation with anhydrous ether with careful protection from moisture. The solid was then dissolved in the reaction vessel in 30 ml. of ethyl acetate from which it precipitated as colorless needles on standing overnight at 0°. This product was centrifuged, washed with anhydrous ether, and dried at high vacuum at room temperature in the centrifuge tube. The yield of colorless extremely hygroscopic needles was 1.8 g. (61%); m.p. 106–110°, raised to 109–111° on recrystallization from ethyl acetate-acetone.

Anal. Calcd. for $C_{10}H_{25}INO_3P$: C, 32.88; H, 6.90; I, 34.75; N, 3.83; P, 8.48. Found: C, 32.5; H, 7.07; I, 34.5; N, 3.40; P, 8.3.

γ-Trimethylammoniumpropylphosphonic acid betaine (I, $n = 3$). The above ester (3.5 g.) was hydrolyzed and the product was isolated in a manner described for the preparation of the analogs I, $n = 1$ and 2, to yield 1.4 g. (80%); m.p. 273–278°, raised to 277–278° on recrystallization from ethanol.

Anal. Calcd. for $C_6H_{16}NO_3P$: C, 39.77; H, 8.90; N, 7.73; P, 17.09; neut. equiv. 181. Found: C, 39.3; H, 8.98; N, 7.74; P, 16.9; neut. equiv. 184 (*p*K, *ca.* 6.8).

CHICAGO 12, ILL.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXXV. Gentrogenin (Botogenin) and Correllogenin, New Sapogenins from *Dioscorea spiculiflora*[2,3,4]

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Two new ketonic sapogenins, gentrogenin (botogenin) and correllogenin, have been isolated from the tubers of *Dioscorea spiculiflora*. Gentrogenin was converted to diosgenin and hecogenin; and correllogenin, to yamogenin and sisalagenin. Accordingly, gentrogenin must be 20α, 22*a*, 25D-, and correllogenin 20α, 22*a*, 25L-spirost-5-en-3β-ol-12-one.

Side chain degradation of gentrogenin gave 5,16-pregnadien-3β-ol-12,20-dione which was converted to 5-pregnen-3β-ol-12,20-dione, allopregnan-3β-ol-12,20-dione, and allopregnan-3,12,20-trione. The properties of gentrogenin, correllogenin and the various pregnene and allopregnane derivatives, differed markedly from values previously presented by Marker for botogenin, neobotogenin, and various side chain degradation product.

Some years ago Marker and Lopez reported the isolation of a new sapogenin from *Dioscorea mexicana* which they called botogenin.[5] It was characterized as 12 keto-diosgenin by conversion to diosgenin and hecogenin. Since such a sapogenin would have been a desirable cortisone precursor, we were alert for it during the screening of a large number of *Dioscorea* species,[6a,b,c] but with negative results. Recently we isolated two isomeric 12 ketonic sapogenins which corresponded in structure to botogenin and neobotogenin.[7] As shown in Table I, the melting points of the new sapogenins and their derivatives were decidedly different from those of the incompletely characterized "botogenin" series. Because of these differences we named the sapogenins gentrogenin (botogenin) and correllogenin.[8a,b]

Gentrogenin and correllogenin were isolated by means of Girard's Reagent T from a crude sapogenin mixture also containing diosgenin and yamogenin. The isomers were best separated by fractional crystallization of their acetates from ethyl

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXXIV, *J. Am. Chem. Soc.*, **78**, 1747 (1956).

(3) A preliminary report has appeared in *J. Am. Chem. Soc.*, **77**, 5196 (1955).

(4) Presented at Delaware Valley Regional meeting, AMERICAN CHEMICAL SOCIETY, Philadelphia, Pa., Feb. 16, 1956; and 129th National Meeting, AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 8–13, 1956.

(5) R. E. Marker and J. Lopez, *J. Am. Chem. Soc.*, **69**, 2397 (1947).

(6) (a) M. E. Wall *et al.*, *J. Am. Pharm. Assoc.*, **43**, 1 (1954). (b) M. E. Wall *et al.*, *J. Am. Pharm. Assoc.*, **43**, 503 (1954). (c) M. E. Wall *et al.*, *J. Am. Pharm. Assoc.*, **44**, 438 (1955).

(7) R. E. Marker, *J. Am. Chem. Soc.*, **71**, 2656 (1949).

(8) (a) These sapogenins were named in honor of Doctors H. S. Gentry and D. S. Correll, Horticultural Crops Research Branch, Agricultural Research Service, United States Department of Agriculture, Beltsville, Md., who obtained the *Dioscorea* samples from which the new sapogenins were obtained. (b) One of the reviewers feels that it was improper to change the earlier name botogenin to gentrogenin since the two sapogenins apparently have the same structure. The other reviewer feels that the renaming was justified. At present we are retaining both names gentrogenin (botogenin) until this issue can be further resolved.

TABLE I

Compound (Reported by Marker[5,7])	Melting Point		Compound
Botogenin	261–263	215–216	Gentrogenin
Botogenin acetate	246–248	227	Gentrogenin acetate
Neobotogenin	246–248	209–211	Correllogenin
Neobotogenin acetate	234	213–214	Correllogenin acetate
I[a] (From botogenin)	226–228	173–175	I[a] (From gentrogenin)
III[b]	205–207	222–223	III[b]
V[c]	262–264	210–212	V[c]

[a] I = 5,16-Pregnadien-3β-ol-12,20-dione 3-acetate. [b] III = 5-Pregnen-3β-ol-12,20-dione 3-acetate. [c] V = Allopregnane-3,12,20-trione.

acetate. In this manner the relatively insoluble gentrogenin acetate was easily separated from correllogenin acetate. Purification of the latter was difficult and was accomplished only by chromatography of the mother liquors from gentrogenin, followed by repeated fractional crystallization.

Gentrogenin and correllogenin were characterized by the reaction sequence shown in Fig. 1. Wolff-Kishner reduction of gentrogenin gave diosgenin, thus establishing all salient features except the location of the carbonyl group. Catalytic hydrogenation of gentrogenin acetate with Adam's catalyst in ether containing 5% acetic acid gave rockogenin acetate which, on oxidation with chromium trioxide-acetic acid, yielded hecogenin. Since the structure of diosgenin was firmly established by Marker,[9] and of hecogenin by Marker[9] and Wagner *et al.*,[9a] gentrogenin may be designated as 20α,22*a*-25D-spirost-5-en-3β-ol-12-one.[10] The infrared spectrum of gentrogenin (*cf.* experimental section) was in accordance with the chemical data, showing the presence of a 12-ketone, nuclear unsaturation, and typical "22*a*" (25D) fingerprint bands.[11a,b]

Wolff-Kishner reduction of correllogenin gave the known yamogenin,[9] thus establishing the compound as a Δ^5-ketonic sapogenin of the 25L series. The infrared spectrum of correllogenin was in accord with these findings and indicated that the carbonyl was probably at C_{12}. Catalytic reduction of correllogenin acetate, followed by oxidation of the intermediate (which was not isolated) gave a compound which, from the method of preparation, infrared spectrum and close resemblance to the recently discovered sisalagenin,[12] we deduce to be the C_{25} epimer of hecogenin. Accordingly, corrello-

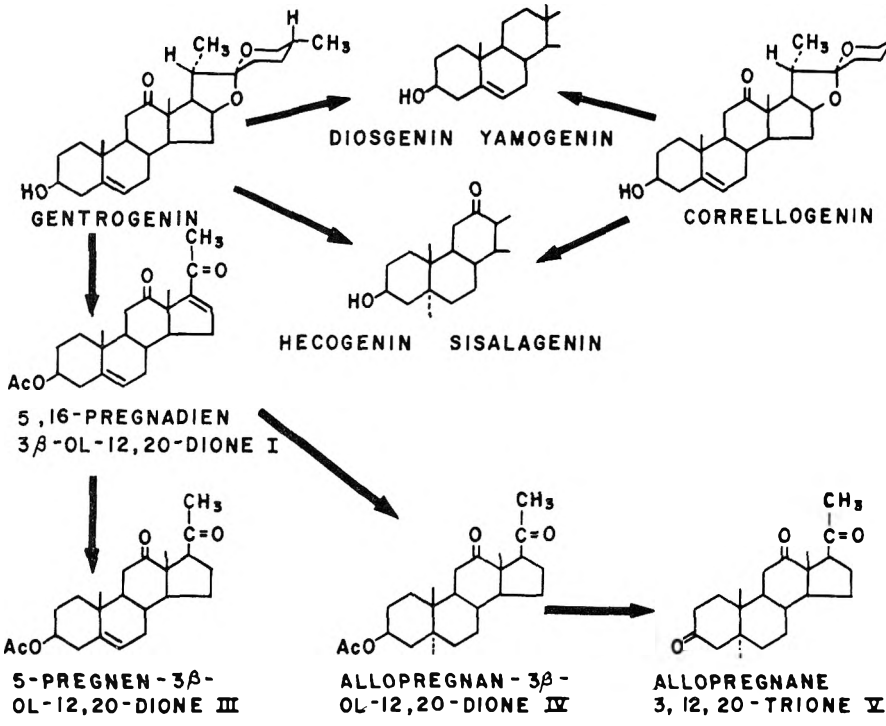


FIG. 1

(9) R. E. Marker *et al.*, *J. Am. Chem. Soc.*, 69, 2167 (1947).

(9a) R. B. Wagner, J. A. Moore, and R. F. Forker, *J. Am. Chem. Soc.*, 72, 1856 (1950).

(10) The stereochemistry of the spiroketal side chain is still in question. Most workers now agree that naturally occurring sapogenins have the 20α- configuration, are identical at C_{22}, and may occur as C_{25} isomers. For leading references see Scheer, Kostic, and Mosettig, *J. Am. Chem. Soc.*, 77, 641 (1955); Ziegler, Rosen, and Shabica, *J. Am. Chem. Soc.*, 77, 1223 (1955); Wall, Serota, and Eddy, *J. Am. Chem. Soc.*, 77, 1230 (1955); Hirschmann, Hirschmann, and Corcoran, *J. Org. Chem.*, 20, 572 (1955); James, *J. Chem. Soc.*, 637 (1955); Callow *et al.*, *J. Chem. Soc.* 1966 (1955); Wall, *Experientia*, 11, 340 (1955).

(11) (a) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, 24, 1337 (1952); (b) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.* 75, 158 (1953).

(12) R. K. Callow and V. H. T. James, *J. Chem. Soc.*, 1671 (1955).

genin must be designated as 20α,22a,25L-spirost-5-en-3β-ol-12-one.

Degradation of the side chain of gentrogenin in our usual manner[13] gave 5,16-pregnadien-3β-ol-12,20-dione 3-acetate (I). The melting point, 173–175°, was about 50° lower than the value reported by Marker.[7] The ultraviolet and infrared spectrum of the compound exhibited the typical hypsochromic shifts noted previously with other 16-dehydro-12,20-pregnenes.[13,14]

Catalytic hydrogenation of I with palladium-barium sulfate gave 5-pregnen-3β-ol-12,20-dione 3-acetate (III), with a melting point considerably higher than the value found by Marker for the same compound (Table I). The infrared spectrum and optical rotation of III was in accord with the assigned structure. Alkaline hydrolysis of I in *t*-butanol gave 5,16-pregnadien-3β-ol-12,20-dione (II). Catalytic hydrogenation in the presence of platinum oxide followed by oxidation with chromium trioxide–pyridine reagent gave allopregnane-3,12,20-trione (V). The properties of V agreed with those described by Wagner, Moore, and Forker.[9a] These workers had noted a 60° discrepancy between the melting points of V prepared by them from hecogenin or desoxycholic acid and V prepared by Marker from hecogenin or botogenin.[7,9] Similar catalytic reduction and oxidation of the 16-dehydropregnene acetate I gave the known allopregnane-3β-ol-12,20-dione 3-acetate (IV) with properties identical to those found previously for the same compound prepared from hecogenin.[13]

Gentrogenin and correllogenin have been found, to date, only in the tubers of *Dioscorea spiculiflora*. This species was found in southern Mexico near the Guatemalan border. The total sapogenin content of several collections has varied from 2–5.5%, dry basis. The ketonic fractions constituted 30–55% of the total sapogenins. Gentrogenin was predominant in this fraction; similarly diosgenin was predominant in the nonketonic fraction, yamogenin being a minor constituent.

We note that sapogenins of the 25L series are of rather infrequent occurrence in nature. It might be reasoned from conformational analysis that 25L sapogenins are less stable than 25D forms (*cf.* references in footnote 10). However, it would seem that specific plant enzyme systems for 25D or 25L configurations must be involved, for in some cases only 25L sapogenins are found.[15]

EXPERIMENTAL

Melting points were obtained with a Kofler micro melting-point apparatus. All optical rotations were determined in chloroform solution. Ultraviolet spectra were obtained in methanol, infrared spectra in carbon disulfide.

Isolation of gentrogenin (botogenin) and correllogenin. Tubers of *Dioscorea spiculiflora*, 21.9 kg., 40% moisture, were ground, extracted with isopropyl alcohol, and the crude sapogenins isolated in our usual manner.[16] The crude sapogenins, 1.0 kg., were refluxed in 5 l. of acetic anhydride. The crystalline but crude sapogenin acetate mixture thus obtained weighed 470 g. It was heated with a mixture of 6 l. of absolute ethanol and 1.2 l. of glacial acetic acid. To the resultant solution was added 150 g. of Girard Reagent T and the mixture refluxed 0.5 hr. The solution was cooled to room temperature and slowly poured over a mixture of 11 kg. of ice and 1.02 kg. of sodium carbonate with continuous stirring. The mixture was diluted with 19 l. of water and extracted with three 10-l. portions of ether, thus removing nonketonic sapogenins. The ether was washed with water and the washings were added to the original aqueous fraction. The aqueous solution was strongly acidified with hydrochloric acid, heated for several hours, and allowed to stand overnight. The ketonic fraction was filtered and washed. After chromatography on Florisil, 45.0 g. of pure ketonic fraction was obtained. Similar chromatography of the nonketonic fraction gave 293 g. of a mixture of diosgenin and yamogenin. Infrared examination indicated that yamogenin was a minor fraction.

Gentrogenin, 20α,22a,25D-spirost-5-en-3β-ol-12-one. The ketonic fraction obtained as described above was dissolved in hot ethyl acetate. The solution was allowed to come slowly to room temperature. Long rods formed which were filtered and crystallized several more times from ethyl acetate to give gentrogenin acetate, m.p. 227°, $[\alpha]_D^{25}$ −56°. The infrared spectrum showed two carbonyl peaks, 1735 cm.$^{-1}$ (acetate), 1712 cm.$^{-1}$ (12-ketone), a weak band at 836 cm.$^{-1}$ (Δ^5 ethylenic band [17a,b]), and the typical "22a"-25D fingerprint spectrum 980 (s), 919 (w), 898 (s), and 863 (w) cm.$^{-1}$.[11a,b]

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.10; H, 9.10.

Hydrolysis of gentrogenin acetate in refluxing methanol containing 5% potassium hydroxide followed by the usual ether work-up, gave gentrogenin, rectangular plates from methanol, m.p. 215–216°, $[\alpha]_D^{25}$ −57°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.46; H, 9.51.

Diosgenin from gentrogenin. One-tenth g. of gentrogenin was submitted to the Huang-Minlon modification of the Wolff-Kishner reaction.[18] After the usual work-up, crystallization from acetone gave 0.08 g. of diosgenin, m.p. 198–200°, infrared spectrum identical to an authentic reference sample.

Rockogenin and hecogenin from gentrogenin. Three-tenths g. of gentrogenin acetate was catalytically hydrogenated at 3 atmospheres pressure with 0.3 g. Adam's catalyst (platinum oxide) in ether containing 5% acetic acid. The product on crystallization from methanol had m.p. 215° with infrared spectrum identical to rockogenin 3-monoacetate prepared by similar reduction of hecogenin acetate. The total reduction product, 0.3 g., consisting of isolated crystals and mother liquors, was taken up in 100 ml. of acetic acid. To this solution, maintained at 25° by a water bath, was added dropwise a solution of 0.3 g. of chromium trioxide in 15 ml. of 80% acetic acid. The mixture was allowed to stand 1 hr. and then was given our usual work-up.[19] Several crystal-

(13) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).

(14) G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *J. Am. Chem. Soc.*, **75**, 4888 (1953).

(15) For example, in *Dioscorea bartlettii* only yamogenin is found. In a number of *Yucca* species, sarsasapogenin is the only sapogenin found.

(16) M. E. Wall, M. M. Krider, E. S. Rothman, and C. R. Eddy, *J. Biol. Chem.*, **198**, 533 (1952).

(17) (a) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951). (b) C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(18) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(19) For details of our work-up procedures, see *J. Am. Chem. Soc.*, **77**, 1230, 5665 (1955).

lizations from methanol gave 0.16 g. of hecogenin acetate, m.p. 245–247°, infrared spectrum identical to an authentic reference sample.

Correllogenin, 20α,22a,25L-spirost-5-en-3β-ol-12-one. The mother liquors from the ethyl acetate crystallization of gentrogenin acetate contained both correllogenin and gentrogenin acetates. Repeated crystallizations from ethyl acetate removed more gentrogenin acetate, leaving the soluble fractions enriched in correllogenin acetate. Chromatography on Florisil and silica gel was not particularly effective but gave a slight enrichment of correllogenin acetate in the more polar eluates. The residues from these treatments were crystallized repeatedly from ethyl acetate–methanol and finally methanol to give correllogenin acetate, needles from methanol, m.p. 213–214°, $[\alpha]_D^{25}$ −60°, infrared spectrum similar to gentrogenin acetate but showed typical 25L fingerprint bands[11a,b], 986 (s), 920 (s), 897 (w), and 852 (w) cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.90; H, 9.18.

Hydrolysis of the acetate gave correllogenin, m.p. 209–211°, $[\alpha]_D^{25}$ −69°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.14; H, 9.63.

Yamogenin from correllogenin. Wolff-Kishner reduction of correllogenin gave yamogenin, m.p. 187–189°, infrared spectrum identical to an authentic specimen.

Sisalagenin from correllogenin. Catalytic hydrogenation of correllogenin acetate followed by chromium trioxide oxidation in the same manner described for gentrogenin gave a product[20] which we believe is the recently isolated sisalagenin acetate,[12] m.p. 214–216°, $[\alpha]_D^{25}$ −12° (lit.[12] gives m.p. 228–232°, $[\alpha]_D^{22}$ −12°), infrared spectrum showed peaks at 1733 (s), 1712 (s), 1071 (s), 1037 (s), 987 (s), 919 (s), 899 (w), 849 (w) cm.$^{-1}$ which were in agreement with data of Callow and James.[12]

5,16-Pregnadien-3β-ol-12,20-dione 3-acetate (I). Eight g. of gentrogenin acetate was refluxed 5 hr. in 40 ml. of acetic anhydride to which was added 1.9 g. of pyridine hydrochloride. The crude pseudogentrogenin diacetate thus obtained was oxidized in our usual manner[13] and the oxidation intermediate treated with potassium hydroxide in *t*-butyl alcohol.[13] After the standard work-up, the product was acetylated and chromatographed on Florisil. Elution with benzene and chloroform followed by crystallization from ether gave 2.3 g. of I, m.p. 170–173°. The analytical sample after 3 ether crystallizations had m.p. 173–175°, $[\alpha]_D^{25}$ +57°, $\lambda_{max.}^{MeOH}$ 227.5 mμ, log ε 3.98; $\nu_{max.}^{CS_2}$ 1737, 1720, and 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.35; H, 8.20.

Alkaline hydrolysis of I in *t*-butyl alcohol–potassium hydroxide gave 5,16-pregnadien-3β-ol-12,20-dione (II), needles from ethyl acetate, m.p. 198–202°, $[\alpha]_D^{25}$ +67.4°.

5-Pregnen-3β-ol-12,20-dione 3-acetate (III). Two-tenths g. of I was dissolved in 100 ml. of ethanol and catalytically hydrogenated in the presence of 0.4 g. of 10% palladium on barium sulfate at 3 atmospheres for 16 hr. After filtration and removal of the ethanol the residue was crystallized from methanol, long rods, m.p. 222–223°, $[\alpha]_D^{25}$ +90.4°, infrared spectrum shows absence of conjugated carbonyl, and presence of two strong carbonyl bands, 1735 cm.$^{-1}$ (acetate), 1710 cm.$^{-1}$ (C_{12} and C_{20} carbonyl).

Allopregnane-3β-ol-12,20-dione 3-acetate (IV). One-tenth g. of I in 47 ml. of ether containing 3 ml. of glacial acetic acid was catalytically hydrogenated in the presence of 0.1 g. of platinum oxide at 3 atmospheres pressure for 16 hr. After the usual work-up, the residual glass was oxidized in chromium trioxide–pyridine.[21] Dilution with water, and ether extraction gave a crude product which was taken up in a small volume of methylene chloride to which was added a large volume of ether. The solution was concentrated on the steam bath. On standing, 30 mg. of crystalline product was obtained, m.p. 190–192° with infrared spectrum identical to an authentic specimen of IV from hecogenin.[13]

Allopregnane-3,12,20-trione (V). Two-tenths g. of II were reduced and oxidized as described under IV. The crude product was chromatographed on Florisil and the benzene and chloroform eluates were combined and triturated with ether. The ether-insoluble residue was crystallized from ethyl acetate as irregular plates, m.p. 210–212° (lit.[9a] gives m.p. 207–208°), infrared spectrum identical with that of an authentic specimen derived from hecogenin.

Acknowledgment. We wish to thank R. F. Mininger for optical rotation data and K. Zbinden for C and H analyses. The infrared spectra were obtained by C. S. Fenske under the supervision of C. R. Eddy.

PHILADELPHIA 18, PENNSYLVANIA

(20) We were unable to obtain enough pure correllogenin acetate to purify adequately the reduction product or obtain analytical data.

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VI.[1] Substituted 3-Azabicyclo[3.2.1]octane Derivatives[2]

LEONARD M. RICE AND CHARLES H. GROGAN

Received July 18, 1956

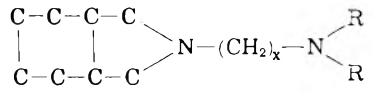
A series of unsymmetrical α,ω-bis-tertiary amines has been prepared in which 3-azabicyclo[3.2.1]octane is employed as one of the bridgehead substituents. The acid addition and bis-quaternary salts of these bases have been prepared and screened for pharmacological activity. These bases were prepared by reaction of d- or dl-camphoric anhydride and the dialkylaminoalkylamines followed by reduction of the resulting imides. Several members of these series were potent hypotensive agents in mammals and were effective when administered orally.

As part of a continuing search for hypotensive agents, many series of symmetrically and unsymmetrically substituted α,ω-bisamines and their acid addition and quaternary salts have been prepared. Among the most active of these substances were members in several series in which various modifi-

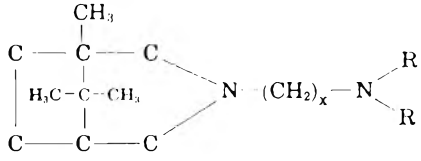
(1) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, 77, 616 (1955).

(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

cations of the isoindole nucleus were employed as one or both of the bridgehead substituents, I.[1,3] In exploring the effects of modifying the heretocyclic nucleus employed as one or both of the terminal substituents, both symmetrically and unsymmetrically substituted series employing the 1,8,8-trimethyl-3-azabicyclo[3.2.1]octane nucleus, II, have been synthesized.



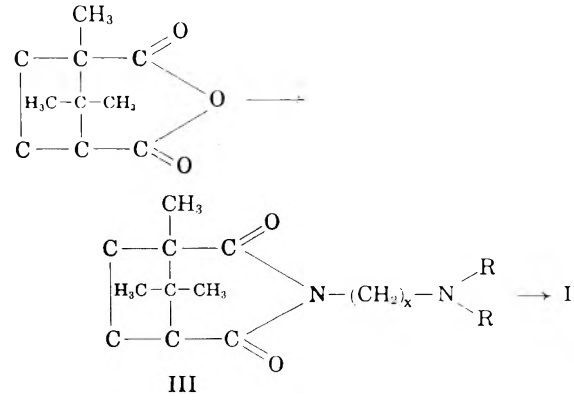
I



II

These compounds were prepared by reacting d- or dl-camphoric anhydride with suitable dialkylaminoalkylamines to obtain the camphorimides, III. Camphorimides in which the N-substituent was dimethylaminoethyl and diethylaminoethyl have been reported by Kurodo and Nishimune[4] and Faust.[5] These imides yielded the base from which the unsymmetrically substituted salts were derived. By reaction with an alkyl amine, such as methyl amine, followed by reduction, a base was obtained which when quaternized with an α,ω-bishalide yielded symmetrically substituted salts.

The reaction was carried out by mixing the anhydride and the appropriate amine in equimolecular amounts and gently heating the partly reacted mass until a clear reaction mixture was obtained. The resulting mixture consisting of camphoramic acid and imide (the latter formed by the heat generated



III

and applied in the reaction) was heated to a temperature of 180° and maintained at that temperature for several hours. Any unreacted camphoramic acid was thus dehydrated and cyclized to the imide by this process.

After allowing the reaction mixture to cool, the material was vacuum distilled and the desired camphorimides were collected in excellent yields in a high state of purity. The imides are tabulated in Table I together with their refractive indices and other pertinent data.

It can be seen that compounds 3 and 4 bear the same substituent on the nitrogen. These two compounds were prepared from d- and dl-camphoric anhydride, respectively, in order to ascertain if one would show an appreciable difference in hypotensive response. In the listed series of compounds it can be seen that the methylene bridging chain between the two nitrogens has from two to five carbon atoms, while the alkyl group attached to the ω-nitrogen has from one to four carbons, or is part of a heterocyclic base such as pyrrolidine or morpholine. The dialkylaminoalkyl camphorimides thus obtained were converted into suitable derivatives, the hydrochlorides and methiodides. The methiodides formed readily and were generally nice crystalline compounds. In Table II are listed the hydrochlorides and methiodides of these compounds.

(3) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

(4) S. Kurodo and K. Nishimune, *J. Pharm. Soc. Japan*, **64**, 160 (1944).

(5) E. S. Faust, U.S. Pat., **1,406,547** (1922).

TABLE I

N-DIALKYLAMINOALKYL CAMPHORIMIDES

N Substitution	Formula	B.P., °C.	Mm.	n_D^{25}	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl[a,b]	$C_{14}H_{24}N_2O_2$	106–108	0.5	1.4895	66.64	66.59	9.59	9.59	11.10	11.45
2. Diethylaminoethyl[a,b]	$C_{16}H_{28}N_2O_2$	114–120	0.2	1.4877	68.54	68.76	10.07	10.38	9.99	10.17
3. Dimethylaminopropyl[b]	$C_{15}H_{26}N_2O_2$	114–119	0.2	1.4893	67.63	67.46	9.84	9.58	10.52	10.31
4. Dimethylaminopropyl[c]	$C_{15}H_{26}N_2O_2$	112–116	0.1	1.4893	67.63	67.38	9.84	9.82	10.52	10.51
5. Diethylaminopropyl[b]	$C_{17}H_{30}N_2O_2$	132–138	0.2	1.4886	69.35	69.65	10.27	10.24	9.52	9.62
6. Diethylaminobutyl[b]	$C_{18}H_{32}N_2O$	137–145	0.4	1.4874	70.09	70.15	10.46	10.58	9.08	8.86
7. Diethylaminoamyl[b]	$C_{19}H_{34}N_2O_2$	157–167	0.4	1.4863	70.76	70.96	10.63	10.66	8.69	8.81
8. Dibutylaminopropyl[b]	$C_{21}H_{38}N_2O_2$	150–155	0.2	1.4880	71.95	72.09	10.93	10.97	7.99	7.88
9. Morpholinoethyl[b]	$C_{16}H_{26}N_2O_3$	138–148	0.3	47–48[d]	65.28	65.57	8.90	9.11	9.52	9.33
10. Pyrrolidinoethyl[b]	$C_{16}H_{26}N_2O_2$	112–115	0.1	1.5028	69.03	69.23	10.06	10.06	9.41	9.40

[a] References (4) and (5). [b] d-Camphoric anhydride as starting material. [c] dl-Camphoric anhydride as starting material. [d] Melting point.

TABLE II

DERIVATIVES OF COMPOUNDS IN TABLE I

Hydrochloride				Methiodide			
		Ionic Chlorine				Ionic Iodine	
Formula	M.p., °C.	Calcd.	Found	Formula	M.p., °C.	Calcd.	Found
1. $C_{14}H_{25}ClN_2O_2$	218.5–219.5	12.28	12.42	$C_{15}H_{27}IN_2O_2$	271–272	32.19	32.41
2. $C_{16}H_{29}ClN_2O$[2]	138.5–139.5[a]	11.19	11.45	$C_{17}H_{31}IN_2O_2$	—	—	—
3. $C_{15}H_{27}ClN_2O$[2]	182–183.5	11.71	11.47	$C_{16}H_{29}IN_2O_2$	283–284	31.08	31.02
4. $C_{15}H_{27}ClN_2O_2$	184–185	11.71	11.87	$C_{16}H_{29}IN_2O_2$	283–284	31.08	31.06
5. $C_{17}H_{31}ClN_2O_2$	139.5–140.5	10.72	11.04	$C_{18}H_{33}IN_2O_2$	177–178	29.08	29.00
6. $C_{18}H_{33}ClN_2O_2$	142–143	10.28	10.16	$C_{19}H_{35}IN_2O_2$	179–180	28.18	27.98
7. $C_{19}H_{35}ClN_2O_2$	162.5–163.5	9.88	9.59	$C_{20}H_{37}IN_2O_2$	162–163	27.33	27.08
8. $C_{21}H_{39}ClN_2O_2$	108–110	9.16	9.38	$C_{22}H_{41}IN_2O_2$	—	25.77	25.63
9. $C_{16}H_{27}ClN_2O_3$	212–213	10.72	10.63	$C_{17}H_{29}IN_2O_3$	252–254	29.09	29.08
10. $C_{16}H_{27}ClN_2O_2$	194–195	11.26	11.44	$C_{17}H_{29}IN_2O_2$	190–191	30.19	30.23

[a] M.p., reported 89–90°C. Reference (5).

The camphorimide bases were next reduced by means of lithium aluminum hydride in ether solution to yield the desired 3-azabicyclooctane bases (II). In all cases, the imides dissolved in anhydrous ether were added to a lithium aluminum hydride solution at such a rate as to just maintain reflux. During the addition of the imide the reaction mixture was stirred vigorously. The addition complex generally precipitated completely, coating the walls of the flask as a metallic-like product. On several occasions the addition product tended to form a hard metallic-like ball which was troublesome, as it would either break the stirrer or stop it. However, outside of these mechanical difficulties the addition proceeded smoothly. After stirring for an additional hour, the reaction mixture was decomposed by the slow dropwise addition of water until the ether ceased to reflux, and the addition complex had completely disappeared. After sufficient water had been added, it was sometimes necessary to continue the stirring for several hours in order to completely decompose the complex which was adhering to the sides of the reaction vessel. The N-dialkylaminoalkyl substituted-1,8,8-trimethyl-3-azabicyclo[3.2.1]-octanes thus prepared were isolated, Table III, as colorless oils by vacuum distillation in 50–65% yields. The products were stable on storage and some samples that have been kept for several years developed only a slight yellow coloration. The reaction was reasonably clean-cut, but judging from the distillation residue, considerable side reaction had occurred or partially reduced material remained. The refractive indices are lower in the bases than in the corresponding imides.

The azabicyclooctane bases were converted into suitable derivatives, hydrochlorides and mono- and dimethiodides. The hydrochlorides formed readily. In contrast to most other series, such as the dialkylaminoalkyl isoindoles, I, the monomethiodides of the azabicyclooctanes formed readily in most cases and in a high state of purity. This particularly was the case when the alkylene chain, between the nitrogens, was four carbons or less. In the isoindole series previously studied this was not generally the case, as the dimethiodide formed very easily. Quaternization of both nitrogens proceeded relatively easily, making isolation of pure monoquaternary salt difficult.

In the cases where the alkylene chain was two or three carbon atoms, the dimethonium salts of the azabicyclooctanes were not formed in appreciable amounts in the usual manner. For example, even on refluxing for several days with an excess of methyl iodide in methanol, there was obtained only a small amount of dimethiodide. This was very surprising, since N-methyl azabicyclooctane (N-methyl cam-

TABLE III

N-DIALKYLAMINOALKYL-1-METHYL-8,8-DIMETHYL-3-AZABICYCLO [3.2.1] OCTANES

				Analyses, %						
				Carbon		Hydrogen		Nitrogen		
N-Substitution	Formula	B.p., °C.	Mm.	Calcd.	Found	Calcd.	Found	Calcd.	Found	n_D^{25}
1. Dimethylaminoethyl	$C_{14}H_{28}N_2$	64–66	0.4	74.94	75.05	12.58	12.44	12.49	12.79	1.4781
2. Dicthylaminoethyl	$C_{16}H_{32}N_2$	70–74	0.1	76.12	76.28	12.78	12.86	11.10	11.28	1.4780
3. Dimethylaminopropyl	$C_{15}H_{30}N_2$	76–80	0.2	75.56	75.21	12.68	12.40	11.75	11.67	1.4772
4. Dimethylaminopropyl	$C_{15}H_{30}N_2$	70–72	0.1	75.56	75.30	12.68	12.30	11.75	11.54	1.4770
5. Diethylaminopropyl	$C_{17}H_{34}N_2$	81–89	0.05	76.62	76.63	12.86	12.73	10.51	10.44	1.4778
6. Diethylaminobutyl	$C_{18}H_{36}N_2$	96–100	0.1	77.07	77.06	12.94	12.92	9.99	9.67	1.4771
7. Diethylaminoamyl	$C_{19}H_{38}N_2$	100–105	0.1	77.48	77.63	13.01	13.10	9.51	9.36	1.4766
8. Dibutylaminopropyl	$C_{21}H_{42}N_2$	106–110	0.1	78.19	77.94	13.12	12.95	8.69	8.23	1.4756
9. Morpholinoethyl	$C_{16}H_{30}N_2O$	102–105	0.1	72.13	71.85	11.35	11.36	10.52	10.31	1.4954
10. Pyrrolidinoethyl	$C_{16}H_{30}N_2$	88–93	0.2	76.74	76.49	12.08	12.42	11.19	10.79	1.4950

phidine) quaternized without difficulty with methylene diiodide and ethylene dibromide to give a bis-quaternary salt. This had not been our experience with the N-methylated isoindole bases.[1] With the N-methyl isoindole bases, only one side of the bis-halide reacted and the product was a β- or γ-halogen alkyl isoindole monoquaternary salt. However, by heating the 3-dialkylaminoalkyl azabicyclooctane bases with an excess of methyl iodide in methanol in a bomb tube at 100°, bis-quaternary salts were readily formed in almost analytically pure state. Table IV shows a compilation of various salts, hydrochlorides, monomethiodides, and dimethiodides which were prepared from the unsymmetrical α,ω-azabicyclooctane bases.

num hydride reduction of N-methyl camphorimide which proceeded in the expected manner with good yield.

Table V shows several members of this type of compound in which the central methylene carbons number from one to six. As was pointed out earlier, it was surprising to have complete quaternization of the N-methyl base as compared to some other series. These symmetrical bis- compounds were quite toxic. Starting with compound number one which has a L.D. 50 in rats of approximately 100 mg./kg. by I.P. injection, there is a steady increase in toxicity to hexamethylene number six.

The compounds were screened for hypotensive activity in dogs by two methods: (a) cannulation of

TABLE IV

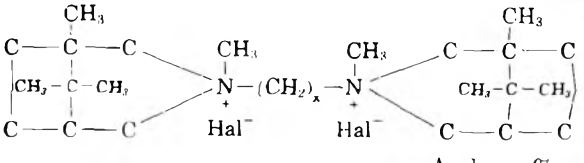
DERIVATIVES OF COMPOUNDS IN TABLE III

	HCl				*Monomethiodide*				Dimethiodide			
		M.p.,	Ionic Chloride			M.p.,	Ionic Iodine			M.p.,	Ionic Iodine	
	Formula	°C.	Calcd.	Found	Formula	°C.	Calcd.	Found	Formula	°C.	Calcd.	Found
1.	$C_{13}H_{30}Cl_2N_2$	263–264	23.85	23.41	$C_{15}H_{31}IN_2$	241	34.65	34.46	$C_{16}H_{34}I_2N_2$	244–245	49.94	50.05
2.	$C_{16}H_{34}Cl_2N_2$	254.5–255.5	21.66	21.77	$C_{17}H_{35}IN_2$	193–194.5	32.18	31.87	$C_{18}H_{38}I_2N_2$	235–236	47.16	47.63
3.	$C_{15}H_{32}Cl_2N_2$	290–291	22.78	22.74	$C_{16}H_{33}IN_2$	237–238	33.37	33.90	$C_{17}H_{36}I_2N_2$	271–273	48.60	48.32
4.	$C_{15}H_{32}Cl_2N_2$	290–291	22.78	22.92	$C_{16}H_{33}IN_2$	237–238	33.37	33.75	$C_{17}H_{36}I_2N_2$	269–271	48.60	48.63
5.	$C_{17}H_{36}Cl_2N_2$	212–214	20.89	20.74	$C_{18}H_{37}IN_2$	196–198	31.07	31.13	$C_{19}H_{40}I_2N_2$	217–219	46.12	45.88
6.	$C_{18}H_{38}Cl_2N_2$	286–286	20.07	19.97	$C_{19}H_{39}IN_2$	172–173	30.04	30.43	$C_{20}H_{42}I_2N_2$	236–237	44.98	44.46
7.	$C_{19}H_{40}Cl_2N_2$	274–275	19.29	19.59	$C_{20}H_{41}IN_2$	—	—	—	$C_{21}H_{44}I_2N_2$	235–236	43.89	44.15
8.	$C_{21}H_{44}Cl_2N_2$	138–140	17.93	17.94	$C_{22}H_{45}IN_2$	—	—	—	$C_{23}H_{48}I_2N_2$	127–130	41.86	41.57
9.	$C_{16}H_{32}Cl_2N_2O$	263–264	20.90	20.72	$C_{17}H_{33}IN_2O$	205–207	31.07	30.94	$C_{18}H_{36}I_2N_2O$	226–228	46.13	45.96
10.	$C_{15}H_{32}Cl_2N_2$	263–265	21.93	22.10	$C_{17}H_{33}IN_2$	224–225	32.35	32.41	$C_{18}H_{36}I_2N_2$	250–251	47.51	47.85

In addition to the above compounds, a series of symmetrical α,ω-bis-azabicyclooctane alkane dimethonium salts were prepared. These were prepared by the reaction of 1,3,8,8-tetramethyl-3-azabicyclo[3.2.1]octane (N-methyl camphidine) with the appropriate α,ω-dihalogenated alkane in a suitable solvent, usually isopropanol, at 100°. The N-methyl camphidine needed for these reactions was conveniently prepared by the lithium alumi-

TABLE V

α,ω-BIS(1,8,8-TRIMETHYL-3-AZABICYCLO[3.2.1]-3-OCTYL)ALKANE METHONIUM IODIDES



			Analyses, %	
		B.P.,	Ionic Iodine	
X	Formula	°C.	Calcd.	Found
1.	$C_{23}H_{44}I_2N_2$	291–294	42.14	41.93
2.	$C_{24}H_{46}Br_2N_2$	200–202	30.59	30.43
3.	$C_{25}H_{48}I_2N_2$	233–235	40.26	40.25
4.	$C_{26}H_{50}I_2N_2$	253–254	39.38	39.52
5.	$C_{27}H_{52}I_2N_2$	255–256	38.55	38.68
6.	$C_{28}H_{54}I_2N_2$	230–231	37.89	37.82

the carotid artery while under Nembutal anesthesia; (b) femoral artery puncture in the intact animal. In the latter method the drugs were administered by I.M., I.V., and oral routes.

When screened in this manner the following information was obtained: The imides as their hydrochloride salts and their methonium salts were inactive. The azabicyclooctane bases as such were inactive as hypotensive agents when tested as their hydrochloride salts except at toxic levels. However, the mono- and bis- quaternary methonium salts were potent as hypotensive agents. In addition to the usual ganglionic blocking, we believe that there is a strong central component of action. In some cases, the hypotensive effect after oral administration or I.M. injection lasted for 26 hr. No difference was noted in response between the d- and dl- form when the ring had a dimethylaminopropyl side chain. In this series it was found that the optimum activity resided in compounds which had 2 to 3 carbons between the nitrogens.

EXPERIMENTAL

N-Methyl camphidine. In a 2-liter 3-necked flask fitted with a mercury sealed stirrer, dropping funnel, and a long condenser to which a calcium chloride tube was attached were placed 19 g. of lithium aluminum hydride and 1 l.

of absolute ether. After all the hydride had dissolved, a solution of 50 g. of N-methyl camphorimide in 500 ml. of absolute ether was added dropwise with rapid stirring. The rate of addition was adjusted so that the mixture refluxed gently. During the addition a fine suspension of the complex precipitated. After the addition was completed, the stirring was continued for several hours and the mixture allowed to stand overnight. The flask was cooled in an ice bath and, with vigorous stirring, the reaction mixture was decomposed by the dropwise addition of water. The addition of water was regulated so that reflux was just maintained and then 10 cc. in excess was added at the end. After decomposition, the mixture was stirred an additional hour and filtered with suction. The inorganic precipitate was well pressed and washed with three portions of ether. After drying over sodium sulfate, the ether was stripped and the residue distilled under reduced pressure. There was obtained 36 g. of material boiling at 99–102° at 38 mm. (68° at 10 mm.) n_D^{25} 1.4776.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.98; H, 12.65; N, 8.37. Found: C, 79.39; H, 12.52; N, 8.45.

The methiodide was prepared by heating with a slight excess of methyl iodide in a bomb tube at 100° for 8 hr. using methanol as a solvent. After recrystallization from methanol-ether the product melted over 300°.

Anal. Calcd. for $C_{12}H_{24}NI$: I, 41.04. Found: I, 40.65.

The hydrochloride was prepared in the usual way by means of alcoholic hydrogen chloride and melted at 226–227° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{11}H_{22}NCl$: Cl, 17.42. Found: Cl, 17.54.

Dialkylaminoalkyl camphorimides. Into a flask fitted with a reflux condenser was placed 0.4 mole of camphoric anhydride. With cooling and intermittent shaking, 0.41 mole of the appropriate dialkylaminoalkylamine was added slowly. After the reaction had subsided, the reaction mixture was heated until a clear homogeneous melt was obtained and then maintained by means of an oil bath at 180° for 2 hr. The resulting crude product was fractionated in vacuum and the pure imide obtained as a colorless oil. (See Table I.)

The hydrochlorides of the above imides were prepared in the usual way by means of alcoholic hydrogen chloride and recrystallized from methanol or isopropanol-ether mixtures.

The methiodides of the above imides were prepared by reaction with methyl iodide in absolute alcohol in the usual way and recrystallized from methanol or isopropanol-ether.

N-Dialkylaminoalkyl-1,8,8-trimethyl-3-azabicyclo-[3.2.1]*-octanes.* These were prepared in a manner analogous to that of the N-methyl camphidine base above. (See Table III.)

The dihydrochlorides and monomethiodides of the N-substituted camphidine bases above were prepared in the usual manner and recrystallized from methanol-ether.

The dimethiodides of these bases were obtained by heating the base in a bomb tube at 100° for 8 hr. with an excess of methyl iodide and were recrystallized from methanol.

α,ω-Bis(1,8,8-trimethyl-3-azabicyclo[3.2.1]-3-octyl)alkane dimethonium salts. (See Table V.)

To 0.06 mole of N-methyl camphidine dissolved in 20 ml. of isopropanol in a bomb tube was added 0.03 mole of the α,ω-dihalogenated alkane. The mixture was allowed to stand at room temperature for 1 hr. and then heated to 100° and maintained at this temperature for an additional 8 hr. The crude product was filtered, washed with alcohol-ether mixture, recrystallized from a mixture of methanol and ethanol, and dried.

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[CONTRIBUTION FROM U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, THE ROBERT A. TAFT SANITARY ENGINEERING CENTER]

Structure of Dactylin

G. E. INGLETT[1]

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Dactylin is shown to be isorhamnetin 3,4′-diglucoside, I.

A flavonoid glycoside, dactylin, was found to occur in pollens of timothy and orchard grass in 1931 by Moore and Moore.[2] This flavonoid glycoside has become of particular importance recently since it was shown by Johnson *et al.*[3] to possess allergenic activity. Whether this activity is associated with the pure dactylin or with impurities in the pigment remains to be established. However, the present studies are concerned only with the structure of dactylin.

Heyl[4] in 1919 isolated a quercetin glucoside as the least soluble flavonoid from ragweed pollen and isorhamnetin by hydrolysis of the more soluble fractions. Since this report, several investigators have reported the presence of flavonoids in pollens.[5–7] Kuhn and Löw[8] have isolated and characterized a flavonoid glycoside of *Crocus Sir John Bright* to be isorhamnetin 3,4′-diglucoside.

Dactylin was obtained as a light yellow solid from a 1955 crop of defatted timothy pollen by alcoholic extraction. It gave only one spot on chromatograms developed in three different solvent systems. Methoxyl content was 3.60%, and the dactylin aglycone, obtained by 2*N* sulfuric acid hydrolysis of dactylin, revealed 6.93% methoxyl content. Infrared spectra, ultraviolet spectra, and melting point data revealed the aglycone to be impure isorhamnetin. Acetylation of dactylin aglycone

(1) Present address, Box 345, Corn Products Refining Co., Argo, Ill.

(2) M. B. Moore and E. E. Moore, *J. Am. Chem. Soc.*, **53**, 2744 (1931).

(3) M. C. Johnson, S. F. Hampton, A. W. Schiele, S. Frankel, *J. Allergy*, **25**, 82 (1954).

(4) F. W. Heyl, *J. Am. Chem. Soc.*, **41**, 1285 (1919).

(5) F. A. Stevens, D. Moore, and H. Baer, *J. Allergy*, **22**, 165 (1951).

(6) M. S. El Ridi, L. A. Strait, and M. H. A. Wafa, *Arch. Biochem. and Biophys.*, **39**, 317 (1952).

(7) G. Tappi and E. Menziani, *Gazz. chim. ital.*, **85**, 703 (1955).

(8) R. Kuhn and I. Löw, *Ber.*, **77**, 196 (1944).

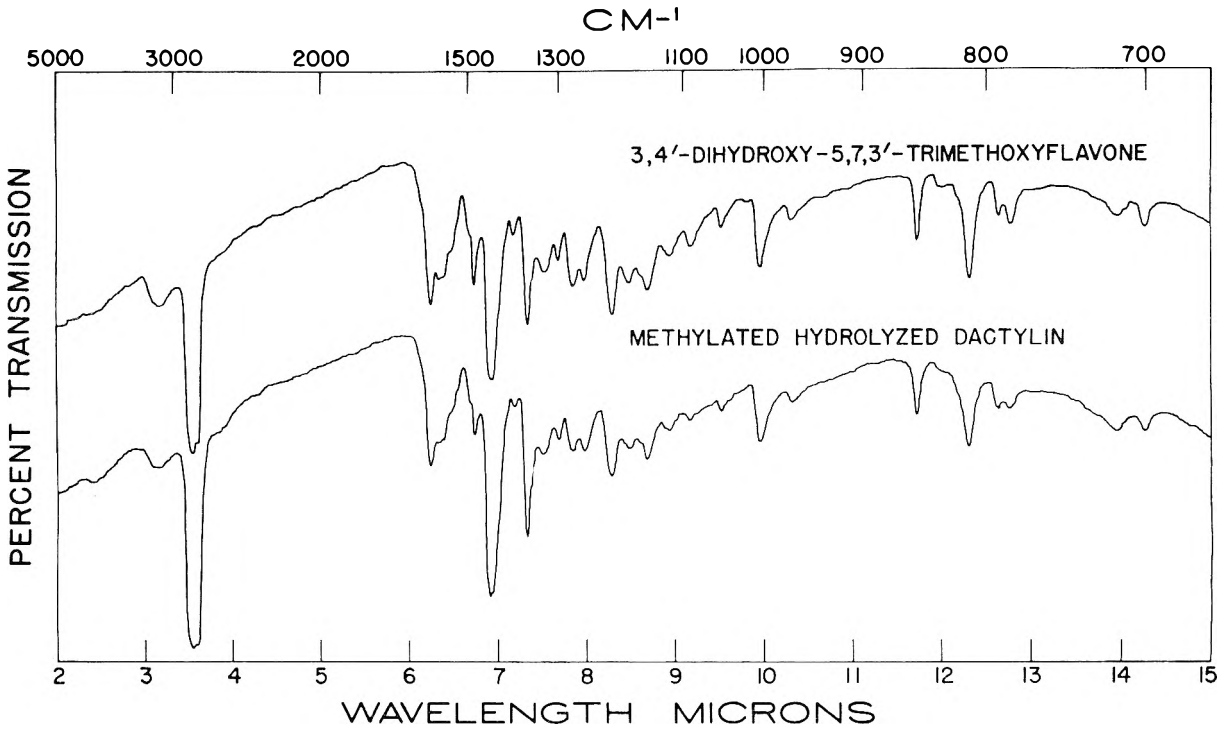
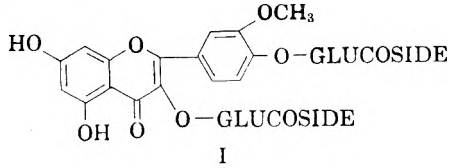


FIG. 1

gave 3,5,7,4'-tetraacetoxy-3'-methoxyflavone that gave an infrared spectrum identical in every respect with a known sample. Methylation of the aglycone with diazomethane gave 3,7,3',4'-tetramethoxy-5-hydroxyflavone that gave an infrared spectrum that was also identical in every respect with a known sample.

When dactylin was methylated and hydrolyzed 3,4'-dihydroxy-5,7,3'-trimethoxyflavone was obtained that was identified by mixed melting point and identical infrared spectrum with a known sample (Fig. 1). The structure of dactylin is, therefore, shown to be isorhamnetin 3,4'-diglucoside (I). It is interesting to note that this compound (I) has the same structure as the one obtained by Kuhn and Löw[8] from the *Crocus Sir John Bright*.



I

EXPERIMENTAL

Dactylin, isolation and properties. A 50 g. sample of timothy pollen (*Phleum pratense*)[9] from a 1955 crop was extracted continuously in a Soxhlet with chloroform for 3 hr. The thimble containing the defatted pollen was dried in the air, and afterward it was extracted continuously with 95% ethanol for 24 hr. The yellow alcoholic solution was evaporated to an oily residue on a steam bath. To the residue 25 ml. of acetone was added, the solution was heated to a boil and decanted, and this process repeated twice more. The remaining gummy residue was dissolved in 10–15 ml. of water on heating to a boil. The solution was filtered and cooled. On storing at 2° for several weeks, crystallization occurred. The crystalline material was collected on a filter and dried, 0.384 g. It was recrystallized from water to give a light yellow solid, 150 mg., m. p. 187–190°. For a 1:1 mixture of $C_{27}H_{30}O_{17}\cdot H_2O$ with $C_{28}H_{32}O_{17}$ the following calculations are given.

Anal. Calcd. for $C_{27}H_{30}O_{17}\cdot H_2O$ with $C_{28}H_{32}O_{17}$: C, 51.38; H, 5.02; OCH_3, 2.41. Found: C, 50.61; H, 5.73; OCH_3, 3.60.

Moore and Moore did not report methoxyl determination of their dactylin samples from orchard grass (*Dactylis glomerata* L.) or timothy pollens, but their carbon and hydrogen analyses agreed with our sample as well as the other general properties of the flavonoid glycoside. Kuhn's[8] flavonoid glycoside, isorhamnetin-3,4'-diglucoside, isolated from the pollen of *Crocus Sir John Bright* had practically the same empirical formula.

Paper chromatography of timothy pollen extracts revealed dactylin to be the major flavonoid glycoside with R_F values of 0.48 and 0.24 in *n*-butyl alcohol–acetic acid–water (8–2–5) at 26° and *m*-cresol–acetic acid–water (48–2–50) at 20°, respectively. Recrystallized dactylin from these extracts gave R_F values of 0.48, 0.42, 0.36, and 0.24 in *n*-butyl alcohol–acetic acid–water (8–2–5) at 26°, *n*-butyl alcohol–acetic acid–water (4–1–5) at 20°, *n*-butyl alcohol–acetic acid–water (4–1–5) at 26°, and *m*-cresol–acetic acid–water (48–2–50) at 20°, respectively. Dactylin was detected on the papergrams by spraying the dried paper strips with 5% aqueous aluminum chloride and observing the yellow fluorescence spot under ultraviolet light in a dark room. In a similar manner, on spraying the strip with aqueous ammonia, a yellow spot can be observed in the visible and fluorescence in the ultraviolet. Ammoniacal silver nitrate was not reduced by dactylin. In a similar manner, vanillin, 2,4-dihydroxybenzaldehyde, 3-hydroxyflavone, 2,4-dihydroxyacetophenone, 2,4-dihydroxybenzoic acid, hesperidin and arbutin, when spotted on paper and sprayed with ammoniacal silver nitrate, did not show any appreciable reaction with this reagent. However, catechol, 2,6-dimethoxyphenol, rutin, quercetin, and isoquercitrin reduced this reagent

(9) Purchased from the Greer Drug Co., Inc., Lenoir, N. C.

immediately, and reduction with isorhamnetin, phloroglucinol, syringic acid, and resorcinol occurred after several minutes.

The extract of orchard grass revealed the presence of dactylin and another component having R_F values of 0.66 and 0.45 in *n*-butyl alcohol–acetic acid–water (8–2–5) at 26° and *m*-cresol–acetic acid–water (48–2–50) at 20°, respectively. Isoquercitrin from the extract of giant ragweed pollen has the same R_F values in these two solvent systems. Identical R_F values to the ones reported by Bates-Smith[10] for isoquercitrin, quercitrin, quercetin, and rutin were obtained in the two solvent systems used at 20°.

An ultraviolet spectrum of dactylin in water gave λ_{max} 252, 262 and 340 mμ (ϵ = 19600, 20500, 14100, respectively). On adding three drops of 0.1*N* sodium hydroxide to the cell, λ_{max} 273 and 364 mμ (ϵ = 25600 and 11500, respectively) peaks were observed.

Dactylin aglycone (isorhamnetin). A 110-mg. sample of dactylin was hydrolyzed on mixing with 20 ml. of 2*N* hydrochloric acid and refluxed for 20 min. A yellow crystalline solid separated and after cooling was collected on a filter. After drying, 47.7 mg. (43.4% of dactylin) of dactylin aglycone was obtained, m.p. 302–304° (dec.)[11], no sublimation noted. Quercetin obtained from the hydrolysis of rutin gave a melting point of 305–308° with sublimation that appears to be a distinguishing feature. For a 1:1 mixture of $C_{15}H_{10}O_7$ with $C_{16}H_{12}O_7$ the following calculations are given.

Anal. Calcd. for $C_{15}H_{10}O_7$ with $C_{16}H_{12}O_7$: C, 60.18; H, 3.59; OCH_3, 5.01. Found: C, 60.41; H, 4.07; OCH_3, 6.93.

Paper chromatography of the dactylin hydrolysis product gave tailing in the solvent systems used for studying dactylin. The material was detected by spraying the dried strips with 5% aluminum chloride solution and observing fluorescence under ultraviolet light. Quercetin and isorhamnetin give identical behavior on papergrams, but no accurate R_F values could be obtained because of excessive tailing.

Paper chromatography of the dactylin hydrolysis filtrate revealed glucose to be the only sugar present. R_F values of 0.21, 0.26, and 0.62 were observed for dactylin sugar that corresponded to the R_F values of glucose in ethyl acetate–pyridine–water (2–1–2), *n*-butyl alcohol–acetic acid–water (4–1–5), and *n*-butyl alcohol–acetic acid–water (8–2–5) solvent systems at 26°. The sugar was detected using anisidine hydrochloride spray. Moore and Moore identified glucosazone from the hydrolysis of their material after reaction with phenylhydrazine, but this osazone could have been derived from fructose or mannose as well as glucose. A quantitative determination of dactylin sugar using the method of Morris[12] on the filtrate gave 58 mg. (53% of dactylin).

The ultraviolet spectrum of dactylin aglycone in 95% ethanol gave λ_{max} 256 (ϵ = 10200) and λ_{max} 373 (ϵ = 21000). On adding a few drops of 0.1*N* sodium hydroxide to the cell, a spectrum was obtained with λ_{max} 248 (ϵ = 7020) and λ_{max} 324 (ϵ = 16400). Similar ultraviolet spectra for isorhamnetin are reported by Kuhn[8] and Tappi and Menziani[7] for isorhamnetin.

Isolation of dactylin aglycone. An alcoholic extract of 50 g. of timothy pollen as described above was evaporated to a small volume. The resulting oily material was suspended in the *n*-butyl alcohol layer of *n*-butyl alcohol–acetic acid–water (4–1–5) mixture and passed over a cellulose column. The cellulose column was prepared from Whatman cellulose powder (Standard Grade) that had previously been washed with the *n*-butyl alcohol mixture and dried. The column (2 cm. × 28 cm.) was composed of approximately 36 layers. A rapid moving, brown colored layer was the first material to pass from the column in 75 ml. of collected effluent. A light yellow band remained on the column and was removed in the following 75 ml. of solvent. The yellow colored fraction was concentrated to near dryness on a steam bath, and the resulting oil was hydrolyzed in 20 min. with 2*N* sulfuric acid. The resulting solid that separated was collected on a filter and washed with 95% ethanol. On drying, 65 mg. sample of yellow dactylin aglycone was obtained.

Acetylated dactylin aglycone (3,5,7,4′-tetraacetoxy-3′-methoxyflavone). In a centrifuge tube, 2.5 ml. of acetic anhydride, 28 mg. of dactylin aglycone and two drops of pyridine were refluxed for 4 hr. The acetic anhydride, acetic acid, and pyridine were removed under a jet of air. Crystallization occurred when a few drops of absolute ethanol were added to the residue. The solid was recrystallized from absolute ethanol to give a white solid, m.p. 199–201°. A second recrystallization from absolute ethanol–acetone gave a solid with m.p. 204–205°.

A sample of 3,5,7,4′-tetraacetoxy-3′-methoxyflavone was prepared by the acetylation of isorhamnetin in the same manner as described to give a melting point of 209–210°. On admixture of 10% acetylated dactylin aglycone with 3,5,7,4′-tetraacetoxy-3′-methoxyflavone, no depression of melting point was observed. Infrared spectra of the two samples were identical in every respect.

Methylated Dactylin Aglycone (3,7,3′,4′-Tetramethoxy-5-hydroxyflavone). A 65 mg. sample of dactylin aglycone was suspended in 5 ml. of methanol, and approximately 700 mg. of diazomethane from nitrosomethylurea in 25 ml. of ether (dried over potassium hydroxide pellets) was added with shaking. The solution became a brick red color, but after standing stoppered overnight, the solution was light amber. Two drops of glacial acetic acid were added to decompose excess diazomethane. The solution was filtered and evaporated to a syrup. Absolute ethanol was added, and, on allowing to evaporate slowly in the cold to a small volume, yellow crystals separated from the solution. The supernatant was removed by decantation and the crystals were dried under a flow of nitrogen to give 18.3 mg. of yellow solid. A second 15.5 mg. crop of crystals was obtained from the mother liquor. The two crops were combined, m.p. 145–146°. The compound was recrystallized from absolute alcohol to give a white solid, m.p. 146–147°.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.67; H, 5.07; OCH_3, 34.66. Found: C, 64.47; H, 5.35; OCH_3, 36.12.

An infrared spectrum of this compound was found to be identical in every respect with 3,7,3′,4′-tetramethoxy-5-hydroxyflavone.

3,7,3′,4′-Tetramethoxy-5-hydroxyflavone. A 178 mg. sample of doubly recrystallized quercetin (from hydrolyzed rutin) was allowed to react with diazomethane by the usual technique. The 41.6 mg. sample of 3,7,3′,4′-tetramethoxy-5-hydroxyflavone was recrystallized from absolute ethanol to give yellow colored needles, m.p. 159.5°, 25.3 mg.

From the mother liquors a second form[13] of 3,7,3′,4′-tetramethoxy-5-hydroxyflavone was obtained as white pellets. The solid was collected on a filter and washed with absolute ethanol, 30.2 mg., m.p. 145–147°. It was recrystallized from absolute alcohol and the white pellets collected on a filter, m.p. 146–148°.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.67; H, 5.07; OCH_3, 34.66. Found: C, 64.74; H, 5.12; OCH_3, 35.63.

Methylated hydrolyzed dactylin (3,4′-dihydroxy-5,7,3′-trimethoxyflavone). A 93.8 mg. sample of recrystallized dactylin was allowed to react with diazomethane by the usual technique. The material obtained of this reaction was hydrolyzed for 10 min. with 2*N* sulfuric acid to give a bright red colored solution that turned yellow on allowing to stand in a hot water bath. Yellow crystals separated and were collected on a filter and dried, 55 mg. The solid was recrystallized from absolute ethanol by allowing the filtered alcoholic

(10) E. C. Bates-Smith, *Partition Chromatography*, Biochemical Society Symposia No. 3, p. 62, 1950.

(11) Fisher-Johns hot stage was used for taking these melting points. The other melting points were obtained in a capillary and are corrected.

(12) D. L. Morris, *Science*, 107, 254 (1948).

(13) A. S. Gomm and M. Nierenstein, *J. Am. Chem. Soc.*, 53, 4408 (1931).

solution to cool overnight in a refrigerator. The crystalline material was collected on a filter and dried, 23.8 mg., m.p. 205–7°. The material was again recrystallized to give a slightly yellow colored solid, m.p. 205–7°.

Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62.77; H, 4.69. Found: C, 61.94; H, 4.81.

On admixture of methylated hydrolyzed dactylin with 3,4′-dihydroxy-5,7,3′-trimethoxyflavone, no depression of melting point was observed. Infrared spectra of the two samples were identical in every respect as shown in Fig. 1.

Acknowledgment. The author wishes to thank Dr. Richard Kuhn, who graciously supplied samples that allowed a rapid solution to this problem.

CINCINNATI, OHIO

[CONTRIBUTION FROM KAY-FRIES CHEMICALS, INC.]

Preparation of Cytosine

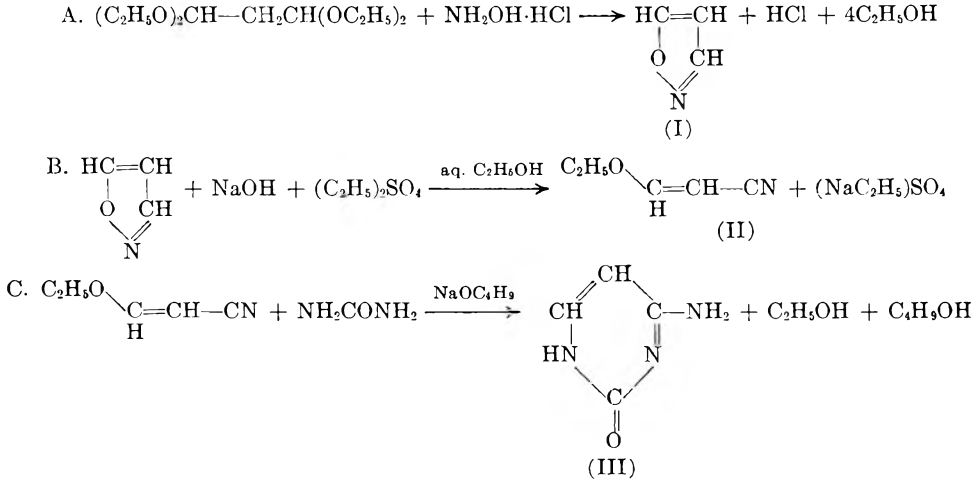
PETER J. TARSIO AND LEONARD NICHOLL

Received July 31, 1956

A new method for the preparation of cytosine is described. Isoxazole is prepared by the reaction of malonaldehyde tetraethyl acetal with hydroxylamine hydrochloride. β-ethoxyacrylonitrile is prepared by reaction of isoxazole with diethyl sulfate in alkaline solution. Cytosine is prepared by condensing β-ethoxyacrylonitrile with urea in a sodium alcoholate solution.

In the development of certain work in this laboratory, cytosine was desired. It therefore became necessary to prepare cytosine in sufficient quantities so that further reactions of it could be studied. The preparation of cytosine from uracil, thiouracel, dithiouracil, and cyanoacetal has been reported.[1–4] The procedures and results obtained by the above methods did not seem suitable for our purposes, since yields are invariably low and the processing of the necessary intermediates is involved and time consuming. Consequently, an alternative method of preparation of cytosine was developed.

This method employed the following sequence of reactions:



Isoxazole (I) was obtained in 70% yield from 1,1,3,3-tetraethoxypropane (malonaldehyde acetal) and hydroxylamine hydrochloride. The reaction of osoxazole with diethyl sulfate and sodium hydroxide to form β-ethoxyacrylonitrile (II) proceeded to give a yield of 85–90% of a mixture of β-ethoxyacrylonitrile and cyanacetaldehyde acetal. The condensation of β-ethoxyacrylonitrile with urea in a refluxing sodium butylate solution resulted in a 43% yield of cytosine (III). All the steps were characterized by the absence of by-products except in the case of β-ethoxyacrylonitrile which invariably contained varying amounts of cyanoacetaldehyde acetal. The β-ethoxyacrylonitrile was obtained substantially pure by dealcoholating a mixture containing the β-ethoxyacrylonitrile and cyanoacetaldehyde acetal with heat at atmospheric pressure.

EXPERIMENTAL

Isoxazole (I). Two hundred twenty grams (1.0 mole) of malonaldehyde tetraethyl acetal prepared by the method of

(1) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930).

(2) D. J. Brown, *J. Soc. Chem. Ind. (London)*, **69**, 353 (1950).

(3) G. Hitchings and P. Russell, *J. Biol. Chem.*, **177**, 357 (1949).

(4) A. Bendich, H. Getler, and G. Brown, *J. Biol. Chem.*, **177**, 565 (1949).

Copenhaver,[5] was added over a 3-hr. period to 76.5 (1.1 moles) of hydroxylamine hydrochloride in 500 ml. water at 60–70°. Heating was continued for an additional hour at 60–70°. The mixture was distilled collecting water, alcohol, and isoxazole to a vapor temperature of 95°.

The distillate was added dropwise to a well stirred saturated solution of an excess of 183 g. cadmium chloride in 150 ml. water. The curdy precipitate that resulted was suction filtered, washed with a little cold water, and sucked as dry as possible. The precipitate was suspended in water and heated to boiling, distilling out a mixture of isoxazole and water. The distillate, which had separated into two phases, was extracted with ether. The ether extract was dried with $CaCl_2$ and distilled. After removal of the ether, there was obtained 49.3 g. (70%) of isoxazole boiling at 93–95°. Speroni and Pino[6] report the boiling point of isoxazole as b_{760} 94.8°.

(Note: A reference to a similar procedure appeared during the preparation of the manuscript.[7])

β-ethoxyacrylonitrile (II). Instead of preparing pure isoxazole for the preparation of β-ethoxyacrylonitrile, it was found advantageous to employ the aqueous alcoholic solution of isoxazole as described under the preparation of isoxazole. Thus, to 561 g. of aqueous alcoholic isoxazole containing 88.5 g. of isoxazole (1.285 moles), determined by alkaline hydrolysis or by isolation with cadmium chloride, was added 570 g. (3.7 moles) of technical diethyl sulfate. The mixture was chilled to 5° with stirring and 606 g. of 24.45% sodium hydroxide (3.7 moles) solution was added over a 4-hr. period, maintaining reaction temperature at 5–10° with the use of an ice bath. Stirring was continued for 2 hr. at 5–10° after the caustic addition. The mixture was slowly warmed up, removing ether and alcohol through a 1.5-ft. packed column. The column was removed and the product removed by steam distillation. The product phase was separated from the aqueous layer, dried with $CaCl_2$ and distilled at reduced pressure. There was obtained 114 g. of product boiling from 80–90° at 12 mm., d_{20}^{20} 0.9463, n_D^{20} 1.4531. Based on nitrogen analysis, the fraction consists of 78.9% β-ethoxyacrylonitrile and 21.1% of cyanoacetaldehyde acetal.

The mixture was heated to boiling at atmospheric pressure until the evolution of alcohol ceased. After removal of residual alcohol under reduced pressure, 108.2 g. β-ethoxyacrylonitrile boiling at 90–91° (19 mm.), d_{20}^{20} 0.9437, n_D^{20} 1.4545, M_D 27.86 (calcd. 27.97) was obtained. Final yield of β-ethoxyacrylonitrile, 86.9% on isoxazole employed. McElvain and Clarke[8] report the following constants for β-ethoxyacrylonitrile b_8 71–72°C, n_D^{25} 1.4520, d_4^{25} 0.945.

Anal. Calcd. for: C_5H_7NO: N, 14.42. Found: N, 14.15.

Cytosine (III). To a cooled solution of 23 g. of sodium (1 g.-atom) in 690 ml. dry butanol, was added 60 g. (1 mole) of dry urea and 97.0 g. (1.0 mole) of β-ethoxyacrylonitrile. The mixture was refluxed (112–115°) for 2 hr. and cooled to 20°. Sulfuric acid (128.0 g.) in 1250 ml. water was added and the mixture was stirred for 0.5 hr. The aqueous layer was separated from the butanol, heated to 80° and 2500 ml. alcohol was added. The mixture was chilled to 0° and the crude cytosine sulfate filtered off. The cytosine sulfate was added to 1 l. of H_2O and alkalized with concentrated ammonium hydroxide until the mixture was slightly alkaline to alkacid paper. The crude cytosine was filtered, added to 1 l. of water, and clarified with charcoal. On cooling there were obtained colorless plates of cytosine. Concentration of the mother liquor yielded an additional amount of cytosine. There was obtained a total of 48.5 g. of cytosine. Yield, 43.7% based on β-ethoxyacrylonitrile employed. Melting point 305° (browns), 319–323° (decomp.) The infrared spectrum of the compound obtained was identical with a known sample of cytosine[9].

Anal. Calcd. for $C_4H_5N_3O$: N, 37.82. Found: N, 37.1.

WEST HAVERSTRAW, N. Y.

(5) U.S. Patent 2,527,533 (Gen. Aniline & Film Corp., Oct. 31, 1950).

(6) G. Speroni and P. Pino, *Proc. XIth Intern. Congr. Pure and Applied Chem. (London)* 2, 311 (1947).

(7) R. Justoni and R. Pessina, *Gazz. chim. ital.*, 85, 34–40 (1955). [*Chem. Abstr.* 50, 4127[d].]

(8) S. McElvain and R. Clarke, *J. Am. Chem. Soc.*, 69, 2657 (1947).

(9) Private communication, Dr. J. S. Fox, Sloan-Kettering Institute for Cancer Research.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

New Fluorine-containing Aromatics as Potential Carcinostats

NG. PH. BUU-HOÏ, N. D. XUONG, AND R. RIPS

Received August 20, 1956

A large number of fluorine-containing aromatic acids, nitriles, and ketones have been synthesized from various fluoro aromatics for biological testing as potential carcinostatic agents.

3-Fluorotyrosine (Pardinon) has been found to inhibit the initiation and development of various tumors in animals, such as grafts of Jensen sarcomas in rats and tumors induced in mice through injection or painting with 3,4-benzpyrene.[1] Further, the same compound and 3-fluoro-4-hydroxyphenylacetic acid (Capacin) have found therapeutic use against hyperthyreosis.[2] Both these biological effects have recently been accounted for on the grounds of an antagonism toward aromatic acids and their metabolites.[3] With this in mind, a large number of new compounds more or less related to that type of molecular structure have now been prepared for biological investigation for possible carcinostatic activity and inhibitory effects on the pituitary secretions.

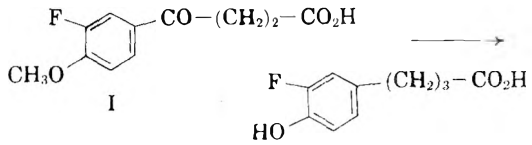
o-Fluoroanisole readily underwent Friedel-Crafts succinoylation to β-(3-fluoro-4-methoxybenzoyl)-

(1) May and Litzka, *Zeitschr. Krebsforsch.*, 48, 376 (1939).

(2) May, *Die Basedowsche Krankheit, Jod und Fluor*, Editio Cantor (Aulendorf), 1950.

(3) Buu-Hoï, Symposium on Chemotherapy of Cancer (Oslo, 1956); *Acta Unio Intern. contra Cancrum*, in press.

propionic acid (I); demethylation occurred during an attempt to reduce this compound by the Huang-Minlon modification of the Kishner-Wolff method,[4] γ-(3-fluoro-4-hydroxyphenyl)butyric acid (II), a higher homolog of Capacin, being obtained.

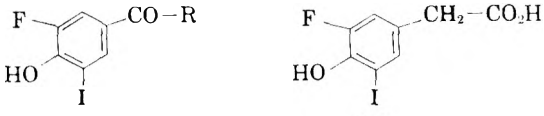


I II

(3-Fluoro-4-methoxyphenyl)butyric acid, prepared by methylation, was readily cyclized to give 6-fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene (III); this ketone, which readily gave 2-arylidene compounds with aromatic aldehydes, yielded on treatment with pyridine hydrochloride the demethylated compound (IV). This

III IV; R = H V; R = I

latter substance could also be prepared in low yield by Friedel-Crafts cyclization of the chloride of acid II, and gave with iodine 6-fluoro-8-iodo-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (V). Other hydroxy ketones containing both fluorine and iodine included 3-fluoro-5-iodo-4-hydroxy-caprophenone (VI), -*n*-decanophenone (VII), -benzophenone (VIII), and -phenacetophenone (IX), which, similarly, were prepared by halogenation of the fluoro ketones with iodone in the presence of mercuric oxide.[5] These various ketones were synthesized in view of the recorded pituitary-inhibitory activity of the similarly built *n*-butyl 3,5-diiodo-4-hydroxybenzoate;[6] the same

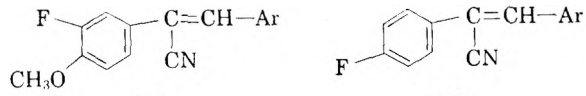


I (X)

VI; R = *n*-C_5H_{11}
VII; R = *n*-C_9H_{19}
VIII; R = C_6H_5
IX; R = CH_2—C_6H_5

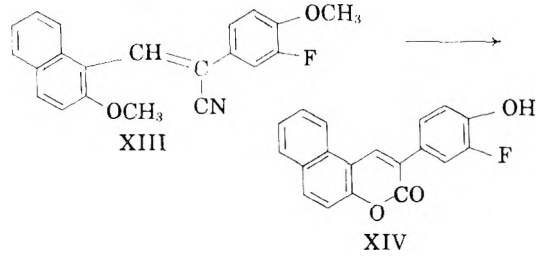
method was used for the preparation of 3-fluoro-5-iodo-4-hydroxyphenylacetic acid (X).

Numerous fluorine-containing stilbene nitriles, listed in Table I, were prepared in excellent yields by the alkali-catalyzed condensation of 3-fluoro-4-methoxybenzyl cyanide[7] with various aromatic aldehydes, and their demethylation afforded the corresponding hydroxystilbene nitriles. In the case



XI XII

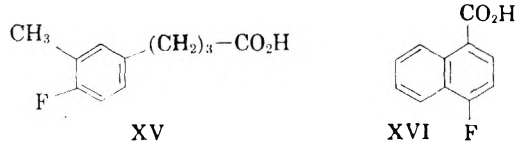
of 1-(3-fluoro-4-methoxyphenyl)-2-(2-methoxy-1-naphthyl)-acrylonitrile (XIII), demethylation resulted in the formation of 3-(3-fluoro-4-hydroxyphenyl)-5,6-benzocoumarin (XIV), in accordance with a recently described[8] coumarin synthesis. Nonoxygenated fluoro nitriles (XII), listed



XIII XIV

in Table II, were obtained by condensing aromatic aldehydes with *p*-fluorobenzyl cyanide in the presence of alkalies. The other nitriles recorded in the same table were obtained in similar manner by condensation of *p*-fluorobenzaldehyde with various arylacetonitriles.

Schöller and Gehrke[9] found that in slices of Jensen sarcoma, glycolysis was inhibited by sodium 4-fluorobenzoate, while the rate of respiration was increased. In view of this interesting property, several new fluorine-containing aromatic acids have now been prepared. *o*-Fluorotoluene was succinoylated to β-(4-fluoro-3-methylbenzoyl)propionic acid, which underwent Kishner-Wolff reduction to γ-(4-fluoro-3-methylphenyl)butyric acid (XV); 4-fluoro-1-naphthoic acid (XVI) was ob-



XV XVI

tained by sodium hypobromite oxidation of 4-fluoro-1-acetonaphthone. In view of the known inhibiting action of ethylenic ketones on certain enzymes, fluorine-containing chalcones were prepared by condensation of 4-fluoro-1-acetonaphthone and similar ketones with various aldehydes, and are listed in Table III, along with chalcones derived from 4-fluorobenzaldehyde; as expected from other similar cases,[10] the latter aldehyde condensed with cyclopentanone and cyclohexanone to give exclusively 2,5-*bis*(4-fluorobenzal)cyclo-

(4) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2478 (1946).
(5) See Buu-Hoï, Xuong, and Lavit, *J. Chem. Soc.*, 1034 (1954).
(6) Barker, Dirks, Garlick, and Klitgaard, *Proc. Soc. Exper. Biol. Med.*, 78, 840 (1951).
(7) Kraft, *Ber.*, 84, 150 (1951).
(8) Buu-Hoï *et al.*, *J. Chem. Soc.*, 2307 (1951); *J. Org. Chem.*, 19, 1391, 1548 (1954).
(9) Schöller and Gehrke, *Klin. Wochenschr.*, 1129 (1930).
(10) Vorländer and Hobohm, *Ber.*, 29, 1840 (1896).

TABLE I

1-SUBSTITUTED 2-(*p*-FLUOROPHENYL)ACRYLONITRILES

Substituent	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
2-Chlorophenyl-	$C_{15}H_9ClFN$	128°	69.9	3.5	69.9	3.3
3-Chlorophenyl-	$C_{15}H_9ClFN$	148	69.9	3.5	69.9	3.6
4-Chlorophenyl-	$C_{15}H_9ClFN$	127	69.9	3.5	70.1	3.6
4-Bromophenyl-	$C_{15}H_9BrFN$	114	59.6	3.0	59.3	3.1
4-Fluorophenyl-	$C_{15}H_9F_2N$	169	74.7	3.7	74.7	3.5
2,4-Dichlorophenyl-	$C_{15}H_8Cl_2FN$	142	61.6	2.7	61.3	2.7
Phenyl-	$C_{15}H_{10}FN$	111	80.7	4.5	80.6	4.6
4-Isopropylphenyl-	$C_{18}H_{16}FN$	116	81.5	6.0	81.7	6.2
2-SUBSTITUTED 1-(*p*-FLUOROPHENYL)ACRYLONITRILES (XII)						
2-Chlorophenyl-	$C_{15}H_9ClFN$	124	69.9	3.5	69.8	3.3
3-Chlorophenyl-	$C_{15}H_9ClFN$	107	69.9	3.5	69.9	3.6
4-Chlorophenyl-	$C_{15}H_9ClFN$	112	69.9	3.5	69.7	3.6
2-Bromophenyl-	$C_{15}H_9BrFN$	125	59.6	3.0	59.3	3.0
3-Bromophenyl-	$C_{15}H_9BrFN$	122	59.6	3.0	59.5	3.2
3,4-Dichlorophenyl-	$C_{15}H_8Cl_2FN$	155	61.6	2.7	61.3	2.8
4-Isopropylphenyl-	$C_{18}H_{16}FN$	99	81.5	6.0	81.7	5.9
1-Naphthyl-	$C_{19}H_{12}FN$	127	83.5	4.4	83.6	4.6
4-Dimethylaminophenyl-	$C_{17}H_{15}FN_2$	178	76.7	5.6	76.9	5.8

TABLE II

2-SUBSTITUTED 1-(3-FLUORO-4-METHOXYPHENYL)ACRYLONITRILES (XI)[a]

Substituent	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
Phenyl	$C_{16}H_{12}FNO$	133°	75.9	4.7	75.6	4.5
2-Furyl	$C_{14}H_{10}FNO_2$	111	69.1	4.1	69.0	4.3
4-Fluorophenyl	$C_{16}H_{11}F_2NO$	181	70.8	4.1	70.5	4.1
2-Chlorophenyl	$C_{16}H_{11}ClFNO$	147	66.8	3.8	66.6	3.8
4-Chlorophenyl	$C_{16}H_{11}ClFNO$	145	66.8	3.8	66.7	3.8
3,4-Dichlorophenyl	$C_{16}H_{10}Cl_2FNO$	183	59.6	3.1	59.5	3.0
4-Isopropylphenyl	$C_{19}H_{18}FNO$	129	77.3	6.1	77.2	6.0
1-Naphthyl	$C_{20}H_{14}FNO$	130	79.2	4.9	79.0	5.1
4-Dimethylaminophenyl	$C_{18}H_{17}FN_2O$	148	73.0	5.7	73.1	5.6
3,4-Dimethoxyphenyl	$C_{18}H_{16}FNO_3$	147	69.0	5.1	68.8	5.2
3,4-Methylenedioxyphenyl	$C_{17}H_{12}FNO_3$	192	68.7	4.0	68.8	4.2
2-Methoxy-1-naphthyl	$C_{21}H_{16}FNO_2$	177	75.7	4.8	75.3	4.7

[a] Prepared by adding a few drops of 25% aqueous sodium hydroxide to a stirred, warm solution of equimolar amounts of 3-fluoro-4-methoxybenzyl cyanide and the appropriate aromatic or heterocyclic aldehyde, and leaving the mixture overnight at room temperature; the precipitate obtained was washed with water and recrystallized from ethanol.

TABLE III

CHALCONES[a] DERIVED FROM *p*-FLUOROBENZALDEHYDE

	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
6-(4-Fluorocinnamoyl)tetralin	$C_{19}H_{17}FO$	75°	81.4	6.1	81.3	6.3
2-(4-Fluorocinnamoyl)naphthalene	$C_{19}H_{13}FO$	144	82.6	4.7	82.8	4.6
1-(4-Fluorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{12}F_2O$	83	77.6	4.1	77.5	4.3
(4-Fluorocinnamoyl)-3,4-dichlorobenzene	$C_{15}H_9Cl_2FO$	143	61.0	3.1	61.2	3.2
(4-Fluorocinnamoyl)-3,4-dimethylbenzene	$C_{17}H_{15}FO$	112	80.3	5.9	80.7	6.2
(4-Fluorocinnamoyl)-4-fluoro-3-methylbenzene	$C_{16}H_{12}F_2O$	124	74.4	4.7	74.2	4.6
(4-Fluorocinnamoyl)-2,4-dimethoxybenzene	$C_{17}H_{15}FO_3$	98	71.3	5.3	71.0	5.5
2-(4-Fluorobenzal)benzosuberone	$C_{18}H_{15}FO$	96	81.2	5.6	81.0	5.5
1-(4-Chlorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{12}ClFO$	112	73.4	3.9	73.4	4.0
1-(2,4-Dichlorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{11}Cl_2FO$	132	66.1	3.2	66.0	3.5
1-(4-Dimethylaminocinnamoyl)-4-fluoronaphthalene	$C_{21}H_{18}FNO$	140	79.0	5.6	78.7	5.8
2,6-bis(4-Fluorobenzal)cyclohexanone	$C_{20}H_{16}F_2O$	157	77.4	5.2	77.1	5.2
2,6-bis(4-Fuorobenzal)cyclopentanone	$C_{19}H_{14}F_2O$	244	77.0	4.7	76.8	4.8

[a] Prepared by shaking for some minutes a solution in ethanol of equimolar amounts of the appropriate ketone and *p*-fluorobenzaldehyde, with a few drops of 25% aqueous sodium hydroxide; recrystallization was effected from ethanol, except for the two last compounds, which were recrystallized from a mixture of ethanol and benzene.

pentanone and 2,6-*bis*(4-fluorobenzal)cyclohexanone, respectively.

EXPERIMENTAL

Succinoylation of o-fluoroanisole. To an ice-cooled solution of 30 g. of succinic anhydride and 31.5 g. of *o*-fluoroanisole in 200 ml. of nitrobenzene, 50 g. of finely powdered aluminum chloride was added in small portions with stirring; the reaction mixture was left at room temperature for 24 hr., then treated with ice and dilute hydrochloric acid. After removal of the nitrobenzene by steam-distillation, the residue was recrystallized from dilute aqueous acetic acid, giving a 96% yield of *β-(3-fluoro-4-methoxybenzoyl)-propionic acid* (I) in the form of shiny colorless prisms, m.p. 170–171°.

Anal. Calcd. for $C_{11}H_{11}FO_4$: C, 58.4; H, 4.9. Found: C, 58.1; H, 5.2.

γ-(3-Fluoro-4-hydroxyphenyl)butyric acid (II). A solution of 70 g. of the foregoing acid and 25 ml. of 98% hydrazine hydrate in 400 ml. of diethylene glycol was heated for 5 min. to allow the hydrazone to form; 64 g. of potassium hydroxide was then added, and the mixture refluxed for 4 hr. with removal of water. Most of the diethylene glycol was distilled off in a vacuum, and the residue was diluted with water and acidified with hydrochloric acid. The reaction product was taken up in ether, the ethereal solution dried over sodium sulfate, and the solvent distilled off. Crystallization of the residue from water gave a 75% yield of large colorless platelets, m.p. 107–108°.

Anal. Calcd. for $C_{10}H_{11}FO_3$: C, 60.6; H, 5.6. Found: C, 60.5; H, 5.8.

Methylation of the foregoing acid with dimethyl sulfate (2 moles) and aqueous sodium hydroxide (2 moles), followed by alkaline hydrolysis of the methyl ester thus obtained, afforded in 98% yield γ-(3-fluoro-4-methoxyphenyl)-butyric acid, which crystallized from a mixture of petroleum ether and benzene in colorless needles, m.p. 62–63°.

Anal. Calcd. for $C_{11}H_{13}FO_3$: C, 62.3; H, 6.1. Found: C, 62.0; H, 6.1.

6-Fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene (III). Fifteen grams of γ-(3-fluoro-4-methoxyphenyl)butyric acid was converted with thionyl chloride into the corresponding acid chloride, which was dissolved in 100 ml. of nitrobenzene; to this ice-cooled solution, 13 g. of aluminum chloride was added in small portions with stirring, and the mixture left 3 hr. at room temperature. After decomposition with ice and hydrochloric acid, and removal of the nitrobenzene by steam-distillation, the residue was taken up in ether, the ethereal solution washed with dilute aqueous sodium hydroxide, then with water, dried over sodium sulfate, and the solvent distilled off. Yield: 7 g. of ketone III, crystallizing from methanol in colorless prisms, m.p. 95°.

Anal. Calcd. for $C_{11}H_{11}FO_2$: C, 68.0; H, 5.7. Found: C, 68.2; H, 5.6.

The semicarbazone crystallized from ethanol in silky colorless needles, m.p. 216–217°.

Anal. Calcd. for $C_{12}H_{14}FN_3O_2$: N, 16.7. Found: N, 16.6.

2-(p-Fluorbenzal)-6-fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. A solution of the foregoing ketone (1 mole) and *p*-fluorobenzaldehyde (1 mole) in ethanol was shaken for some minutes with a few drops of a 20% aqueous solution of sodium hydroxide; the precipitate formed was collected, washed with water, and recrystallized from ethanol, giving silky colorless needles, m.p. 132°, in almost theoretical yield.

Anal. Calcd. for $C_{18}H_{14}F_2O_2$: C, 72.0; H, 4.7. Found: C, 71.9; H, 4.5.

2-(p-Chlorobenzal)-6-fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene, similarly prepared with *p*-chlorobenzaldehyde, crystallized from ethanol in lustrous colorless leaflets, m.p. 136°.

Anal. Calcd. for $C_{18}H_{14}ClFO_2$: C, 68.2; H, 4.4. Found: C, 68.0; H, 4.4.

6-Fluoro-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (IV). (a) A mixture of 2 g. of the tetralone (III) and 6 g. of pyridine hydrochloride was gently refluxed for 15 min., and water added after cooling; the precipitate crystallized from aqueous methanol in colorless tablets, m.p. 186–187°. Yield: 1 g. (b) The same product was obtained in poor yield by treating acid III with thionyl chloride, and cyclizing the crude acid chloride thus obtained by aluminum chloride in nitrobenzene solution in the usual way.

Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.7; H, 5.0. Found: C, 67.0; H, 5.0.

6-Fluoro-8-iodo-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (V). To a solution of 4.5 g. of the foregoing ketone in 50 ml. of ethanol, 6 g. of yellow mercuric oxide was added; 1 g. of iodine in ethanol was then shaken in portion-wise. After filtration and concentration of the filtrate, the reaction product was precipitated with water, and recrystallized from that solvent, giving 4 g. of fine gray-tinged prisms, m.p. 150°.

Anal. Calcd. for $C_{10}H_8FIO_2$: C, 39.2; H, 2.6. Found: C, 38.8; H, 2.5.

Iodination of fluorohydroxy ketones. The same procedure as above was used for the preparation of the following ketones:

3-Fluoro-5-iodo-4-hydroxycaprophenone (VI), which crystallized from aqueous ethanol in lustrous colorless leaflets, m.p. 102°.

Anal. Calcd. for $C_{12}H_{14}FIO_2$: C, 42.9; H, 4.2. Found: C, 42.6; H, 4.2.

3-Fluoro-5-iodo-4-decanophenone (VII), which crystallized from petroleum ether in fine colorless needles, m.p. 73°.

Anal. Calcd. for $C_{16}H_{22}FIO_2$: C, 48.9; H, 5.6. Found: C, 49.0; H, 5.6.

3-Fluoro-5-iodo-4-benzophenone (VIII), fine yellowish prisms from ethanol, m.p. 178°.

Anal. Calcd. for $C_{13}H_8FIO_2$: C, 45.6; H, 2.3. Found: C, 45.3; H, 2.1.

3-Fluoro-5-iodo-4-phenacetophenone (IX), fine yellowish prisms from ethanol, m.p. 172°.

Anal. Calcd. for $C_{14}H_{10}FIO_2$: C, 47.2; H, 2.8. Found: C, 47.0; H, 2.8.

3-Fluoro-5-iodo-4-hydroxyphenylacetic acid (X). Similarly prepared from 3-fluoro-4-hydroxyphenylacetic acid, this compound crystallized from water in shiny colorless leaflets, m.p. 164°.

Anal. Calcd. for $C_8H_6FIO_3$: C, 32.4; H, 2.0. Found: C, 32.1; H, 2.1.

3-(3-Fluoro-4-hydroxyphenyl)-5,6-benzocoumarin (XIV). A mixture of 1 g. of acrylonitrile XIII and 6 g. of redistilled pyridine hydrochloride was refluxed for 30 min., and dilute hydrochloric acid added after cooling. After 5 more minutes' refluxing for hydrolyzing the iminocoumarin formed, the precipitate obtained was washed with water and recrystallized from a mixture of ethanol and benzene, giving pale yellow needles, m.p. 255°.

Anal. Calcd. for $C_{19}H_{11}FO_3$: C, 74.5; H, 3.6. Found: C, 74.1; H, 3.5.

A similar technique applied to other methoxy acrylonitriles listed in Table I gave the following hydroxy compounds:

1-Phenyl-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, crystallizing from aqueous ethanol in fine colorless prisms, m.p. 184°.

Anal. Calcd. for $C_{15}H_{10}FNO$: C, 75.3; H, 4.2. Found: C, 75.0; H, 4.0.

1-(2-Chlorophenyl)-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, fine colorless prisms from aqueous ethanol, m.p. 171°.

Anal. Calcd. for $C_{15}H_9ClFNO$: C, 65.8; H, 3.3. Found: C, 65.6; H, 3.1.

1-(1-Naphthyl)-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, fine yellowish prisms from aqueous ethanol, m.p. 193°.

Anal. Calcd. for $C_{19}H_{12}FNO$: C, 78.9; H, 4.2. Found: C, 78.6; H, 4.1.

β-(4-Fluoro-3-methylbenzoyl)propionic acid. A mixture of 55 g. of *o*-fluorotoluene, 50 g. of succinic anhydride, and 75 g. of finely powdered aluminum chloride in 150 ml. of carbon disulfide was refluxed for 4 hr. on the water bath, and then left overnight at room temperature. After decomposition with ice and hydrochloric acid and evaporation of the solvent, the reaction product was taken up in ether, the etheral solution washed with water and dried over sodium sulfate, and the solvent distilled off. Crystallization of the solid residue from benzene gave 30 g. of colorless prisms, m.p. 119°. The position of the fluorine atom in this compound is assumed from analogy with the acylations.[11]

Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.9; H, 5.3. Found: C, 63.2; H, 5.2.

γ-(4-Fluoro-3-methylphenyl)butyric acid (XV). Prepared as for acid II, this compound crystallized from water in shiny colorless tablets, m.p. 64–65°.

Anal. Calcd. for $C_{11}H_{13}FO_2$: C, 67.3; H, 6.6. Found: C 67.0; H, 6.6.

4-Fluoro-1-acetonaphthone. Obtained in 70% yield from 48 g. of 1-fluoronaphthalene, 28 g. acetyl chloride, and 70 g. of aluminum chloride in carbon disulfide as in the case of β-(4-fluoro-3-methylbenzoyl)propionic acid; the ketone was a pale yellow oil, b.p. 288°, n_D^{20} 1.6071.

Anal. Calcd. for $C_{12}H_9FO$: C, 76.6; H, 4.8. Found: C, 76.5; H, 4.6.

4-Fluoro-1-naphthoic acid (XV). Fifteen grams of the foregoing ketone was shaken with an aqueous solution of sodium hypobromite (prepared from 13 ml. of bromine and 26 g. of sodium hydroxide) for 2 hr. at room temperature, the neutral impurities were removed by water-extraction, and the aqueous solution was treated with sodium bisulfite, then acidified with hydrochloric acid. The precipitate, obtained in 70% yield, crystallized from benzene in fine, colorless, sublimable needles, m.p. 226°.

Anal. Calcd. for $C_{11}H_7FO_2$: C, 69.5; H, 3.7. Found: C, 69.2; H, 3.4.

(11) Buu-Hoï and Jacquignon, *J. Chem. Soc.*, 4173 (1952).

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

Addition of Mercaptoacetic Acid to Terpenes and Related Compounds

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The reaction of mercaptoacetic acid with *d*- and *l*-limonenes, dipentene, α-pinene, β-pinene, camphene, myrcene, anethole, oleic acid, and allyl chloride was studied. Ultraviolet light and peroxides generally accelerate the reactions and evidence is presented that atmospheric oxygen is sufficient to induce a rapid reaction with *d*-limonene. A different adduct to *d*-limonene was obtained in the presence of sulfuric acid. The products were characterized as *S*-benzylthiuronium salts.

In view of the sparsity of solid derivatives of terpenes, the action of mercaptoacetic acid on several representatives of this class of compounds was studied. Although the adducts were expected to be liquids, the carboxyl groups of the adducts should furnish a point for preparing solid derivatives, such as *S*-benzylthiuronium salts.

As ordinarily carried out, the addition of mercaptans, including mercaptoacetic acid, to unsaturated compounds is generally presumed to be a radical-type reaction. Kharasch, Read, and Mayo[2] have observed that the addition of mercaptoacetic acid to styrene and isobutylene is definitely peroxide-catalyzed and that no reaction occurs in the presence of 5 mole percent of hydroquinone. However, Hoog and Eichwald[3] found that mercaptoacetic acid adds to many "peroxide-free" olefins without ultraviolet light.

Vincent and Etzel[4] have reported the use of the mercaptoacetic acid adducts to limonene, pinene, and camphene as milling aids for butadiene-styrene copolymers. Isobornyl carboxymethyl sulfide was prepared at 95° in the presence of *p*-toluenesulfonic acid from camphene and mercaptoacetic acid. The products were not characterized.

During the course of the present work, it was observed that mercaptoacetic acid does add vigorously to *d*-limonene which had been freed of peroxides by distillation, treatment with ferrous salts or absorption of the peroxides on alumina. The products are the same as those obtained in the presence of peroxides and reaction is inhibited by hydroquinone. It appears, therefore, that atmospheric oxygen is sufficient to induce radical-type reactions in this example.

Under appropriate conditions, either a 2:1 or 1:1 adduct to *d*-limonene may be obtained. The 2:1 adduct, as well as the *S*-benzylthiuronium salt isolated from it, retained optical activity. Thus, the addition to at least one of the double bonds occurs contrary to Markownikoff's rule, as ionic addition to both double bonds would afford a symmetrical molecule.

Cunneen[5] has previously reported the "normal" addition of mercaptoacetic acid to l-methylcyclohexene in the presence of sulfuric acid. Under similar conditions a reaction of mercaptoacetic

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(2) M. S. Kharasch, A. T. Read, and F. R. Mayo, *Chemistry & Industry*, 752 (1938).

(3) H. Hoog and E. Eichwald, *Rec. trav. chim.*, 58, 481 (1939).

(4) J. R. Vincent and G. Etzel, U.S. Patent 2,429,858 (1947); *cf. Chem. Abstr.*, 42, 1449 (1948).

(5) J. I. Cunneen, *J. Chem. Soc.*, 36 (1947).

acid with *d*-limonene occurs. The product is different from that obtained in the presence of peroxides. The *S*-benzylthiuronium salt isolated from the 1:1 adduct is optically inactive and appears to be identical with that obtained from dipentene under similar conditions. The adduct itself retained only a small amount of activity. The loss of optical activity may be explained by ionic addition to the ring double bond which results in a symmetrical adduct or it may be due to racemization induced by sulfuric acid. Sulfuric acid is known to polymerize *d*-limonene to optically inactive substances.[6] Apparently addition occurred much more rapidly than polymerization, as excellent yields of the 1:1 adduct were obtained. The possibility that racemization occurs without polymerization cannot, however, be excluded. The 2:1 adduct to *d*-limonene prepared in the presence of sulfuric acid was, of course, also devoid of optical activity.

Reaction of mercaptoacetic acid with α-pinene, β-pinene, camphene, and myrcene was also observed to proceed readily in the presence of peroxides or ultraviolet light. Neither pinene sample employed was optically pure and the *S*-benzylthiuronium salts isolated by crystallization were inactive, although the crude adducts retained some activity. The camphene employed was the racemate. It was not determined whether the pinene skeleton remains intact during the course of the reactions. The crystal structures of the three salts from the pinenes and camphene all appear to be different, but nonidentity could not be established by the mixed melting point criterion.

Several optical isomers would be predicted in the peroxidic addition to the limonenes, pinenes, and camphene. In the present work, only that isomer or racemate of the salt which was most easily crystallized was isolated and these were obtained in relatively low yields. Survey experiments indicated that lower-melting, isomeric salts might be separated by fractional crystallization if desired. Such crystallizations must be carried out rapidly, as the salts decompose slowly in boiling solvents.

Adducts to anethole and oleic acid prepared in the presence of peroxides were characterized by means of the *S*-benzylthiuronium salts.

Thiomalic acid was observed to add to anethole in the presence of ultraviolet light and a solid adduct was isolated.

EXPERIMENTAL

All melting points reported herein are uncorrected. The peroxide number (P.N.) refers to the milliequivalents of iodine liberated from potassium iodide–acetic acid per liter of unsaturated compound. Optical rotations were taken with a Rudolph precision Model 80 polarimeter. Ultraviolet light was supplied by a 0.25-ampere, 115-volt, 60-cycle lamp.

The materials employed were good commercial grades unless specified in the Acknowledgments. Mercaptoacetic acid was vacuum distilled at 13 to 20 mm. unless otherwise specified.

General method. Mercaptoacetic acid is sparingly soluble in all the unsaturated compounds studied herein except anethole. Most of the reactions proceed with evolution of heat. Therefore, it is advantageous to observe whether a homogeneous layer is formed and to follow temperature changes in determining when reaction occurs.

The mixture of mercaptoacetic acid and the unsaturated compound was stirred vigorously. When reaction was complete, the mixture was washed with water and the crude adduct was extracted with ether or benzene. The solvent was evaporated, the residue dissolved in dilute alkali, any insoluble material separated, and the aqueous solution acidified with dilute hydrochloric acid. The adduct was dried *in vacuo* over sulfuric acid.

A further purification of the adducts may be accomplished by preparing a benzene solution (1 g. in 30 ml.), passing the solution through a column of silica gel or alumina, eluting the adduct with ethanol and evaporating the solvent. This treatment was not generally required for our purposes.

S-Benzylthiuronium salts were prepared by a conventional method[7] in approximately 5 millimole quantities.

Data obtained on the adducts are recorded in Table I, and that on the *S*-benzylthiuronium salts in Table II.

d-Limonene. The *2:1 adduct prepared in the presence of peroxides* was obtained using 5.00 g. of *d*-limonene (n_D^{20}, 1.4720; $[\alpha]_D^{20}$, +118; P.N., 47) and 10.00 g. of mercaptoacetic acid. With stirring, the temperature rose rapidly to 60° and a homogeneous solution was formed. The adduct was isolated and the *S*-benzylthiuronium salt was prepared by the general procedure. Upon standing in a vacuum desiccator for several weeks, the adduct partially crystallized. The mixture was pressed between circles of filter paper and the crystals melted at 65–66°. Analyses indicated that the solid was one of the optical isomers of the adduct.

Anal. Calcd. for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.80; H, 7.83.

The S-benzylthiuronium salt melted at the same temperature as the salt isolated from the crude mixture of adducts and the melting point of mixtures was the same as those of individual samples.

A potassium acid salt of the crude adduct was obtained in 40% yield by dissolving 1.00-g. quantities of the adduct in equimolar amounts of 20% potassium hydroxide, placing the solution in a refrigerator overnight and separating the crystals.

Anal. Calcd. for $C_{14}H_{23}KO_4S_2$: K, 10.89. Found: K, 10.64.

A dipotassium salt was precipitated in 85% yield by dissolving 1.00 g. of the adduct in a solution of potassium hydroxide in 95% ethanol containing excess alkali.

Anal. Calcd. for $C_{14}H_{22}K_2O_4S_2$: K, 19.60. Found: K, 19.55.

The *2:1 adduct prepared in the presence of sulfuric acid* was obtained using 10.0 g. of freshly distilled *d*-limonene, 20.0 g. of mercaptoacetic acid, and 10 drops of sulfuric acid.

The *1:1 adduct prepared in the presence of sulfuric acid* was obtained using 10.0 g. of peroxide-free *d*-limonene, 6.80 g. of mercaptoacetic acid, and 4 drops of 80% sulfuric acid.

l-Limonene. The 2:1 adduct was prepared using 5.00 g. of *l*-limonene (n_D^{20}, 1.4740; $[\alpha]_D^{20}$, −97; P.N., 15) and 10.00 g. of mercaptoacetic acid.

Dipentene. The sample of dipentene (n_D^{20}, 1.4752; P.N., 14) reacted more slowly than did the limonenes alone and ultraviolet light was employed. The quantities used were the same as those used in preparing the corresponding adducts to *d*-limonene.

α-Pinene. The adduct was prepared using 5.0 g. of α-

(6) A. M. Clover, *Philippine J. Sci.*, 2, 1; *Chem. Zentr.*, I, 1793 (1907).

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 202.

TABLE I

ADDUCTS OF MERCAPTOACETIC ACID AND UNSATURATED COMPOUNDS

Compound	Yield, %	n_D^{20}	Optical rotation[a] $[\alpha]_D^{20}$	Formula	Analyses Calcd. C	Found C	Calcd. H	Found H
d-Limonene[b,c]	85	1.536	+48	$C_{14}H_{24}O_3S_2$	52.47	52.44	7.55	7.98
d-Limonene[b,d]	64	1.531	+58	$C_{12}H_{20}O_2S$	63.13	62.92	8.83	8.54
d-Limonene[c,e]	86	1.532	0	$C_{14}H_{24}O_4S_2$	52.47	52.77	7.55	7.93
d-Limonene[d,e]	79	1.536	+1	$C_{12}H_{20}O_2S$	63.13	62.84	8.83	8.61
l-Limonene[b,c]	80	1.538	−43	$C_{14}H_{24}O_4S_2$	52.47	52.45	7.55	7.63
Dipentene[b,c,f]	80	1.534		$C_{14}H_{24}OS_2$	52.47	52.62	7.55	7.84
Dipentene[d,e]	78	1.530		$C_{12}H_{20}O_2S$	63.13	63.01	8.83	8.72
α-Pinene[b,f]	63	1.518	−13	$C_{12}H_{20}O_2S$	63.13	62.83	8.83	8.48
β-Pinene[b]	82	1.542	−30	$C_{12}H_{20}O_2S$	63.13	62.85	8.83	8.72
dl-Camphene[f,g]	83	1.520		$C_{12}H_{20}O_2S$	63.13	63.29	8.83	8.91
Anethole[b,f,h]	90	1.559		$C_{12}H_{16}O_2S$	59.97	60.14	6.71	7.00
Oleic acid[f,g]	84	1.483		$C_{20}H_{38}O_4S$	64.13	63.77	10.22	10.14
Allyl chloride[b]	74	1.530		$C_5H_9ClO_2S$	35.61	35.49	5.38	5.50

[a] In ethanol (c = 1.00). [b] Peroxidic. [c] 2:1 adduct. [d] 1:1 adduct. [e] In presence of sulfuric acid. [f] In presence of ultraviolet light. [g] Heated to 50°. [h] Reaction time: 3.5 hr.

TABLE II

S-BENZYLTHIURONIUM SALTS OF THE ADDUCTS

Compound	Yield, %	M.P. (°C)	Optical Rotation[a] $[\alpha]_D^{20}$	Formula	Analyses Calcd. C	Found C	Calcd. H	Found H
d-Limonene[b,c]	26	171–172	+47	$C_{30}H_{44}N_4O_4S_4$	55.18	55.00	6.79	7.08
d-Limonene[b,d]	28	177–178	+58	$C_{20}H_{30}N_2O_2S_2$	60.87	60.43	7.66	7.48[e]
d-Limonene[c,f]	33	151–152	0	$C_{30}H_{44}N_4O_4S_4$	55.18	55.55	6.79	6.96
d-Limonene[d,f]	34	135–136	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.56	7.66	7.95
l-Limonene[b,c]	28	171–172	−42	$C_{30}H_{44}N_4O_4S_4$	55.18	55.23	6.79	6.88
Dipentene[b,c,g]	26	160–161		$C_{30}H_{44}N_4O_4S_4$	55.18	55.20	6.79	7.14
Dipentene[d,f]	32	135–136		$C_{20}H_{30}N_2O_2S_2$	60.87	60.62	7.66	7.84
α-Pinene[b,g]	26	156.5–157.5[h]	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.90	7.66	7.90
β-Pinene[b]	18	161–162[h]	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.52	7.66	7.95
Camphene[g]	66	167–168[h]		$C_{20}H_{30}N_2O_2S_2$	60.87	60.63	7.66	7.75
Anethole[b]	35	154–155		$C_{20}H_{26}N_2O_2S_2$	59.08	59.09	6.44	6.82
Oleic acid[g,i]	58	128–129		$C_{36}H_{58}N_4O_4S_3$	61.15	61.52	8.27	8.57[j]
Allyl chloride[b]	51	156–157		$C_{13}H_{19}ClN_2O_2S_2$	46.62	46.99	5.72	5.79

[a] In 95% ethanol (c = 0.50). [b] Peroxidic. [c] 2:1 adduct. [d] 1:1 adduct. [e] *Anal.*: Calcd. for $C_{20}H_{30}N_2O_2S_2$: N, 7.10. Found: N, 7.10. [f] Prepared in the presence of sulfuric acid. [g] Prepared in the presence of ultraviolet light. [h] Mixed melting points of salts: α-pinene and β-pinene, 155–161°; α-pinene and camphene, 155–165°; β-pinene and camphene, 159–165°. [i] di-*S*-benzylthiouronium salt. [j] *Anal.* Calcd. for $C_{36}H_{58}N_4O_4S_3$: N, 7.93. Found: N, 7.49.

pinene (n_D^{20}, 1.4663; $[\alpha]_D^{20}$, +20, P.N., 28) and 5.0 g. of mercaptoacetic acid in the presence of ultraviolet light.

β-Pinene. To obtain the adduct, 5.0 g. of β-pinene (n_D^{20} 1.4802; $[\alpha]_D^{20}$, −36; P. N., 21) and 6.4 g. of mercaptoacetic acid were used.

dl-Camphene. A mixture of 10.0 g. of camphene (m.p. 44–46°; P.N., 1) and 9.1 g. of 80% aqueous mercaptoacetic acid was stirred, heated to 50° and irradiated with ultraviolet light.

Anethole. The adduct was prepared using 10.0 g. of anethole (n_D^{20}, 1.5596; P.N., 6) and 7.0 g. of mercaptoacetic acid in the presence of ultraviolet light. Reaction at room temperature without light was slow. At 45° reaction occurred readily and the melting point and mixed melting point of the *S*-benzylthiuronium salt was identical with that obtained using ultraviolet light.

Oleic acid. A mixture of 17.9 g. of freshly vacuum distilled oleic acid (n_D^{20}, 1.4581) and 10.4 g. of 80% mercaptoacetic acid was stirred, heated to 50° and irradiated with ultraviolet light.

Allyl chloride. A mixture of 20.0 g. of allyl chloride (n_D^{20}, 1.4092; P.N., 60) and 31.5 g. of 80% mercaptoacetic acid was allowed to react under a reflux condenser. Reaction with freshly distilled mercaptoacetic acid was slow, but the addition of water to dilute the acid to 80% resulted in a rapid temperature rise and the formation of a homogeneous solution. No reaction was observed between peroxide-free allyl chloride and distilled mercaptoacetic acid in the presence of sulfuric acid.

Myrcene. A sample of peroxidic myrcene (n_D^{20}, 1.4717; P.N., 12) was observed to react rapidly with mercaptoacetic acid but the product was not characterized.

Addition of thiomalic acid to anethole. A solution of 3.00 g. of thiomalic acid (m.p. 149–150°) and 2.60 g. of anethole in 10 ml. of ethanol was irradiated with ultraviolet light for 2 hr. The resulting solution was diluted with 100 ml. of water, basified, and extracted with benzene. The aqueous solution was acidified with dilute hydrochloric acid and the crude adduct (4.82 g. after being dried) was obtained as a semisolid. The adduct was recrystallized from water several times and 2.95 g. of colorless solid was obtained (m.p. 107–108°).

Anal. Calcd. for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.02; H, 5.86.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

1-Aryl-3,3-dialkyltriazenes as Tumor Inhibitors

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A series of 1-aryl-3,3-dialkyltriazenes was prepared by coupling a diazonium salt with a secondary (occasionally primary) amine in basic medium. Preliminary tests against Sarcoma-180 in the mouse indicate that at least one methyl group at N-3 is essential for activity.

The recent observation that 1-phenyl-3,3-dimethyltriazene (I, Ar = C_6H_5) and its *p*-tolyl and *p*-nitrophenyl analogs exhibited inhibition of mouse Sarcoma-180[1] prompted the synthesis and testing of a variety of their relatives. We wish to report the preparation and properties of some of these compounds, together with preliminary tests

$$\overset{1}{\text{Ar}}\text{N}=\overset{2}{\text{N}}-\overset{3}{\text{N}}(\text{CH}_3)_2 \qquad \text{I}$$

against mouse Sarcoma-180.[2]

The method of synthesis of these triazenes involved coupling of an aryldiazonium chloride with an amine, usually in a basic aqueous solution. The various modifications of this procedure are given in the experimental section. The physical properties are given in Table I.

Structural variations of I included introduction of one or more substituents in the aryl group at N-1 or use of a heterocyclic aryl group, and replacing one or both methyl groups at N-3 by hydrogen, higher alkyl and substituted alkyl, or a heterocyclic ring containing N-3. The changes were accomplished by use of an appropriately substituted diazonium salt or the desired primary or secondary aliphatic amine.

When a diazonium salt was coupled with methylamine, both mono- and disubstitution occurred, and the product was a mixture of the 1-aryl-3-methyltriazene and the 1,5-diaryl-3-methylpentazdiene (II). These were readily separated by virtue of the insolubility of II in methanol. Some of the triazenes with a hydrogen at N-3 were thermally unstable and decomposed vigorously on attempted vacuum distillation.

$$\text{ArN}=\text{N}-\text{N}(\text{CH}_3)-\text{N}=\text{N}-\text{Ar} \qquad \text{II}$$

The products derived by coupling diazonium salts with ethylenimine were likewise thermally unstable. Those which were solids could in some cases be purified by careful crystallization, but the liquids invariably decomposed on distillation. The isolated product from benzene- or *p*-toluenediazonium chloride and ethylenimine was the aryl azide. The other product (not isolated) was presumably ethylene. This facile pyrolytic cleavage at 60–75° of triazenes has not previously been reported.

$$\text{ArN}=\text{N}-\text{N}\begin{array}{l}\text{CH}_2\\|\\\text{CH}_2\end{array} \longrightarrow \text{ArN}_3 + \text{CH}_2=\text{CH}_2$$

It would be of interest to study the pyrolysis of the unstable 1-aryl-3-alkyltriazenes, which might give an aryl azide and an alkane.

The preliminary results of animal tests show that tumor inhibition is exhibited to some extent only by triazenes having at least one methyl group at N-3, including 1-phenyl-, 1-*p*-nitrophenyl-, 1-*p*-methoxyphenyl-, 1-*o*-tolyl-, and 1-*m*-trifluoromethyl-3,3-dimethyltriazene. 1-*p*-Tolyl-3-methyltriazene and 1-*p*-tolyl-3-methyl-3-cyclohexyltriazene also showed some activity. 1-Phenyl-3,3-dialkyltriazenes where both alkyl groups were larger than methyl, as well as those containing a heterocyclic ring incorporating N-3, were inactive.

EXPERIMENTAL

The aromatic amines were commercial samples, purified when deemed necessary. The aliphatic amines were obtained chiefly from the Eastman Kodak Co. and were used as received in most cases.

The aromatic amine was diazotized in the presence of 3 moles of hydrochloric acid, except in the few cases where the amine was so weakly basic as to require more acid. The solution was then filtered. The coupling with the aliphatic amine was carried out in one of the following ways, where the letters refer to the procedures in Table I.

(1) Clarke, Barclay, Stock, and Rondestvedt, *Proc. Soc. Expt. Biol. Med.*, 90, 484 (1955).

(2) Testing is being carried out at the Sloan-Kettering Institute for Cancer Research, under the direction of Dr. D. A. Clarke and Dr. C. Chester Stock. The details will be reported elsewhere.

TABLE I

PROPERTIES OF TRIAZENES ArN=N—N(R)(R′)

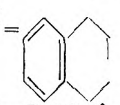
Ar	R	R′	Method	Yield, %	M.P.° (B.P.°/Mm.)	Formula	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Cryst. Solv.[a]	Color, Form
Phenyl	$HOCH_2CH_2$	$HOCH_2CH_2$	A	82	(140–160/1, dec.)	$C_{10}H_{15}N_3O_2$	57.40	7.23	57.52	7.14		
	n-C_3H_7	*n*-C_3H_7	A	82	(100–104/0.5)	$C_{12}H_{19}N_3$	70.20	9.33	70.18	9.19		
	i-C_3H_7	*i*-C_3H_7	A	69	40.0–40.2	$C_{12}H_{19}N_3$	70.20	9.33	70.26	9.29		
	n-C_4H_9	*n*-C_4H_9	A	84	(123–125/0.8)	$C_{14}H_{23}N_3$	72.05	9.94	72.08	9.80		
	i-C_4H_9	*i*-C_4H_9	A	75	(106–108/0.7)	$C_{14}H_{23}N_3$	72.05	9.94	72.24	9.76		
	s-C_4H_9	*s*-C_4H_9	A	71	(109–111/0.3)	$C_{14}H_{23}N_3$	72.05	9.94	71.95	9.65		
	n-C_5H_{11}	*n*-C_5H_{11}	B	60	(140–141.5/1.0)	$C_{16}H_{27}N_3$	73.51	10.41	72.49	10.00		
	i-C_5H_{11}	*i*-C_5H_{11}	B	62	(128–130/1.0)	$C_{16}H_{27}N_3$	73.51	10.41	73.53	10.26		
	n-C_6H_{13}	*n*-C_6H_{13}	B	70	(156–158/0.6)	$C_{18}H_{31}N_3$	74.69	10.80	74.81	10.49		
	i-C_6H_{13}	*i*-C_6H_{13}	B	48	(144–145/0.7)	$C_{18}H_{31}N_3$	74.69	10.80	74.62	10.58		
	cyclohexyl	cyclohexyl	B	38	127–128	$C_{18}H_{27}N_3$	75.74	9.54	75.92	9.43	B	White prisms
	RR′ = tetramethylene		A	86	49–50	$C_{10}H_{13}N_3$	68.54	7.48	68.66	7.53	P1	White needles
o-Tolyl	CH_3	CH_3	A	86	(78–79/0.5)[b]							
p-Tolyl	CH_3	cyclohexyl	C	85	(122/0.1)	$C_{14}H_{21}N_3$	72.68	9.15	72.53	9.03		
	CH_3	phenyl	D	84	66.5–68[c]	$C_{14}H_{15}N_3$	74.63	6.71	74.75	6.68	P1	Yellow leaflets
	CH_3	H	—		81–82[e]	$C_8H_{11}N_3$	64.40	7.43	64.36	7.34	MW	Creamy leaflets
	CH_3	*p*-tolylazo-	E[d]		—	$C_{15}H_{17}N_5$	67.39	6.41	67.58	6.51	P3	Yellow needles
	RR′ = 		C	66	75–76	$C_{16}H_{17}N_3$	76.46	6.82	76.09	6.81	P2	Pink needles
	RR′ = CH_3O 		C	82	71.5–72.5	$C_{17}H_{19}N_3O$	72.56	6.89	72.59	6.75	P2	Orange-red plates
2,3-Xylyl	CH_3	CH_3	A	79	(120–121/5)	$C_{10}H_{15}N_3$	67.76	8.53	67.80	8.43		
2,4-Xylyl	CH_3	CH_3	C	90	53–53.5	$C_{10}H_{15}N_3$	67.76	8.53	67.83	8.40	P1	Beige plates
2,6-Xylyl	CH_3	CH_3	C	74	(72–73/0.3)	$C_{10}H_{15}N_3$	67.76	8.53	67.79	8.48		
Mesityl	CH_3	CH_3	C	80	(83/0.4)[f]	$C_{11}H_{17}N_3$	69.07	8.96	69.09	8.76		
2,6-Diethylphenyl	CH_3	CH_3	A	45	(94.0–94.5/0.3)	$C_{12}H_{19}N_3$	70.20	9.33	70.64	9.20		
p-Hydroxyphenyl	CH_3	CH_3	C	19	93.5 (dec.)	$C_8H_{11}N_3O$	58.16	6.71	58.47	6.60	B;E-P2	Yellow rect. leaflets
o-Anisyl	CH_3	CH_3	C	86	(89.5–90.5/0.2)[g]	$C_9H_{13}N_3O$	60.31	7.31	60.20	7.12		
p-Anisyl	CH_3	cyclohexyl	C	80	(152/0.4)	$C_{14}H_{21}N_3O$	67.98	8.52	67.86	8.29		
	CH_3	*p*-anisylazo	E	—	110–110.5 dec.[h]	$C_{15}H_{17}N_5O_2$	60.19	5.72	60.34	5.94	P3; M	Deep yellow needles
o-Phenetyl	CH_3	CH_3	C	90	(104.5/0.4)	$C_{10}H_{15}N_3O$	62.15	7.82	62.35	7.65		
m-Phenetyl	CH_3	CH_3	C	92	60.5–61.5	$C_{10}H_{15}N_3O$	62.15	7.82	62.07	7.81	P1; M	Pale brown prisms
p-Phenetyl	CH_3	CH_3	C	100	53.5–54	$C_{10}H_{15}N_3O$	62.15	7.82	61.79	7.71	P1	Buff plates
2,5-Diethoxyphenyl	CH_3	CH_3	A	33	(139–140/0.5)	$C_{12}H_{19}N_3O_2$	60.73	8.07	59.41	7.63		
p-Dimethylamino-phenyl	CH_3	CH_3	C	100	92–93.5	$C_{10}H_{16}N_4$	62.47	8.39	62.92	8.19	MW; P3	Yellow laths

TABLE I *Continued*

Ar	R	R′	Method	Yield, %	M.P.°/(B.P.°/Mm.)	Formula	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Cryst. Solv.[a]	Color, Form
m-Bromophenyl	CH_3	CH_3	A	93	(101–102/0.25)	$C_8H_{10}BrN_3$	42.12	4.42	42.22	4.40		
p-Bromophenyl	CH_3	CH_3	D	59	63–63.5[b]						P1	Buff needles
	CH_3	H		—	86–87[c]						P2; MW	Creamy plates
	CH_3	*p*-bromophenylazo	E	—	142–142.5 (dec.)	$C_{13}H_{11}Br_2N_5$	40.25	2.79	40.31	2.64	B	Yellow laths
	RR′ = ethylene		F	33	56–56.5 (dec.)	$C_8H_8N_3Br$[d]	42.50	3.57	42.66	3.60	P1	Yellow prisms
o-Chlorophenyl	CH_3	CH_3	A	83	(146.3–146.5/12)[e]							
m-Chlorophenyl	CH_3	CH_3	A	96	(97–99/0.4)[m]							
m-Trifluoromethylphenyl	CH_3	CH_3	A	87	(76–78/1.3)	$C_9H_{10}F_3N_3$	49.77	4.64	50.87	4.80		
o-Nitrophenyl	CH_3	CH_3	C	85	32.5–33.5[n]	$C_8H_{10}N_4O_3$	49.48	5.19	49.52	5.07		
p-Nitrophenyl	CH_3	cyclohexyl	C	87	81–82	$C_{13}H_{18}N_4O_2$	59.52	6.92	59.52	6.65	P2	Orange needles
5-Chloro-2-methoxyphenyl	CH_3	CH_3	A	74	56.5–57.0	$C_9H_{12}ClN_3O$	50.59	5.66	50.73	5.54	P2; B	Yellow-orange Needles
2-Methoxy-4-nitrophenyl	CH_3	CH_3	C	92	113–113.5	$C_9H_{12}N_4O_3$	48.20	5.39	48.23	5.27	B-P1	Yellow needles
2-Methoxy-5-nitrophenyl	CH_3	CH_3	C	100	140.5–141	$C_9H_{12}N_4O_3$[o]	48.20	5.39	48.30	5.32	Bu; P3	Yellow-orange needles
4-Methyoxy-2-nitrophenyl	CH_3	CH_3	A	75	57–58	$C_9H_{12}N_4O_3$	48.20	5.39	48.33	5.30	B; E	Red-orange prisms
α-Naphthyl	CH_3	CH_3	G	48	38.5–39	$C_{12}H_{13}N_3$	72.33	6.58	72.58	6.42	P1	Red-purple prisms
β-Naphthyl	CH_3	CH_3	G	94	57–57.2[p]	$C_{12}H_{13}N_3$	72.33	6.58	72.25	6.49	P1	Red-brown prisms
3-Trifluoromethyl-4-nitrophenyl	CH_3	CH_3	C	85	70.5–71.5	$C_9H_9F_3N_4O_2$[q]	41.23	3.50	42.47	3.94	B-P1	
2-Methyl-4-nitrophenyl	CH_3	CH_3	C	100	120–120.5	$C_9H_{12}N_4O_2$	51.91	5.81	52.15	5.72	P3	Yellow leaflets or needles
4,4′-biphenylenebis	CH_3	CH_3	C	100	176–176.5	$C_{16}H_{20}N_6$	64.84	6.80	64.70	6.79	B; E	Yellow leaflets
2-Thiazolyl	CH_3	CH_3	H	33	75–75.5	$C_5H_8N_4S$	38.44	5.16	38.46	4.99	I; C-P1	Yellow laths
3-Quinolyl	CH_3	CH_3	C[r]	good	131.5 expl.[s]	$C_{11}H_{12}N_4$[t,u]	65.98	6.04	62.30	4.15	A[v]	Orange prisms
3-Pyridyl	CH_3	CH_3	C[r]	76	(81/0.3)	$C_7H_{10}N_4$[w]	55.98	6.71	55.49	6.88		

[a] P1 = pet. ether 40–60°; P2 = pet. ether 60–75°; P3 = pet. ether 90–100°; B = benzene; M = methanol; E = ethanol; W = water; I = isopropyl ether; C = carbon tetrachloride; A = acetone; Bu = butanol. [b] Cook *et al.*, *J. Am. Chem. Soc.*, 142 (1950), gave b.p. 128–129° (12 mm.). [c] Day, Campbell, and Coppinger, *J. Am. Chem. Soc.*, **73**, 4687 (1951), gave m.p. 67–67.8°, but no yield. [d] Goldschmidt and Badl, *Ber.*, **22**, 935 (1889), obtained only the pentazdiene. [e] Dimroth, Eble, and Gruhl, *Ber.*, **40**, 2397 (1907), prepared it by a Grignard reaction and give m.p. 81.5°. [f] Melts near 10°. [g] Adams and Hey, *J. Chem. Soc.*, 1521 (1951), gave b.p. 155° (18 mm.). [h] Goldschmidt and Badl[d] gave m.p. 111–112°. [i] Hunter, *J. Chem. Soc.*, 320 (1937), gave m.p. 62.5° but no yield. [j] Dimroth, Eble and Gruhl[e] gave m.p. 86–86.5°; *via* Grignard. [k] % N: calcd. 18.59, found 18.47. [l] LeFevre and Liddicoet, *J. Chem. Soc.*, 2743 (1951), gave b.p. 164–166° (27 mm.); there is a misprint in the paper, where this compound is called the *para* isomer. [m] Reported[f] b.p. 148–151° (20 mm.), no yield. [n] Reported[f] m.p. 31–32°; no yield given. [o] % N: calcd. 24.99; found 25.21. [p] Reported[3] m.p. 57–58°, no yield. This compound is incorrectly listed in *Chem. Abstr.* **38**, 74[2] (1944), as the β-isomer. [q] % N: calcd. 21.37, found 21.81. [r] Four moles of sulfuric acid used instead of hydrochloric acid during the diazotization. [s] Adams, Hey, Mammalis, and Parker, *J. Chem. Soc.*, 3181 (1949) gave m.p. 80–90° dec., and no analysis. [t] % N: calcd. 27.98; found 23.4. [u] Explodes during microanalysis. [v] The crude product is very unstable. It must be filtered and washed thoroughly with ice water, then recrystallized while wet. If it is allowed to dry while crude, it decomposes in a puff of smoke. The purified material darkens rapidly, but less dramatically, on storage. [w] % N: calcd. 37.3; found 37.61.

Method A.[3] The low-molecular weight, water-soluble amine was mixed with an excess of sodium carbonate solution containing ice, and the diazonium solution was added rapidly dropwise during about 10 to 20 min. (0.1–0.3 molar scale). After being stirred for about 0.5 hr. at 5–10°, the product was isolated as described below.

Method B. Water-insoluble amines were dissolved in water containing one equivalent of hydrochloric acid. This cold solution was mixed with the diazonium solution, and the entire mixture was added to an excess of cold sodium carbonate solution.

Method C. The amine was dissolved in the diazonium solution (water-insoluble amines were dissolved first in dilute acid), and sodium hydroxide solution was added at 5–10° until the mixture was alkaline. The use of sodium hydroxide as base is novel, and it offers advantages of convenience and yield over the sodium carbonate procedure.

Method D. Like Method C, except that sodium acetate was used as the base.

Method E. Methylamine was added to the diazonium solution until the mixture was alkaline (large excess). The crude product was collected, washed with water, and triturated with methanol. The pentazdiene was insoluble in methanol. Addition of water to the filtrate precipitated the triazene. The product from *p*-anisyldiazonium chloride and methylamine was a solid pentazdiene and a liquid triazene (?) which exploded on distillation. The product from benzenediazonium chloride and *t*-butylamine was a liquid which exploded on attempted distillation.

Method F. Sodium acetate solution was added to the diazonium solution to remove mineral acidity. Two equivalents of ethylenimine were then added, followed by an excess of sodium acetate. The product was filtered off. An additional quantity of product was obtained by adding sodium carbonate to the filtrate.

Method G. Like Method D, except that sodium carbonate was added after the addition of sodium acetate.

Method H. The amine (0.2 mole) in 150 g. of concentrated sulfuric acid and 70 g. of water was diazotized with sodium nitrite. The procedure then followed Method C.

Isolation of products. Following coupling by one of the above procedures, the liquid products were separated and the aqueous layer was extracted with ether, benzene, carbon tetrachloride, or petroleum ether (b.p. 60–75°). The combined organic layers were washed with water, dried with potassium carbonate or sodium or magnesium sulfate, then vacuum-distilled.

The solid products were collected, washed with water, and dried. Occasionally, the aqueous filtrates were extracted with an organic solvent and the extracts were evaporated. The low-melting, low-molecular weight products were in general vacuum-distilled before crystallization; the high-molecular weight triazenes were crystallized, often with the aid of charcoal. Petroleum ether was usually a satisfactory crystallization solvent, though for the less soluble compounds, some benzene was added. Occasionally methanol or butyl alcohol was used.

Formation of azides on pyrolysis of 1-aryl-3,3-ethylenetriazenes. p-Toluenediazonium chloride was coupled with ethylenimine according to Method F. The dark red oil could not be induced to crystallize from petroleum ether. After vacuum drying, it was analyzed.

Anal.[4] Calcd. for $C_9H_{11}N_3$ (triazene): C, 67.05; H, 6.88. Found: C, 67.84; H, 6.10.

This oil decomposed steadily on attempted distillation, giving a product, b.p. 31.5° (0.15 mm.); reported for *p*-tolyl azide, b.p. 80° (10 mm.).[6]

Anal. Calcd. for $C_7H_7N_3$: C, 63.13; H, 5.30. Found: C, 63.58; H, 5.31.

Method F applied to *p*-anisyldiazonium chloride gave an oil which was not analyzed but was distilled directly. The distillate boiled at 45–46° (0.1 mm.). The analysis suggests a mixture of 60% of *p*-anisyl azide and 40% of 1-*p*-anisyl-3,3-ethylenetriazene.

Anal. Calcd. for mixture of 60% $C_7H_7N_3O$ and 40% $C_9H_{11}N_3O$: C, 58.18; H, 5.34. Found: C, 58.20; H, 4.94.

Method F applied to benzenediazonium chloride gave a crude product which decomposed on distillation. The redistilled volatile material boiled at 63–66° (21 mm.); reported for phenyl azide, b.p. 66–68° (21 mm.).[6] The infrared spectrum exhibits a strong band at 2120 cm.$^{-1}$ which is characteristic of aryl azides; authentic triazenes do not absorb in this region. Its ultraviolet spectrum showed peaks at 285, 278, and 248 mμ, with intense end absoprtion.

p-Nitrobenzenediazonium chlorides and ethylenimine appeared to give the triazene, m.p. 70–70.5° (vigorous dec.), yellow leaflets from petroleum ether (60–75°). However, on standing, it decomposed to impure *p*-nitrophenyl azide.

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(4) Microanalyses by Spang Microanalytical Laboratory and by Anna Griffin in this laboratory.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Dimethylhydrazones of Aliphatic, Aromatic, and Heterocyclic Aldehydes and Their Infrared Absorption Characteristics

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A series of 37 aldehyde dimethylhydrazones have been prepared as isosteres of the tumor-growth retardant 3,3-dimethyl-2-phenyltriazene. Infrared absorption data clearly establish a band at 1640–1590 cm.$^{-1}$ characteristic of the C=N linkage and, as the strongest absorption in the spectra, a band at 1070–960 cm.$^{-1}$ which can be correlated with the electron releasing or electron attracting character of the substituents in the benzene ring of the aromatic aldehyde dimethylhydrazones.

The observation that 3,3-dimethyl-1-phenyltriazene, $C_6H_5N{=}N{-}N(CH_3)_2$, is an effective material for the retardation of tumor growth[1] suggested that the isosteric grouping, $>C{=}N{-}N(CH_3)_2$, might confer a similar activity on the aldehyde dimethylhydrazones in which the group is found. This class of compounds is practically completely unknown. The only previously recorded examples are the dimethylhydrazones of benzaldehyde,[2] *p*-isopropylbenzaldehyde,[2] furfural,[2] cyclohexanal,[2] formaldehyde,[3] and acetaldehyde.[3] Thirty-seven additional derivatives have now been prepared and their properties are described in the tables along with infrared absorption characteristics.

The availability of infrared data for these compounds makes it possible to establish new structural correlations for the atomic groups present. The series of aliphatic aldehyde dimethylhydrazones all show an absorption in the 1610 cm.$^{-1}$ region which is attributable to the C=N stretching vibrations. This is apparently the first location of the frequency (C=N) in compounds containing the $>C{=}N{-}N<$ group. In the series of dimethylhydrazones of formaldehyde-acetaldehyde-acetone the band shifts from 1585 cm.$^{-1}$ to 1610 cm.$^{-1}$ to 1639 cm.$^{-1}$. A similar shift occurs with increasing methyl substitution on the C=C band and can be attributed to either a weighting effect or the electron release characteristics of the methyl group. For the glyoxal derivative, the band is split into bands at 1678 cm.$^{-1}$ and 1550 cm.$^{-1}$, presumably as a result of mechanical interaction or resonance between the two identical C=N bonds in which one band is raised, the other lowered with the average at 1614 cm.$^{-1}$.[4] Conjugation with the benzene ring would probably place this absorption band in the 1590 cm.$^{-1}$ region which is intermediate between the 1600 cm.$^{-1}$ and 1580 cm.$^{-1}$ benzene C=C absorption bands. As a result the C=N band is obscured in the aromatic aldehyde derivatives, and a similar situation exists in the heterocyclic series. These types show two characteristic absorption bands at 1613–1587 cm.$^{-1}$ and 1580–1555 cm.$^{-1}$ and, in about a fourth of the examples, a third band at 1681–1616 cm.$^{-1}$.

The presence of two absorption bands centered at about 1471 cm.$^{-1}$ and 1450 cm.$^{-1}$ in nearly all of the dimethylhydrazones are characteristic carbon-hydrogen deformation modes associated with methyl (and methylene where present) groupings. These along with strong, characteristic C—H absorption bands in the 2941–2778 cm.$^{-1}$ range are of confirmatory interest. Additional characteristic bands occurring in spectra of all types of dimethylhydrazones are found near 1282 cm.$^{-1}$, 1136 cm.$^{-1}$, and 870–905 cm.$^{-1}$. The last probably results from contributions from the C—H out of plane deformation also characteristic of the aldehyde CHO group[5] and the N—N stretching band,[6] both of which are known to occur in this region. It is present in 36 out of 38 compounds. The two exceptions are the acetaldehyde derivative and the acetone derivative.

Perhaps the strongest, and therefore most characteristic, band observed with every one of the 38 derivatives prepared is the 1066–963 cm.$^{-1}$ region. Shifts in this band can be correlated with the electron releasing and attracting nature of the substituents in the aryl groups. Such correlations have been recorded relating shifts in the carbonyl absorption band to Hammett *sigma* values for substituted benzoic acid,[7] dibenzoyl peroxides,[8] and acetophenones.[9] Fig. 1 shows a plot of the wave length at which this absorption band occurs *vs.* Hammett *sigma* values for fifteen *m*- and *p*-substituted aryl and the pyridine aldehydes. The

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TABLE I

DIMETHYLHYDRAZONES OF ALIPHATIC CARBONYL COMPOUNDS

Carbonyl Compound	Yield, %	B.P. (°C.)	n_D/T	Nitrogen Analysis		Principal Infrared Absorption Bands[a]						
				Calcd.	Found							
Formaldehyde[b]	70	69–71	1.4266/27	—[b]	—	1585s[c]	1477m	1451m	1393w	—	1261m	1135m	1008vs	887s
Acetaldehyde[b]	44	90–93	1.4326/28	32.53	31.28[d]	1610m[e]	1471s	1447s	1379s	1348m	1255s	1142s	1017vs	855s
Isobutyraldehyde	64	125–127	1.4355/27	24.53	24.43	1613m	1473s	1449m	1385m	1366m	1256s	1142m	1020vs	887m
Hexanal	60	181–184	1.4452/27	19.70	19.67	1608w	1468s	1445m	1379w	—	1252m	1136m	1015s	879m
Octanal	65	114–115/3	1.4489/29	16.45	16.67	1610w[f]	1471s	1447m	1395w	1357w	1255m	1139m	1031s	874m
Decanal	66	113–115/2	1.4517/29	14.12	14.29	1613m[g]	1471s	1447m	1379w	1357w	1256m	1139m	1031s	870m
Glutaraldehyde	64	113 6/3	1.4903/26	30.41	30.15	1613m[h]	1475s	1449s	1404w	1364w	1258s	1143s	1033s	877m
Acetone	75	92–94	1.4255/27	27.97	27.93	1639s[i]	1473s	1451s	1370m	1361s	1256m	1153m	1020s	852m
Acetylacetone	72	76–79/5	1.4728/27	30.41	29.22[d]	1616s[j]	1468s	1453m	—	1359m	1290m	1153m	1020s	894w
Glyoxal	60	105/10	1.5626/27	39.40	39.35	1678w	1468s	1443s	1420s	1379w	1259s	1133s	1013s	892s
						1527s								

[a] In the 1660–850 cm.$^{-1}$ range. All measured in carbon tetrachloride solution. [b] F. Klages *et al.*, *Ann.*, **547**, 1–38 (1941). [c] Also 1410w, 1170m, 1036m. [d] The low nitrogen values are attributed to the presence of traces of water which could not be removed by techniques successfully used with others in this series which are also hygroscopic and form constant boiling mixtures. The acetylacetone product rapidly turns colored on exposure to air, apparently undergoing oxidation. [e] Also 1404w, 935m. [f] Also 1412w. [g] Also 1404w, 1010m, 893m. [h] Also 1010 m. [i] Also 1610m, 1439s, 1220w, 1198m, 1081m, 964s. [j] Also 1570m, 1437m, 1190m, 1087w, 1058m, 986w, 977w, 919w.

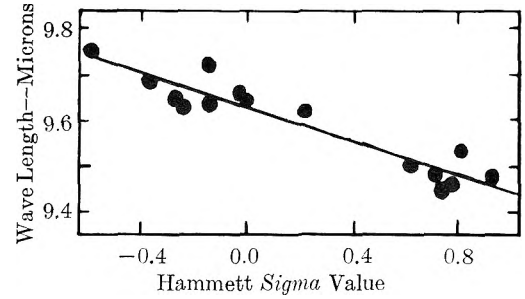

FIG. 1. INFRARED ABSORPTION *vs.* HAMMETT *sigma* VALUE FOR SUBSTITUTED ARYL DIMETHYLHYDRAZONES.

presence of this strong band at 965 cm.$^{-1}$, the highest value of the entire series, in acetone dimethylhydrazone, can be attributed to the electron release characteristics of the two methyl groups indicating the importance of hyperconjugation structures. This is not, however, consistent with the observation that this band occurs at 1008 cm.$^{-1}$ in formaldehyde dimethylhydrazone and 1028 cm.$^{-1}$ in acetaldehyde dimethylhydrazone. One would expect a value for the formaldehyde derivative below that for the acetaldehyde derivative.

Preliminary incomplete data on the evaluation of these materials in tumor growth retardation studies have shown that pyridine-3-carboxaldehyde dimethylhydrazone has a ±, − rating at a dose level of 30 mg./kg. in tests on experimental mouse sarcoma 180.[10] Tests with pyridine-2,6-dicarboxaldehyde dimethylhydrazone and with pyridine-4-carboxaldehyde methylhydrazone have shown ± (250 mg./kg.), − (125 mg./kg.) and ±, ? (125 mg./kg.) ratings, respectively. Many of the others are toxic. These results do not establish either strong or consistent activity and additional testing to determine the meaning of these results is necessary.

EXPERIMENTAL[11]

Details of typical preparations of materials listed in the tables are given. The aldehydes, dimethylhydrazine, and methylhydrazine were obtained from commercial sources.[12] Most of the heterocyclic hydrazones were unstable and turned dark on standing.

Isobutyraldehyde dimethylhydrazone. A solution of 7.0 g. (0.1 mole) of isobutyraldehyde and 7.0 g. (0.116 mole) o dimethylhydrazine was heated to reflux and cooled. Solid sodium hydroxide was added to induce the separation of two layers. The nonaqueous layer was separated and the treatment with solid sodium hydroxide was repeated until no aqueous layer separated. Distillation from sodium hydroxide gave 7.0 g., 64%, of isobutyraldehyde dimethylhydrazone, b.p. 125–127°.

(10) The authors are indebted to Dr. C. C. Stock and Dr. D. A. Clarke, Sloan-Kettering Institute, for conducting these evaluations. The testing procedure and rating scale have been described by Stock *et. al.*, *Cancer Research, Suppl. No. 1*, p. 91 (1953) and *Suppl. No. 2*, p. 179 (1955).

(11) Analyses by Micro Tech Laboratories, Skokie, Ill.

(12) The authors acknowledge with thanks the gift of samples of acetylacetone and glutaraldehyde from Carbide and Carbon Chemicals Corp. and of 2,5-diethoxyterephthalaldehyde from Tennessee Eastman Co.

TABLE II.—Dimethylhydrazones of Substituted Benzaldehydes

Substituent	Yield, %	B.P. or M.P. (°C.)	Physical Data[a]	Nitrogen Analysis Calcd.	Found	Principal Infrared Absorption Bands[b]											
—[c]	71	b100/3	1.5930/29	—	—	—	1595s	1570s	—	1475s	1449s	1404w	1370s	1276s	1136s[d]	1036S	885m	T
2-Hydroxy	59	b128/4	1.6078/23	17.06	17.16	1629m	1603s	1575m	1502m	1488s	1453m[e]	1408m	1374m[f]	1282[g]	1143m[d]	1036S[h]	897m	L
4-Hydroxy	50	m153	EW	17.27	17.18	1616s	1600m	1580m	1520s	1477m	1451s	1410w	1379m[f]	1277s[g]	1140m[d]	1031S[h]	898s	K
2-Methoxy	71	b118/3	1.6065/11	15.72	15.63	—	1610s	1567m	1497s	1475s	1445s	1410w	1368w[f]	1259s[g]	1139m[d]	1036S[h]	893m	L
4-Methoxy	70	b120/3	1.6048/11	15.72	15.60	1616s	1603m	1572m	1517s	1475s	1449s[e]	1408w	1372m[f]	1247S[g]	1142m[d]	1036S[h]	894s	L
2-Ethoxy	66	b136/4	1.5863/13	14.57	14.80	—	1610s	1570m	1499s	1479s	1466s[e]	1401w	1368w[f]	1253S[g]	1143m[d]	1049S[h]	893s	L
4-Chloro	83	m72	EW	15.38	15.37	—	1595s	1555w	1493s	1473s	1445m[e]	1401m	1362m	1279m[g,i]	1134s[d]	1038s[h]	885s	T
3-Nitro	63	m45	M	21.75	21.70	—	1597m	1572m[j]	1538S	1479s	1449m[e]	1412w	1362S[f]	1259w	1138m[d]	1055S[h]	866m	T
4-Nitro	78	m112	E	21.75	21.88	—	1603m	1563s	1522s	1477m	1447w[e]	1387w	1348S[f]	1261w[g,i]	1135m[d]	1056S[h]	880m	T
4-Dimethylamino	26	m74	EW	21.97[k]	22.06	1616s			1524m	1475w	1449m	—	1355s	1266w[g,i]	1136m	1025S[h]	889m	T
4-Isopropyl[c]	90	b131/6	1.5665/29			1618w	1597m	1563w	1515w	1477s	1451m[e]	1389w	1368m	1280m	1142s	1037S[h]	892s	L
4-Acetamido	25	m166	EW	20.47	20.63	1681s	1600m	1572m	1513s	1466m	1447w[e]	1404m	1368m[f]	1244m	1131m	1035S	887m	L
2,4-Dihydroxy	39	m149	MW	15.55	15.48	1623s	1608s	1575m	1513s	1466m	1445sh	—	1344s	1250s[g,i]	1149s[d]	1022m[h]	878s	K
2-Hydroxy-3-methoxy	51	m88	EW	14.42	14.23	1647w	1605w	1572s	—	1473s	1453m[e]	1410m	1372w	1264S	1143m[i]	1050s[h]	900	L
3-Methoxy-4-hydroxy	89	m88	EW	14.42	14.58	—	1613m	1582m	1515s	1453s	1433s[e]	1385m	1362m	1276S[g,i]	1136m[d]	1037S[h]	894s	T
2-Hydroxy-5-nitro	50	m168	N	20.09	19.98	1623w	1587m	1558m	—	1464s	1433m	1397m	1348s	1282s[g,i]	1124m[d]	1048m[h]	905s	K
3,4-Dimethoxy	45	m40	D	13.45	13.34	—	1608m	1572m	1515s	1471s	1449m[e]	—	1370ws	1274s	1142s	1029s[h]	894s	L
2,3-Dimethoxy	62	b130/2	1.5942/11	13.45	13.53	—	1600s	1572m	1488S	1453s	1410m[e]	1404m	1362s[f]	1285s[g,i]	1139s[d]	1042S[h]	894m	L
3,4-Diethoxy	30	m64	M	11.86	11.91	—	1608m	1572m	1520S	1488s	1453m[e]	1399s	1374m[f]	1272S[g,i]	1144s[d]	1037S[h]	896s	T
4-Aldehydo[l]	76	m182	E	25.67	25.36	—	1592m	1580m	1548m	1471s	1445m	1408w	1366m	1277m	1134s[d]	1033S	883s	L
4-Aldehydo-2,5-Diethoxy[l]	22	m147	MW	18.29	18.07	—	—	1577m	1502m	1475s	1453s	1397m	1366w	1272m[g,i]	1136m[d]	1024s[h]	905s	T

[a] n_D for liquids—solvents for recrystallization of solids; E, ethanol; W, water; M, methanol; N, nitromethane; D, diethyl ether. [b] In the 1680–870 cm.$^{-1}$ range. Medium: T, CCl_4; L, $CHCl_3$; K, KBr. [c] D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949). [d] Additional bands at 1115–1053. [e] Additional bands at 1445–1406. [f] Additional bands at 1333–1304. [g] One to three additional bands 1212–1157. [h] One to three additional bands at 1013–909. [i] Additional bands at 1263–1229. [j] Additional bands at 1553s. [k] Calcd. C, 69.07; H, 8.96. Found, C, 69.12; H, 8.90. [l] bis(Dimethylhydrazone).

TABLE III.—Dimethylhydrazones of Heterocyclic Aldehydes

Aldehyde	Yield, %	B.P. or M.P. (°C.)	Nitrogen Analysis Calcd.	Found	Principal Infrared Absorption Bands[a]									
Pyridine-2	77	b128/13[b]	28.17	28.32	1595sh	1575s	1468s	1439s	1427m	1361m	1285m	1135m[c]	1048S[d]	892s[e]
Pyridine-3	82	b138/10[f]	28.17	28.17	1595s	1565m	1477s	1453m	1422m	1372m	1285m	1136m[c]	1042s[d]	886m
Pyridine-4	73	m65–6	28.17	27.87	1600s	1582s	1477m	1449m	1418m	1370s	1295s	1134m[c]	1053S[d]	876s
6-Methylpyridine-2	94	m51–3	25.75	25.40	1600s	1577S	1460s		1412m	1359m	1279s	1157m[c]	1057S[d]	899s[e]
Pyridine-2,6-di	82	m125–6	31.94	32.01		1575s	1460s	1431m	1414m	1351s	1279s	1136s	1058S[d]	890s[e]
Thiophene-2	87	b125/7[g]	18.17	18.31		1575m	1477s	1449m	1427m	1366m	1282s	1139s[c]	1042S[d]	878s
3,4-Dihydro-2H-pyran-2	88	b98/8[h]	18.17	18.13	1647s	1613m	1475m	1449m		1389w	1266sh[i]	1140m[c]	1066S[d]	903w
Furan-2	87[j]	b82/4.5	—	—	1603w	1582m	1486m	1466s 1445m	1420w	1342s	1266s	1130m[c]	1034S[d]	883s[e]

[a] In the range 1680–870 cm.$^{-1}$ All run in carbon tetrachloride. [b] n_D^{28} 1.6038; picrate, m.p. 185°. [c] Additional bands at 1136–1066. [d] Additional band at 1026–926. [e] Additional bands at 890–870. [f] n_D^{28} 1.6048; picrate, m.p. 180°. [g] n_D^{27} 1.6284. [h] n_D^{27} 1.4970. [i] Additional bands at 1241 vs. [j] n_D^{26} 1.5753, D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949).

o-Ethoxybenzaldehyde dimethylhydrazone. A solution of 15 g. (0.1 mole) of *o*-ethoxybenzaldehyde and 7.0 g. (0.116 mole) of dimethylhydrazine was refluxed 3 hr. Distillation of the reaction mixture, after evaporation of the excess hydrazine, gave 12.6 g., 66%, of the product, b.p. 136–138°/4 mm.

2,5-Diethoxyterephthalaldehyde bis(dimethylhydrazone). A solution of 6.6 g. (0.03 mole) of 2,5-diethoxyterephthalaldehyde and 5.0 g. (0.083 mole) of dimethylhydrazine in 25 ml. of alcohol was refluxed for 3 hr. The solid which precipitated on cooling was recrystallized from methanol-water to give 2.0 g., 22%, of the product, m.p. 147–148°.

p-Dimethylaminobenzaldehyde dimethylhydrazone. A solution of 15 g. (0.1 mole) of *p*-dimethylaminobenzaldehyde and 7.0 g. (0.116 mole) of dimethylhydrazine in 30 ml. of concentrated hydrochloric acid and 25 ml. of ethanol was refluxed for 3 hr. The solution was made basic with concentrated ammonium hydroxide, filtered hot, and cooled to precipitate the crude product. Recrystallization from ethanol-water gave 5.0 g., 26%, of the product, m.p. 74–75°.

Pyridine-2-carboxaldehyde dimethylhydrazone. A mixture of 5.35 g. (0.05 mole) of pyridine-2-carboxaldehyde and 4.0 g. (0.067 mole) of dimethylhydrazine was fractionated after standing 1 hr. to give 5.7 g., 77%, of the crude product, b.p. 128–132°/13 mm. Refractionation gave the pure product, b.p. 128–130°/13 mm., n_D^{28} 1.6038. The picrate prepared from this product melts at 185–186°.

Pyridine-4-carboxaldehyde dimethylhydrazone. This product was prepared by the procedure given for the isomeric 2-carboxaldehyde. The fraction b.p. 136–149°/21 mm. solidified in the receiver. Recrystallization from petroleum ether gave 73% of the product, m.p. 60–64°. Additional recrystallization from petroleum ether and from water gave the pure product, m.p. 65–66°.

Infrared spectra were determined using a Baird double beam recording spectrophotometer with sodium chloride optics. All measurements were calibrated against the 3.419μ band for polystyrene. The medium used is given in the tables of data. Solutions were run at approximately 5% concentrations. The abbreviations used signify w (weak), m (medium), s (strong), S or vs (very strong), sh (shoulder)

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Infrared Spectra of Allenic Compounds

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From the inspection of the infrared spectra of 58 allenic compounds, 48 of them from the literature, 2 resynthesized, and 8 synthesized for this study, it was concluded that the bands at 1950 and 850 cm.$^{-1}$ are characteristic of the allene bond system with certain variations due to substitution. The antisymmetrical stretching frequency at 1950 cm.$^{-1}$ appears as a doublet when the allene group is terminal and is substituted by an electron-attracting group (CO_2H, CO_2R, $CONH_2$, COCl, COR, CF_3, CN). Its intensity decreases with increasing substitution of electronically similar groups. The band at 850 cm.$^{-1}$ is characteristic of the terminal $=CH_2$ group and its absence is good evidence for the absence of terminal allenes. It has an overtone at 1700 cm.$^{-1}$ of low intensity. The synthesis of the new allenes is described.

Because of the increasing interest in allenic compounds it became important to develop fast and safe methods for their identification. The present paper deals with the application of infrared spectroscopy to this problem. Certain empirical rules became apparent which were successfully tested and applied to all available allenic compounds. Some allenic compounds were especially synthesized for this study; other data were collected from the literature or obtained by personal communications with other investigators. In some cases infrared spectra of the allenic compounds prepared by other workers was determined in our laboratories.[2]

For the identification of allenes two bands are of special interest. In the 1950 cm.$^{-1}$ region, ν_1 (due to the antisymmetrical C=C=C stretching vibration) sometimes appears as a doublet,[3] and ν_2 (due to torsional motion of an allenic terminal methylene) in the 850 cm.$^{-1}$ region. The latter band has an overtone, $2\nu_2$ at 1700 cm.$^{-1}$ The presence of ν_1 and ν_2 and their relative intensities clearly differentiates between allenes containing various substituents. Tables I to V list the allenic compounds available for this study and the position and intensities of the ν_1, ν_2 and $2\nu_2$ bands.

Explanation of Tables I to V. Tables I to V contain pertinent infrared data collected during this study for allenic compounds. These data were obtained from many different sources, under diversified conditions and using many different instruments. Therefore, the actual frequencies of the absorption bands listed in these tables are quite uncertain.

Frequencies are in reciprocal centimeters (cm.$^{-1}$). The frequency of a band is followed by an intensity description. The usual terms (v = very, s = strong, m = medium, w = weak) are used.

The meanings of other terms are: — = no appreciable absorption band; na = information for this frequency range is not available; [] = "ac-

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(2) We wish to thank Dr. Foil A. Miller and his coworkers for all the determinations and for the fruitful discussions.

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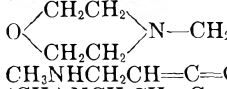
TABLE I

MONOSUBSTITUTED ALLENES

No.	Compound	Reference	ν_1	$2\nu_2$	ν_2
1	$H_2C{=}C{=}CH_2$	[4]	1957 v s	1687 w	842 m
2	$CH_3CH{=}C{=}CH_2$	[5]	1961 v s	1701 m	858 v s
3	$C_4H_9CH{=}C{=}CH_2$	[6]	1945 v s	1685 m	848 v s
4	$C_6H_5CH{=}C{=}CH_2$	[7]	1925 s	—	860 m
5	$ClCH{=}C{=}CH_2$	[8,9]	1960 w	1750 w	—
6	$BrCH{=}C{=}CH_2$	[8,9]	1960 w	1750 w	875 v s
7	$ICH{=}C{=}CH_2$	[8]	1940 w	na	na
8	$HO_2CCH{=}C{=}CH_2$	[10,11]	1930, 1900 s	[1670] v s	850 s
9	$CF_3CH{=}C{=}CH_2$	[12]	2000, 1970 s	1695	na
10	$C_2H_5OCH{=}C{=}CH_2$	[13]	1970 (?)	na	na
11	$C_6H_5OCH{=}C{=}CH_2$	[14]	1950 m	—	835 m
12	$HO_2CCH_2CH{=}C{=}CH_2$	[15,16]	1967 v s	na	na
13	$HOCH_2CH{=}C{=}CH_2$	[17]	1980 s	1707 m	853 v s
14	$CH_3(CH_2)_5CHOHCH{=}C{=}CH_2$	[18]	1953	na	na
15	$(C_2H_5)_2NCH_2CH{=}C{=}CH_2$	[19,20]	1960 s	1965 m	850 s
16		[19,20]	1957 s	1700 m	855 s
17	$CH_3NHCH_2CH{=}C{=}CH_2$	[19,20]	1957 s	1700 m	850 s
18	$(CH_3)_2NCH_2CH{=}C{=}CH_2$	[19,20]	1960 s	1705 m	844 s
19	$HOCH_2CH_2CH{=}C{=}CH_2$	[21,22]	1957 s	—	842 s
20	$CH_3CHOHCH_2CH{=}C{=}CH_2$	[21]	1970 (?)	na	na

cidental band," *i.e.*, that a band occurs in the frequency range but that it is not considered to be due to the vibration specified at the head of the column; ? = assignment indicated is doubtful; (?) = relative intensity not known.

The frequency assignments are: ν_1 = band near 1950 cm.$^{-1}$ due to antisymmetrical C=C=C stretching vibration; ν_2 = band near 850 cm.$^{-1}$ due to torsional motion of an allenic terminal methylene group; $2\nu_2$ = overtone of ν_2.

Certain correlations between the structures of allenic compounds and their infrared spectra can now be made:

1. The only allenic compounds for which ν_1 appears as a doublet (*e.g.* 1930 and 1950 cm.$^{-1}$) are those containing a terminal allenic grouping ($C{=}C{=}CH_2$) and which have one of the following groups directly attached to the allenic system: $-CO_2H$, $-CO_2R$, $-CONH_2$, $-COCl$, $-CO-R$, $-CF_3$, $-CN$. The same groups are predominately *meta*-directing when attached to a benzene nucleus. It is likely that the origin of the splitting of ν_1 is in the electron-withdrawing property of these groups.

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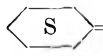
(38) J. H. Wotiz and R. J. Palchak, *J. Am. Chem. Soc.*, **73**, 1971 (1951).

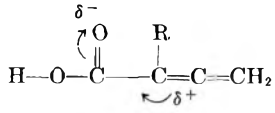
(39) J. H. Ford, C. D. Thompson, and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 2619 (1935).

(40) Incorrectly identified in the original reference.

TABLE II

DISUBSTITUTED ALLENES

No.	Compound	Reference	ν_1	$2\nu_2$	ν_2
21	$(CH_3)_2C{=}C{=}CH_2$	22,23	1930 s	1685 w	845 v s
22	$CH_3(C_2H_5)C{=}C{=}CH_2$	22	1960 s	1700 w	847 s
23		22	1955 s	1680 w	843 s
24	$C_4H_9{-}C(C_2H_5){=}C{=}CH_2$	24	1925 m	1675 v w	845 s
25	$C_3H_7C(CO_2H){=}C{=}CH_2$	3	1950, 1930 s	[1650] s	840 s
26	$C_3H_7C(CONH_2){=}C{=}CH_2$	3	1950, 1930 s	na	na
27	$C_4H_9C(CO_2H){=}C{=}CH_2$	25	1950, 1930 s	[1700] v s	850 s
28	$C_4H_9C(CONH_2){=}C{=}CH_2$	3	1950, 1930 s	na	na
29	$C_4H_9C(CO_2CH_3){=}C{=}CH_2$	25	1950, 1930 s	[1700] v s	850 s
30	$C_5H_{11}C(CO_2H){=}C{=}CH_2$	3	1950, 1930 s	na	na
31	$C_4H_9C(COCl){=}C{=}CH_2$	26	1930, 1900 s	[1720] v s	847 v s
32	$C_4H_9C(CH_3C{=}O){=}C{=}CH_2$	26	1930, 1910 s	[1685] v s	855 s
33	$C_4H_9C(CH_3C{=}N{-}NH{-}C_6H_3(NO_2)_2(2,4)){=}C{=}CH_2$	26	1910 m	[1700] s	856 m
34	$C_5H_{11}C(C{\equiv}N){=}C{=}CH_2$	27	1925, 1910 w	[1700] w	?870 m
35	$C_4H_9C(CH_2OH){=}C{=}CH_2$	26	1930 s	1700 w	848 s
36	$C_4H_9C(CH_2OCC_6H_3(NO_2)_2(3,5)){=}C{=}CH_2$	26	1925 s	[1700] v s	855 s
37	$(CH_3)_3CCHOHC(C_4H_9){=}C{=}CH_2$	26	1940 w	[1725] w	845 m



2. The increase in substitution about the allene by alkyl or aryl groups decreases the intensity of ν_1. In the case of tetraphenylallene (compound 54) this band is "absent." The presence of the allene grouping was recently demonstrated[41] by nuclear magnetic resonance studies.

3. The intensity of ν_1 is not greatly affected by an increase in substitution about the allene, if the substituents are different in their electronic behavior (*e.g.* compound 55).

4. The absence of ν_2 (850 cm.$^{-1}$) band is evidence for the absence of a terminal allene.

5. The $2\nu_2$ (1700 cm.$^{-1}$) absorption band is of little use for the characterization of allenes because it is a weak band which appears in a region frequently occupied by bands due to other bonds.

The position and intensities of ν_1 and ν_2 can be explained by making formal analogies between the allenic bond and a double bond.[1]

(41) J. H. Wotiz, D. O'Reilly and D. E. Mancuso, unpublished.

EXPERIMENTAL

A number of the compounds listed in Tables I to V are

TABLE III

DISUBSTITUTED ALLENES (NON-TERMINAL)

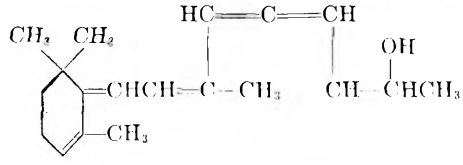
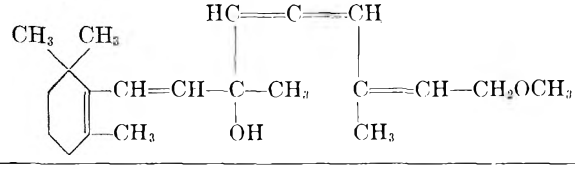
No.	Compound	Reference	ν_1
38	2-Naphthyl—CH=C=CH—C_6H_4Br-*p*	28	1915 (?)
39	*p*-C_6H_5-C_6H_4—CH=C=CH—C_6H_5	29	1930 s
40	1,3-Heptamethyleneallene	30	1940 s
41	CH_3CH=C=$CHCO_2H$	31	1970 (?)
42	HO_2CCH=C=$CHCO_2H$	32,33	1970 s
43	CH_3O_2CCH=C=$CHCO_2CH_3$	32,33	1971 s
44	$(CH_3)_3CCOCH$=C=CH—C_4H_9	26	1925 w
45	$CH_3(CH_2)_5COCH$=C=$CH(CH_2)_7CO_2H$	18,34	1947 s
46	$H(C\equiv C)_2$—CH=C=$CH(CH=CH)_2CH_2CO_2H$	35	1930 w
47	$H(C\equiv C)_2$—CH=C=$CH(CH=CH)_2CH_2CO_2CH_3$	35	1930 w
48		36	1925 w
49		37	1940 m

TABLE IV

TRISUBSTITUTED ALLENES

No.	Compound	Reference	ν_1
50	C_4H_9C=C=$C(CO_2H)$—H (CH_3)	38,3	1960 s
51	$(CH_3)_2C$=C=$CHCH_3$	26	1940 w
52	$(C_6H_5)_2C$=C=CHC_6H_5	29	(2000–1900) v w
53	$(CH_3)_2C$=C=$CHCH(CH_3)_2$	17	1940 w

TABLE V

TETRASUBSTITUTED ALLENES

No.	Compound	Reference	ν_1
54	$(C_6H_5)C$=C=$C(C_6H_5)_2$	23	[1920] w
55	C_4H_9C=C=$C(CO_2H)$—CH_3	38,3	1930 m
56	$(CH_3)_3CC$=C=$C(Br)$—C_6H_5	39,11	1925 m
57	$(CH_3)_3C$—C=C=$C(CO_2H)$—C_6H_5	39,11	1920 m
58	$(C_2H_5)_2C(CH_3)$—C=C=$C(CO_2H)$—C_6H_5	39,40	1900 s

new and their method of synthesis is described here along with some reactions which were found unsatisfactory.

Butylbutadienoyl Chloride (Comp. 31). Sodium butylbutadienoate was prepared in 99% yield by adding a solution of sodium hydroxide to butylbutadienoic acid[25] until the solution was slightly basic to Alkacid paper. The water was then removed by lyophilization (freeze drying). The sodium salt (53 g., 0.31 mole) was added in portions to a solution of 47 g. (0.37 mole) of oxalyl chloride in 100 ml. of dry, thiophene-free benzene.[42] After the gas evolution ceased, the sodium chloride was removed by filtration and the filtrate distilled yielding 35 g. (71% yield) of the acid chloride, b.p. 73–74° at 8 mm., n_D^{25} 1.4812.

Anal. Calcd for $C_8H_{11}OCl$: C, 60.6; H, 7.0. Found:[43] C, 60.0; H, 6.7.

Attempted preparation of the acid chloride from the acid using thionylchloride gave products of high chlorine content which were difficult to avoid or to remove by distillation.

3-Butyl-3,4-pentadiene-2-one, (Comp. 33) was prepared by the method of Cason,[44] using 0.077 mole of methylmagnesium bromide, 7 g. (0.04 mole) of anhydrous cadmium chloride and 12 g. (0.076 mole) of butylbutadienoyl chloride in 50 ml. of benzene. The reaction product was hydrolyzed with ammonium chloride solution and the ether-benzene layer washed with sodium carbonate solution. Distillation yielded 4 g. of fraction, b.p. 47–51° at 2 mm., n_D^{25} 1.4740, which gave a positive halogen test with alcoholic silver nitrate. The unreacted acid chloride was removed by adding it to 10 ml. of liquid ammonia. After the vigorous reaction ceased the ammonia was evaporated, the residue suspended in ether and the ammonium chloride removed by filtration. The filtrate yielded 1 g. of the ketone, b.p. 60° at 3 mm.

Anal. Calcd. for $C_9H_{14}O$: C, 78.2; H, 10.2. Found: C, 78.8; H, 10.4.

Its 2,4-*dinitrophenylhydrazone* (Comp. 33) was recrystallized from ethanol and melted at 137–138°.

Attempts to prepare Comp. 32 by the low temperature acetylation[45] of the Grignard reagent derived from 1-bromo-2-heptyne[25]

$$\left[\begin{array}{l} C_4H_9C\equiv C-C^-H_2 \\ \quad\quad\quad\ddots \\ C_4H_9\dot{C}=C=CH_2 \end{array}\right] Mg^+Br$$

were unsuccessful as a complex mixture of products which contained mostly the acetylenic ketone $C_4H_9C\equiv CCH_2$—CO—CH_3 was formed. The reaction of the above mentioned Grignard reagent with propionitrile, followed by hydrolysis, also yielded a mixture from which it was impossible to isolate the desired allenic ketone.

2-Butyl-2,3-butadienol-1 (Comp. 35). The Grignard re-

(42) R. Adams and L. H. Ulich, *J. Am. Chem. Soc.*, **42**, 599 (1920).

(43) Microanalytical Laboratory, University of Pittsburgh.

(44) J. Cason, *J. Am. Chem. Soc.*, 68, 2078 (1946).

(45) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

agent from 58 g. (0.33 mole) of 1-bromo-2-heptyne was prepared as previously described.[25] Gaseous formaldehyde was prepared by the thermal decomposition of 60 g. of paraformaldehyde. The reaction product of the formaldehyde with the Grignard reagent was hydrolyzed with ammonium chloride solution, the ether layer washed with sodium bisulfite and dried. Distillation yielded 69 g. of liquid boiling from 75–88° at 3 to 1 mm. pressure, n_D^{25} 1.4645–1.4630. Redistillation yielded 32 g. (76% yield) of the allenic alcohol, b.p. 57° at 0.6 mm. n_D^{25} 1.4686.

Anal. Calcd. for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.1; H, 11.8.

Its *3,5-dinitrobenzoate* (Comp. 36) was crystallized from petroleum ether (b.p. 30–60°) to a constant melting point of 36–37°.

Anal. Calcd. for $C_{15}H_{16}N_2O_6$: C, 56.2; H, 5.0. Found: C, 56.2; H, 5.4.

When a sample of it was mixed 3,5-dinitrobenzoate derived from 3-octynol-1[46] a ten degree melting point depression was noted.

2,2-Dimethyl-4-butyl-4,5-hexadiene-3-ol (Comp. 37) was prepared by the Reformatsky reaction using 18 g. (0.28 gram-atom) of freshly sanded zinc strips, 44 g. (0.25 mole) of 1-bromo-2-heptyne and 24 g. (0.3 mole) trimethylacetaldehyde, and a mixture of ether, benzene, tetrahydrofurane, and dioxane as solvents. The reaction started during the removal of ether by distillation. The reaction product was hydrolyzed by pouring it on a mixture of ice and acetic acid. The products were dissolved in ether and the ether solution washed with sodium carbonate. Distillation yielded 24.7 g. (66% yield) of product boiling from 76–84° at 2 mm., n_D^{25} 1.4551–1.4547, and 12 g. of higher boiling liquids.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.1; H, 12.2. Found C, 79.1; H, 12.5.

Infrared analysis showed the fraction, b.p. 82° at 2 mm., n_D^{25} 1.4550 to be the allenic alcohol contaminated with some of its acetylenic isomer, $C_4H_9C{\equiv}CCH_2CHOH{-}C(CH_3)_3$ (very weak C≡C band at 2200 cm.$^{-1}$).

2,2-Dimethyldeca-4,5-dien-3-one. (Comp. 44). The mixture of Comp. 37 and its acetylenic isomer (7 g., 0.038 mole) was dissolved in 20 ml. of acetone, cooled to −4°, and oxidized by the addition of 3.3 g. (0.033 mole) of chromium trioxide in a solution of 2.8 ml. of sulfuric acid and 20 ml. of water.[47] The temperature was kept under 5° by external cooling. The reaction product was continuously extracted with ether for 12 hr. The ether extract was washed with a small portion of water and dried. Evaporation of the ether left 7.6 g. of a residue which upon distillation yielded 3.1 g. of product, b.p. 88–91° at 0.7 mm., n_D^{25} 1.4504–1.4495.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 77.9; H, 12.5.

(46) M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949).

(47) K. Bowden, I. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Spectroscopic analysis showed that the allenic alcohol was destroyed by the oxidation and that the distillate was a mixture of the starting acetylenic alcohol and its oxidation product, $C_4H_9C{\equiv}C{-}CH_2{-}CO{-}C(CH_3)_3$. To 1 g. of this mixture in 10 ml. of ethanol was added 20 ml. of 5% aqueous sodium carbonate.[48] The mixture was agitated at 50° under nitrogen for 24 hr., and then extracted with ether. Distillation yielded Comp. 44, b.p. 65° at 0.8 mm., n_D^{25} 1.4523.

2-Methyl-2-chloro-3-pentyne. Into a solution of 151 g. (1.5 moles) of 2-methyl-3-pentynol[49] (prepared in 39% yield by the condensation of propynylmagnesium bromide and acetone, b.p. 55° at 25 mm., n_D^{18} 1.4438) in 400 ml. of dry petroleum ether (b.p. 30–60°) containing 2 g. of hydroquinone and 60 g. of powdered calcium chloride, was passed anhydrous hydrogen chloride.[50]

The temperature was kept at 0°. The solution was treated with solid anhydrous potassium carbonate, filtered and distilled, yielding 120 g. (67% yield), b.p. 55° at 70 mm., n_D^{25} 1.4475. Its infrared spectrum contained the C≡C stretching frequency at 2210 cm.$^{-1}$ and was void of absorption bands in the double bond absorption region. Attempted preparation of the chloride as described by Zakharova[49] or by using thionyl chloride gave impure products.

2-Methyl-2,3-pentadiene (Comp. 51) was prepared by the dehalogenation[6,22] of 38 g. (0.33 mole) of 2-methyl-2-chloro-3-pentyne using 14 g. (0.37 mole) of lithium aluminum hydride in 1000 ml. of dry dioxane. Upon distillation, 4.7 g. (18% yield), b.p. 70–72°, n_D^{25} 1.4285, of the allene was isolated. Its infrared and Raman effect analyses revealed the presence of less than 20% of its acetylenic isomer, $(CH_3)_2CH{-}C{\equiv}C{-}CH_3$.[51]

Tetraphenylallene (Comp. 54) was prepared by the dehydrohalogenation of 213 g. (0.5 mole) of 2-bromo-1,1,3,3-tetraphenylpropene[52] (prepared by Wen-Yang Wen) using 100 g. of potassium hydroxide in 500 ml. of refluxing alcohol. From 190 g. of the crude product, 90 g. (53% yield) of the pure allene, m.p. 164–165°, was obtained by crystallization from acetone. Its infrared spectrum contains a band at 1920 cm.$^{-1}$, which is due, however, to the phenyl ring. Its Raman effect[2] analysis revealed a weak line at 1938 cm.$^{-1}$ due to the allene. Because of the large amount of light scattering which caused a heavy background on the Raman plate, it was impossible to establish the exact intensity of the bands.

PITTSBURGH 13, PA.

(48) L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1740 (1955).

(49) A. I. Zakharova, *J. Gen. Chem. (USSR)*, **17**, 1277 (1947); [*Chem. Abstr.* **42**, 3722 (1948)].

(50) A. Buroway and E. Spinner, *J. Chem. Soc.*, 3752 (1954).

(51) Grédy, *Bull. soc. chim. France*, **2**, 1951 (1935).

(52) D. Volander and C. Siebert, *Ber.*, **39**, 1024 (1906).

[CONTRIBUTION FROM DEPAUW UNIVERSITY AND THE INDIANA STATE BOARD OF HEALTH]

A Study of the Infrared Spectra of Some Alkyl-Substituted Carbostyrils

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The infrared spectra of several substituted carbostyrils are presented and discussed.

Characteristic absorption bands originating in the out-of-plane deformation vibrations of the hydrogen atoms on an aromatic ring have been found to appear in the infrared spectrum between 1225 and 650 cm.$^{-1}$ Well established correlations between the positions of these bands and various

types of aromatic substitution compounds have made possible the identification of isomeric compounds in many cases.

Although phenyl ring generalizations can be applied to heterocyclic aromatics such as quinoline and pyridine,[1] all interpretations of infrared spectra of this type substance must be made with some caution until spectra of known compounds are established. For the past several years a number of studies in this laboratory have been concerned with the properties of alkyl substituted carbostyrils. Except for a few reports[2,3] the infrared spectra of carbostyrils or 2-quinolones have not been studied nor interpreted. It is the purpose of this article to record the infrared spectra of a number of these compounds and to correlate the observed bands in the 1000 to 650 cm.$^{-1}$ region with the structures of the molecules. The preparation of the substituted carbostyrils has already been described.[4,5] In this study two new compounds have been prepared, 1,4,6-trimethylcarbostyril and a compound which, from an interpretation of its infrared spectrum, has been assigned the structure of 1,4,7-trimethylcarbostyril. These two compounds were prepared by the action of diketene on *p*-N-methyltoluidine and *m*-N-methyltoluidine. In the reaction of diketene on the latter and subsequent ring closure in concentrated sulfuric acid, two compounds, 1,4,5- and 1,4,7-trimethylcarbostyril, are possible. Previous studies on quinoline compounds have shown that generally steric influences have favored the formation of a 4,7-substituted compound over its 4,5-isomer. A study of the spectra plus confirming chemical data has indicated that 1,4,7-trimethylcarbostyril is the isomer formed in this case.

Discussion of the spectra. The spectra were obtained on carbon disulfide solutions in a 0.098-mm. cell, except for one (A) which is a composite of a carbon tetrachloride solution up to 1300 cm.$^{-1}$ and a carbon disulfide solution the remainder of the spectrum. A rock salt plate was in the reference beam. The instrument, a Baird Associates, was run on slow scan through the entire region of interest. Solute concentrations were approximately 50 mg./ml. except 1,4-dimethyl, and 1,4,6- and 1,4,7-trimethylcarbostyrils which were saturated solutions. The spectra are recorded in Fig. 1 along with the spectrum of carbon disulfide for comparison purposes. Significant bands were accurately measured and the relative intensities were given to bands based on the strong band appearing at 13.4 μ in the spectra A through F and the strong band at 12.4 μ in G and H. In Table I the following designations are made for intensities. The letters v s

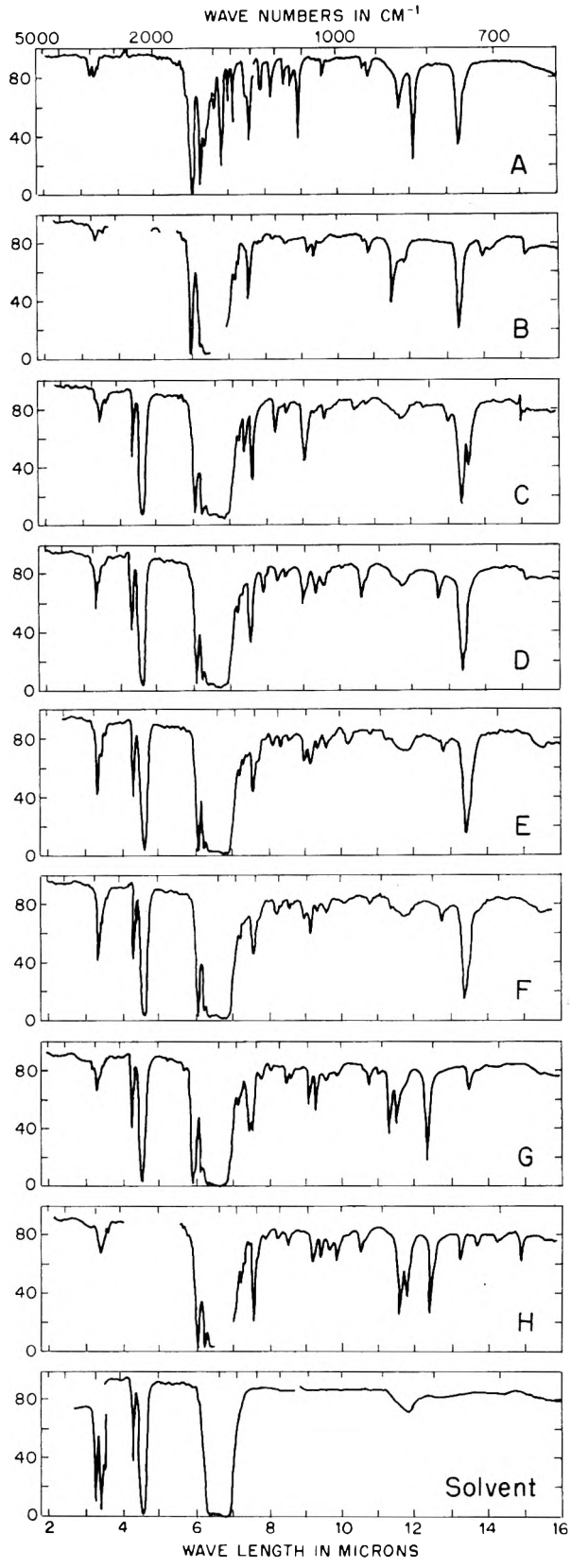

FIG. 1

(1) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 234.

(2) B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.*, **73**, 2641 (1951).

(3) J. A. Gibson, W. Kynaston, and A. S. Lindsey, *J. Chem. Soc.*, 4340 (1955).

(4) C. E. Kaslow and D. J. Cook, *J. Am. Chem. Soc.*, **67**, 1969 (1945).

(5) D. J. Cook and W. C. Lawall, *J. Am. Chem. Soc.*, **70**, 1918 (1948).

are given those bands whose intensity is greater than that of the 13.4 μ or 12.4 μ bands, s when intensity is equal to 13.4 μ or 12.4 μ bands, m when two thirds to one third the intensity of the strong band, w when the intensity is one third to one fourth that of the strong band and v w when less than one fourth the intensity of the strong band. A study of the spectrum of carbon disulfide in Fig. 1 will show that the sharp bands at 4.2 μ and 4.6 μ and the broad bands at approximately 6.3 μ to 7.2 μ and near 11.7 μ are solvent bands.

compound is anomalous. In the spectrum for 1,4-dimethylcarbostyril (B) a medium intense band appears at 867 cm.$^{-1}$ and can be assigned to the vibration arising from the one hydrogen of the heterocyclic ring. The spectra, C, D, E and F, are those of compounds with substituents on the 1, 3, and 4 positions and which show only one strong absorption peak at 746–747 cm.$^{-1}$. These spectra establish this peak as due to the vibration of the four adjacent hydrogens in the homocyclic ring.

An inspection of the spectrum for the known com-

TABLE I

SIGNIFICANT ABSORPTION BANDS FOR ALKYL CARBOSTYRILS

Carbostyril		Lactam Vibrations		H-Deformation Vibrations		N-Alkyl Vibration (?)	
		Microns	Wave Nos.	Microns	Wave Nos.	Microns	Wave Nos.
N-Methyl	(A)	6.04	1656 v s	11.74	852 m	7.65	1307 m
				12.12	825 v s		
				13.35	749 s		
1,4-Dimethyl	(B)	6.05	1653 v s	11.53	867 m	7.62	1312 m
				13.35	749 s		
1,3,4-Trimethyl	(C)	6.12	1634 v s	13.03	767 v w	7.62	1312 m
				13.39	747 s		
				13.60	735 w		
1,4-Dimethyl-3-ethyl	(D)	6.12	1634 v s	12.75	784 v w	7.62	1312 m
				13.39	747 s		
1,4-Dimethyl-3-propyl	(E)	6.12	1634 v s	12.79	781 v w	7.62	1312 m
				13.40	746 s		
1,4-Dimethyl-3-butyl	(F)	6.12	1634 v s	12.77	782 v w	7.62	1312 m
				13.40	746 s		
1,4,6-Trimethyl	(G)	6.03	1658 v s	11.39	879 m	7.62	1312 m
				11.59	862 m		
				12.41	806 s		
1,4,7-Trimethyl	(H)	6.03	1658 v s	11.56	865 s	7.58	1319 v s
				11.75	853 m		
				12.40	806 s		

In all spectra the lactam band falls between 1658 and 1634 cm.$^{-1}$ as previously reported.[2] Substitution in the hetero ring appears to decrease the frequency of the vibration, while substitution in the homocyclic ring appears to increase the frequency. There is a medium band common to all spectra between 1307 and 1319 cm.$^{-1}$ which is possibly due to the N-alkyl group in each molecule. The spectra of carbostyrils made in this laboratory which have no substituent on the nitrogen do not show this absorption peak. In all the compounds where methyl substitution is only in the hetero ring, it is to be noted that a strong band appears between 746 and 749 cm.$^{-1}$ and in the compounds with a methyl substituent in the 6 or 7 positions no strong band appears in this region. The position and intensity of this band can be identified as due to the four adjacent hydrogens in the homocyclic ring. In the spectrum for N-methylcarbostyril (A) another strong band appears at 825 cm.$^{-1}$ which, based on literature information[1] as to position and intensity, can be recognized as due to the vibration of the two adjacent hydrogens in the heterocyclic ring. The medium intense 852 cm.$^{-1}$ band for the

pound 1,4,6-trimethylcarbostyril (G) shows a strong band at 806 cm.$^{-1}$ which can be assigned to the vibration of the two hydrogens in the homocyclic ring while medium intense bands appearing at 862 and 879 cm.$^{-1}$ can be due to the single hydrogen atoms in the homocyclic and heterocyclic rings. Since both of these bands fall in the region indicative of one unsubstituted hydrogen, no attempt has been made to decide which one is more significant. The similar spectrum of the compound assigned the 1,4,7-trimethylcarbostyril structure (H) plus the lack of any medium intense band in the 725–680 cm.$^{-1}$ region, which would be indicative of the presence of three adjacent hydrogens, appears sufficient evidence to assign this compound a structure containing two and one unsubstituted hydrogens and not three adjacent hydrogens as would be found in the isomer 1,4,5-trimethylcarbostyril.

That the evidence given by the infrared data is correct was supported by the following chemical study. When the compound believed to be 1,4,7-trimethylcarbostyril was oxidized with selenium dioxide, the 4-formyl derivative was formed which

was further oxidized with dichromate and acid to 1,7-dimethyl-4-carboxycarbostyril. Decarboxylation of this product led to a substance which melted at 105–107°. This agrees with the reported melting point for 1,7-dimethylcarbostyril.[6]

EXPERIMENTAL[7]

The 1,4-dimethyl and 1,3,4-trimethylcarbostyrils have been previously reported.[4,5] 1,4,6- and 1,4,7-Trimethylcarbostyrils are new compounds and were prepared by the action of diketene on *p*-N-methyltoluidine and *m*-N-methyltoluidine. The description of the preparation of one of these compounds follows.

1,4,6-Trimethylcarbostyril. A mixture of 33.9 g. (0.28 mole) of *p*-N-methyltoluidine and 50 ml. of benzene was heated to reflux. Diketene (34.5 g., 0.41 mole) was added dropwise over a period of 3 hr. The benzene was removed under reduced pressure and the residue poured into 100 ml. of concentrated sulfuric acid in 5-ml. portions so as to keep the temperature below 70°. The sulfuric acid mixture was then heated on the steam bath for 15 min. This mixture was then poured into 1 l. of ice water and neutralized with solid sodium hydroxide. After standing overnight the solid was collected and crystallized from ethanol. A recrystallization of the product from ethanol-water gave a white product melting at 106–107°. The yield was 90%.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found N, 7.17.

1,4,7-Trimethylcarbostyril. This compound was prepared in an exactly analogous manner starting with *m*-N-methyltoluidine. The yield was 93.5% and the compound melted at 103–104°. No other compound was isolated. This compound and 1,4,6-trimethylcarbostyril are both prone to retain large quantities of alcohol from the solvent, and constant melting points can be obtained only after lengthy drying in vacuum over anhydrous calcium chloride.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.15.

1,6-Dimethyl-4-formylcarbostyril. This compound was obtained (38% yield) as lemon-yellow needles, m.p. 181–183°, by a method previously described.[8]

Anal. Calcd. for $C_{12}H_{11}NO_2$: N, 6.96. Found: N, 7.21.

1,7-Dimethyl-4-formylcarbostyril. This compound was obtained (69% yield) as orange-yellow needles, m.p. 185–187°, by a method described earlier.[3]

Anal. Calcd. for $C_{12}H_{11}NO_2$: N, 6.96. Found: N, 6.91.

1,6-Dimethyl-4-carboxycarbostyril. A mixture of 8 g. (0.039 mole) of 1,6-dimethyl-4-formylcarbostyril and 3.51 g. of sodium dichromate (0.0134 mole) was suspended in 100 ml. water and mixed with a mechanical stirrer. Thirteen and one-tenth g. of concentrated sulfuric acid was added dropwise. After addition was complete the mixture was heated on the steam bath for 30 min. After cooling in ice the solid was collected and dissolved in 22 ml. of a 5% sodium hydroxide solution and filtered. Upon acidification of the filtrate with hydrochloric acid, 19.8 g. (61%) of the product was obtained. Recrystallization of a sample from ethanol and water gave pale yellow crystals which charred at 270° and decomposed at 290–295°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: N, 6.45; Neut. equiv., 217. Found: N, 6.70; Neut. equiv., 220.

1,7-Dimethyl-4-carboxycarbostyril. This compound was prepared in a manner analogous to that described above. The substance decomposed at 238–240°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: N, 6.45. Found: N, 6.78.

1,7-Dimethylcarbostyril. A 2.4-g. sample (0.011 mole) of 1,7-dimethyl-4-carboxycarbostyril was ground with 1.5 g. of soft glass and placed in a small distilling flask. The flask was left open to the air and heated in a Wood's metal bath at a temperature of 300–350° for 24 hr. At the end of this time the liquid was distilled under a pressure of 2 mm. The red-orange distillate solidified on cooling and was recrystallized from 15 ml. petroleum ether (35–60°) containing a few drops of benzene to bring the product into solution. A m.p. was 87–97°. A vacuum sublimation of this substance gave pale yellow needles, m.p. 105–107°. The reported m.p. is 107–108°.[6]

Acknowledgment. The financial aid received from the Du Pont Co. of Willmington, Del., by one of the authors (D. J. C.) in the form of a summer research grant is acknowledged with appreciation.

GREENCASTLE, IND.

(6) A. Kent, D. McNeal, and R. M. Cowper, *J. Chem. Soc.*, 1858 (1939).

(7) Melting points are uncorrected.

(8) Cook and Stamper, *J. Am. Chem. Soc.*, 69, 1467 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OHIO UNIVERSITY]

Fulvenes. III. Heat of Combustion and Resonance Energy[1]

JESSE H. DAY AND CHARLES OESTREICH[2]

Received July 30, 1956

The heats of combustion and the calculated resonance energies are reported for dimethylfulvene and diphenylfulvene. The reported values are consistent with the known properties of the fulvenes.

Although the fulvenes have been known for more than half a century[3] and many theoretical calculations made of the resonance energy of fulvene,[4] no experimental data for the estimation of resonance energies have appeared. This paper reports the heats

(1) Taken in part from the M.S. thesis of Charles Oestreich, June 1956.

(2) Present address, Department of Chemistry, Virginia Military Institute.

(3) J. Thiele, *Ber.*, **33**, 666 (1900).

(4) For a list of references see J. H. Day, *Chem. Revs.*, **53**, 167 (1953). Also see B. Pullman and A. Pullman, *Les Theories Electroniques de la Chimie Organique*, Masson et Cie, Paris, 1952.

of combustion and calculated resonance energies for dimethylfulvene and diphenylfulvene.

The data for the heats of combustion are summarized in Table I. These values and the resonance energy values in Table II should prove of value in the explanation and prediction of the chemical properties of the fulvenes. The methods of molecular orbitals and of valence bonds have in the past agreed less well for fulvene than for most other hydrocarbons, and the present data may prove useful in this connection.

from a plot of the logarithm of the vapor pressure against the reciprocal of the temperature, and found to be 10.56 kcal./mole. The needed heat of sublimation of diphenylfulvene was estimated in two ways: (1) by a method relying on the additivity of heat of sublimation values for the atoms in a hydrocarbon series,[6] and (2) by comparing the heats of sublimation of five hydrocarbons of nearly the same molecular weight as diphenylfulvene which have comparable structures. These estimates lead to a value lying between 23.5 and 26.1 kcal./mole.

TABLE I

REPRESENTATIVE DATA FOR THE HEATS OF COMBUSTION OF DIMETHYLFULVENE

Run	Weight Sample, G.	Calorimeter Temp. rise °C.	Heat Evolved in Cal.	HNO_3 Corr.	Fuse Wire Corr.	Capsule Wt.	Capsule Corr.	Net Heat in Kcal./Mole[a]
1	0.7312	6.112	15004	31.0	30.0	0.1425	1142	1113.2
2	.6521	5.522	13556	28.4	22.5	.1462	1223	1115.5
3	.6623	5.542	13605	27.2	30.0	.1292	1093	1114.3
4	.6847	5.767	14157	31.3	32.5	.1439	1153	1114.7
5	.5028	4.322	10601	23.6	35.0	.1303	1049	1114.7
			Representative Data for the Heats of Combustion of Diphenylfulvene					
1	0.3007	2.160	5301.6	9.4	25.0			2241.3
2	.3708	2.659	6527.6	11.9	28.5			2238.6
3	.3961	2.851	6999.0	11.6	38.0			2244.8
4	.3017	2.175	5339.4	10.6	34.0			2241.4

[a] The last column is the net heat evolved at constant volume. When the Washburn correction is made, and the heat of combustion corrected to constant pressure at 25° with reactants and products in their standard states, the average values become, for dimethylfulvene 1116.1 kcal./mole, for diphenylfulvene 2243.7 kcal./mole. The values at 25° and 1 atmosphere pressure for the reactants and products in the gaseous state are estimated to be for dimethylfulvene 1125.0 kcal./mole, for diphenylfulvene 2268.7 kcal./mole. (The water equivalent of the calorimeter at 25° was 2454.9 ± 0.9; the gelatine capsules had a heat of combustion of 8015 B.t.u./lb.)

TABLE II

RESONANCE ENERGIES OF TWO FULVENES

	Heat of Combustion[a]		Resonance Energy, Kcal./Mole
	Calcd.	Exper.	
Dimethylfulvene	1136.9	1125.0	11.9
Diphenylfulvene	2354.1	2268.7	85.4

[a] The calculated heats of combustion were made using the table of Klages' values as reported in Wheland.[5]

Much of the work that has been done with fulvenes has not required a high degree of purity. In this work considerable care was taken to insure maximum purity; the details are described in the experimental section.

The resonance energies were calculated by the usual subtraction of the measured heat of combustion (corrected to be that for gaseous reactants to gaseous products at 25°) from the theoretical value calculated using the tables compiled by Klages. Use of Franklin's tables[5] gives slightly higher values of the resonance energy. The data on the heat of vaporization of dimethylfulvene were calculated

An intermediate value of 25 kcal./mole was arbitrarily selected.

The resonance contribution of the fulvene moiety of the diphenylfulvene can be estimated by subtracting the resonance energies of two phenyl groups from the total resonance energy of diphenylfulvene. This gives a value of 12.6 kcal./mole for the fulvene part. The good agreement between the resonance values of dimethylfulvene and the fulvene moiety in diphenylfulvene is no doubt to some extent fortuitous. Since the calculation of resonance energies from heats of combustion and from tables of bond values are subject to a number of uncertainties, such that resonance energies of the order of three or four kcal./mole may or may not be real, we feel justified only in the following conclusions: that the resonance energy of the fulvene moiety is large enough to be real, is about one-third that of benzene, and is roughly half way between that of cyclopentadiene and that of such rings as thiophene and furan. It is interesting that one calculation of the resonance energy of fulvene gives a value of about 11 kcal./mole.[7]

The values reported here are consistent with the

(5) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, New York, 1955, pp. 86–105.

(6) V. Tateveskii, *Doklady Akad. Nauk. S.S.S.R.*, 75, 819 (1950); [*Chem. Abstr.*, 45, 6038c (1951)].

(7) G. W. Wheland, *J. Am. Chem. Soc.*, 63, 2025 (1941).

little that is known of the chemistry of the simple fulvenes, since they behave like aliphatic compounds with some aromatic properties. They undergo the Diels-Alder reaction either as a diene or as a dienophile, they hydrogenate more like aliphatics than aromatics, and certain of them can undergo either addition or substitution under the proper conditions.[8] The effects on the fulvene moiety of substituents on the exo-cyclic carbon atom probably have little to do with the resonance of the fulvene part, since the ultraviolet and visible spectra of fulvene itself are virtually identical with those of the aliphatic substituted fulvenes.[9] The resonance of the fulvene part extends little or not at all beyond the exo-cyclic carbon atom, since even methyl groups suffer some steric effects and larger groups are tightly packed and restricted, judging from Fischer-Hirshfelder models. In diphenylfulvene the crowding is so great that it is hard to imagine any reasonable excited state which could achieve the required planarity between any two of the three rings. We feel this is ample justification in calculating the resonance energy of the fulvene part of diphenylfulvene by subtracting the energy of two isolated benzene rings (or by subtracting the resonance energy of benzophenone) from that of the whole molecule.

There is no doubt that fulvenes have some aromatic character. The aromatic sextet of electrons usually associated with five or six member aromatic rings can be written for fulvene if we allow one of the sextet to be written outside the ring. Fulvenes have a dipole moment of consequence,[10,11] with the ring negative and the exo-cyclic carbon atom positive. The outside electron is thus not really totally outside, and from this consideration alone one might predict as a first approximation that fulvene would be somewhat aromatic, but not as strongly so as structures which include the entire aromatic sextet within the ring. This interpretation is at least in accord with the facts.

It would be of great interest to determine the resonance energy of these fulvenes from heats of hydrogenation, since these data are subject to smaller uncertainty than heats of combustion. Bond distances from x-ray or electron diffraction studies would also be very welcome.

We are pleased to acknowledge the generous financial support of the Socony-Mobil Oil Co.

EXPERIMENTAL

The heats of combustion were determined using a series 1200 Parr oxygen bomb calorimeter, with a platinum combustion cup. The calorimeter was calibrated under the conditions of use with benzoic acid tablets standardized by the National Bureau of Standards. Parr calibrated mercury thermometers were used.

Dimethylfulvene was made by the usual method,[3] but with cooling of the reaction flask and attachment of a reflux condenser to minimize loss of cyclopentadiene. The product was steam distilled, the oil layer dried over Drierite, then distilled through a 34-plate column, b.p. 40° at 4 mm. Hg. Only the center cut from each distillation was used, and combustion runs were made only on freshly distilled product. The liquid sample was enclosed in a gelatin capsule for weighing and for combustion.

The diphenylfulvene was prepared in the usual manner,[3] and recrystallized from methyl alcohol several times until the melting point was not improved by further recrystallization; m.p. 81.5–81.7°. The recrystallization was done by cooling a warm saturated solution. A hot solution results in the formation of a precipitate, which is probably an oxidation product.[12] The final product was dried *in vacuo* at 25°. Further estimates of purity were made by adding various amounts of the most likely impurity, benzophenone, to the purified diphenylfulvene and noting the melting point depression and the increase in melting point range thus caused. By extrapolation on a graph of melting point depression *versus* melting point, the maximum amount of benzophenone impurity in the purified diphenylfulvene was calculated to be less than 0.2%. Spectra of the purified diphenylfulvene, by itself and with known added amounts of benzophenone, were run. From these data the maximum amount of benzophenone present was estimated to be less than 0.1%. The diphenylfulvene was pressed into pellets for weighing and combustion.

Analysis of spectral data was made on a Beckmann DU Spectrophotometer.

ATHENS, OHIO

(8) J. H. Day and C. Pidwerbesky, *J. Org. Chem.*, **20**, 89 (1955).

(9) J. Thiec and J. Wiemann, *Bull. soc. chim. France*, 177 (1956).

(10) G. W. Wheland, and D. E. Mann, *J. Chem. Phys.*, **17**, 264 (1949).

(11) E. D. Bergman, and E. Fisher, *Bull. soc. chim. France*, **17**, 1084 (1950).

(12) C. Engler, *Z. Elektrochem.*, **18**, 945 (1912).

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Formazyl Complexes of the Quinoline Series

MUVAFFAK SEYHAN[1] AND W. CONARD FERNELIUS

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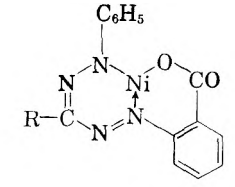
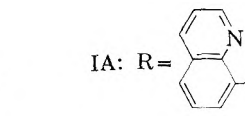
Three formazyl compounds of the general formula $C_6H_5NH—N=CR—N=NC_6H_4COOH$ are described where R represents various quinoline radicals and the carboxy group is in the *ortho* position relative to the formazan chain. These compounds form well defined complexes with nickel and uranyl ions. Three formazyl compounds of the type $C_6H_5NH—N=CR—N=NC_6H_5$ are also described. These do not form nickel and uranyl derivatives but those where R = 6-methyl- and 7-methyl-2-quinolyl readily form addition compounds with $CoCl_2$.

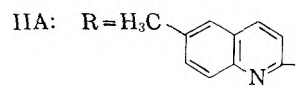
Formazyl compounds with a carboxy group in the *ortho* position relative to the formazan chain have pronounced complex-forming ability. A series of such complexes derived from the basic substance $R—C(N—NHC_6H_5)(N=NC_6H_4COOH(o))$ where R represents a heterocyclic radical, have been described in recent times.[2] The formation of complexes results through the substitution of hydrogen from the imino and carboxy groups by metal ions in alcohol solution. In most of the complexes which have been investigated the metal exhibits a smaller coordination number than the usual one. For example, in all nickel complexes it appears that only three of the coordinating positions of nickel are occupied[2e,f,g] while in the uranium complexes the uranium exhibits in some cases the usual coordination number of 6[2b,d] and in others, by contrast, the apparent coordination number 5.[2a,c] In all of the formazyl complexes so far investigated which are derived from the above parent substance, only the substituent R on the carbon atom of the formazan chain was different. Consequently, one is led to think that the indefiniteness of the coordination number of the uranium complexes must be dependent upon the nature of the R group. For the further clarification of this behavior, three new formazyl compounds have been prepared with R = 8-quinolyl(I), 6-methyl-2-quinolyl(II), and 7-methyl-2-quinolyl(III). These form with nickel sulfate in alcoholic solution highly colored crystalline complexes whose analyses are consistent with the formulas IA, IIA, and IIIA.



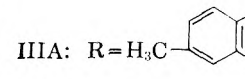
IA: R=



IIA: R=H_3C



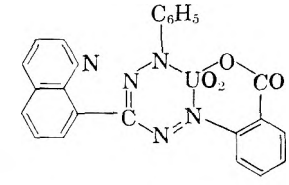
IIIA: R=H_3C

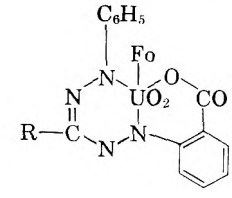


The formazyl compounds were prepared by coupling diazotized anthranilic acid with the corresponding aldehyde-phenylhydrazone in strongly alkaline solution: 8-quinolinecarboxaldehyde,[3] 6-methyl-2-quinolinecarboxaldehyde,[4] and 7-methyl-2-quinolinecarboxaldehyde.[5] As expected, in all of the nickel complexes, the nickel is linked with only three ligands.

The same formazyl compounds form with uranyl acetate in alcoholic solution, the uranium complexes of the constitutional formulas IB, IIB, and IIIB.

IB,





IIB, R = 6-methyl-2-quinolyl
IIIB, R = 7-methyl-2-quinolyl

The symbol Fo in formulas IIB and IIIB signifies a molecule of the corresponding formazyl compound attached to the uranium atoms. While the precipitation of the uranium complexes IIB and IIIB results spontaneously from bringing together the alcoholic solutions of the component, the formation of IB requires some time.

As the above structural formulas show, the uranium in IB manifests the coordination number 5 and

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(2) (a) M. Seyhan, *Chem. Ber.*, **87**, 396 (1954); (b) *Chem. Ber.*, **87**, 1124 (1954); (c) *Chem. Ber.*, **88**, 212 (1955); (d) *Chem. Ber.*, **88**, 646 (1955); (e) *Chem. Ber.*, **88**, 1454 (1955); (f) *Monatsh.*, **86**, 545 (1955); (g) *Monatsh.*, **87**, 234 (1956); (h) M. Seyhan and W. C. Fernelius, *Chem. Ber.*, **89**, 2482 (1956).

(3) V. M. Radionov and M. A. Berkengeim, *J. Gen. Chem. (U.S.S.R.)*, **14**, 330–6 (1944); [*Chem. Abstr.*, **39**, 4077 (1945)]; F. Gialdi and R. Ponci, *Farm. sci. e tec. (Pavia)*, **6**, 327–31 (1951); [*Chem. Abstr.*, **45**, 9117 (1951)].

(4) C. A. Bühler and S. P. Edwards, *J. Am. Chem. Soc.*, **74**, 978 (1952).

(5) M. Seyhan and W. C. Fernelius, *Chem. Ber.*, **89**, 2212 (1956).

in IIB and IIIB the coordination number 6. Whether the position of the ring nitrogen is the answer to the lack of the agreement of the coordination number or whether the presence of the methyl group exerts an influence cannot be said with certainty. For a definite assertion concerning such relationships, other methods of investigation must be employed.

An investigation was also undertaken with formazyl compounds not substituted in the *o*- position, *i.e.*, of the following type R—C(=N—NHC$_6$H$_5$)—N=NC$_6$H$_5$. The formazyl compounds which resulted from the coupling of diazotized aniline with the corresponding aldehyde-phenylhydrazone in strongly alkaline solution show no especial tendency for the formation of uranium or nickel complexes. The formazyls where R = 6- and 7-methyl-2-quinolyl (V and VI, respectively) yield in alcoholic solution with $CoCl_2 \cdot 6H_2O$ dark green crystals of the composition: formazyl·$CoCl_2$ while the formazyl where R = 8-quinolyl(IV) forms no such complex with cobalt(II) chloride.

EXPERIMENTAL[7]

8-Quinolinecarboxaldehyde.[3] A mixture of 10 g. 8-methylquinoline (b.p.$_{27}$ 132°) and 8.5 g. freshly prepared and unsublimed selenium dioxide was cautiously heated to 180–190° for 2 hr. using an air condenser. After cooling, the mixture, which in the meantime had solidified to a yellowish mass, was dissolved in 40 ml. 1:1 hydrochloric acid, filtered from the separated metallic selenium and decolorized with animal charcoal. Upon making the filtrate alkaline, the aldehyde precipitates as yellowish crystals: m.p. 92–93°. Yield 5.1 g.

8-Quinolinecarboxaldehydephenylhydrazone.[6] Yellow crystals from alcohol, m.p. 176°.

6-Methyl-2-quinolinecarboxaldehyde.[4] To a warm solution of 11 g. freshly prepared and unsublimed selenium dioxide in 100 ml. dioxane containing 4% water was added a solution of 11 g. 2,6-dimethylquinoline in 30 ml. dioxane. After 2 hr. heating under reflux, colorless crystals (m.p. 108–109°) were obtained by steam distillation. Yield 4.4 g.

6-Methyl-2-quinolinecarboxaldehydephenylhydrazone. Yellow crystals from alcohol, m.p. 198–199°.

Anal. Calcd. for $C_{17}H_{15}N_3$: N, 16.08. Found: N, 16.08.

6-Methyl-2-quinolinecarboxaldehyde-4-nitrophenylhydrazone. Dark yellow crystals from alcohol, m.p. 269–270°.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: N, 18.29. Found: N, 18.29.

6-Methyl-2-quinolinecarboxaldehyde-2,4-dinitrophenylhydrazone. Dark yellow crystals from alcohol, m.p. 252–253°.

Anal. Calcd. for $C_{17}H_{13}N_5O_4$: N, 19.94. Found: N, 20.12.

7-Methyl-2-quinolinecarboxaldehyde.[5] The oxidation of 1.7 g. 2,7-dimethylquinoline with 3.0 g. selenium dioxide gave colorless crystals, m.p. 69–70°. Yield 0.6 g.

7-Methyl-2-quinolinecarboxaldehyde-2-phenylhydrazone.[5] Yellow crystals from alcohol, m.p. 202–203°.

C-Substituted N-phenyl-N'-[2-carboxyphenyl]formazans (I–III). Five hundred fifty milligrams of anthranilic acid was dissolved in 2 ml. concentrated hydrochloric acid and diazotized with a concentrated solution of 340 mg. $NaNO_2$ at −5°. The diazonium solution was added to one of 770 mg. 8-quinolinecarboxaldehyde phenylhydrazone and 800 mg. sodium hydroxide in 120 ml. methanol at 0°. The mixture became red immediately. After 4 hr. it was filtered from some separated 8-quinolinecarboxaldehyde phenylhydrazone and acidified with glacial acetic acid. Upon the addition of water the red formazyl compound precipitated. It was recrystallized from alcohol.

The analogous formazans were prepared in the same manner using the corresponding aldehyde phenylhydrazones (Table I).

C-Substituted N,N'-diphenylformazans (IV–VI). One hundred milligrams of diazotized aniline was coupled with a strongly alkaline methanol solution of 200 mg. 8-quinolinecarboxaldehyde phenylhydrazone. After 3 hr. the mixture was filtered and the clear red solution acidified with acetic acid. Upon the addition of water, IV precipitated as red crystals. Upon the addition of 20% perchloric acid to the acetic acid solution of IV, the perchlorate precipitates as dark red crystals.

The analogous formazans were prepared in the same manner using the corresponding aldehyde phenylhydrazones (Table II).

TABLE I

C-SUBSTITUTED *N*-PHENYL-*N'*-[2-CARBOXYPHENYL]FORMAZANS

Compound	Anthranilic Acid, Mg.	Aldehyde, Mg.	Yield, Mg.	M.P., °C.	Calcd. Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	550	770	660	208–209 (d)	$C_{23}H_{17}N_5O_2$			17.71			17.61
II	225	340	225	186 (d)	$C_{24}H_{19}N_5O_2$	70.39	4.68	17.10	70.57	4.88	17.08
III	225	340	380	200 (d)	$C_{24}H_{19}N_5O_2$	70.39	4.68	17.10	70.01	4.86	17.31

TABLE II

C-SUBSTITUTED *N,N'*-DIPHENYLFORMAZANS

Compound	Aniline, Mg.	Aldehyde, Mg.	Yield, Mg.	$HClO_4$ Salt, M.P., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H
IV	100	200	105	163–165 (d)	$C_{22}H_{17}N_5 \cdot HClO_4$	58.47	4.02	57.97	3.98
V	225	450	100	208 (d)	$C_{23}H_{19}N_5 \cdot HClO_4$	59.29	4.33	59.12	4.57
VI	100	180	110	189–190 (d)	$C_{23}H_{19}N_5 \cdot HClO_4$	59.29	4.33	58.95	3.96

(6) J. Howitz and W. Schwenk, *Ber.*, **38**, 1282 (1905).

(7) All melting points are uncorrected. The microanalyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

TABLE III

ANALYTICAL AND OTHER DATA ON METAL COMPLEXES

Compound	Color	M.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Ni	Found C	Found H	Found N	Found Ni
IA	Black green	>300	$C_{23}H_{15}O_2N_5Ni$				12.98				13.43
IIA	Dark green	>300	$C_{24}H_{17}O_2N_5Ni$			15.02				14.89	
IIIA	Dark green	>300	$C_{24}H_{17}O_2N_5Ni$	61.83	3.68			60.83	3.86		
IB	Dark red	>330	$C_{23}H_{15}O_4N_5U$	41.63	2.28	10.56		39.96	2.79	9.90	
IIB	Dark red	236–237 (d)	$C_{48}H_{36}O_6N_{10}U$	53.03	3.34	12.89		52.99	3.53	13.36	
IIIB	Dark red	232–233 (d)	$C_{48}H_{36}O_6N_{10}U$	53.03	3.34	12.89		52.72	3.51	13.69	
VA	Dark green	263–264 (d)	$C_{23}H_{19}N_5 \cdot CoCl_2$	55.77	3.87	14.14		55.93	3.92	14.30	
VIA	Dark green	265 (d)	$C_{23}H_{19}N_5 \cdot CoCl_2$	55.77	3.87	14.14		56.12	4.20	14.36	

Nickel complexes (IA–IIIA). An alcoholic solution of 50 mg. of I was treated with a concentrated aqueous solution of 50 mg. nickel sulfate and of 50 mg. sodium acetate. The deep green solution was concentrated somewhat, the microcrystals which separated after cooling were sucked dry and rewashed thoroughly with water and then alcohol.

The other nickel complexes (Table III) were prepared similarly.

Uranyl complex (IB). An alcoholic solution of 50 mg. of I and 50 mg. uranyl acetate was heated on a waterbath under reflux for an hour and allowed to stand overnight. On the next day, the crystals which had separated were filtered and thoroughly washed with alcohol (Table III).

Uranyl complexes (IIB and IIIB). A warm alcoholic solution of 50 mg. compound II and 50 mg. uranyl acetate were brought together; the uranyl complex precipitated immediately and was recrystallized from alcohol. The complex IIIB was prepared analogously (Table III).

Cobalt complexes (VA and VIA). An alcoholic solution of 100 mg. of compound V and 65 mg. $CoCl_2 \cdot 6H_2O$ was heated on a water bath for about 0.25 hr. Crystals which separated were filtered and washed with alcohol. The complex VIA was prepared in the same way (Table III).

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Notes

A department for short papers of immediate interest.

Corn Plant Resistance Factor

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Received November 8, 1956

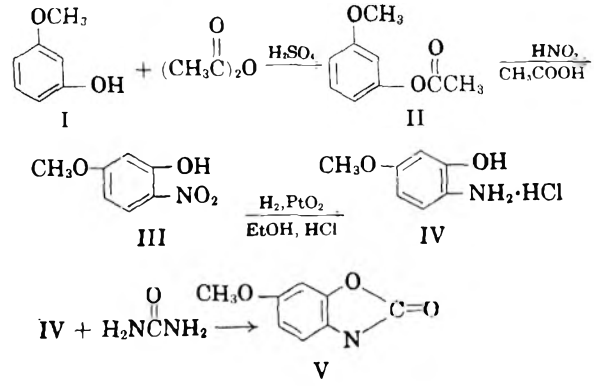
We have isolated a compound from the corn plant which appears to be partially responsible for the resistance of the plant to attack by the European corn borer. Virtanen and Hietala[1] previously reported a compound to be present in the rye plant which is benzoxazolinone. They found this compound prevented the growth of *Fusarium nivale*, a rye plant rot. After corresponding with a former member of our group Virtanen assumed a product he isolated from wheat and maize plants to be 6-methoxy-2(3)-benzoxazolinone[2] but never confirmed this assignment.

We have synthesized 6-methoxy-2(3)-benzoxazolinone and have shown it to be identical with the natural product by infrared spectra comparison and by mixed melting point. In our isolation procedure we designated the naturally occurring compound as *factor A* and found it to have the following constants: m.p. 154–155°; $\lambda_{max}^{H_2O}$ 230, 287 (E_{max} 10,000, 4,500); benzoyl derivative m.p. 161–163°; benzene sulfonyl derivative m.p. 163–164°.

Anal. Calcd. for $C_8H_7O_3N$: C, 58.18; H, 4.27; N, 8.48; CH_3O-, 18.75; Mol. Wt., 165. Found C, 58.41; H, 4.29; N, 8.40; CH_3O-, 18.46; Mol. Wt., 171 (ebulloscopic).

The material was readily recrystallized from water and was found to be soluble in dilute sodium hydroxide. On reviewing our infrared spectra, our analysis, the chemical nature of the compound and its degradation products, we decided to synthesize a methoxy-2(3)-benzoxazolinone. The 5-methoxy-2(3)-benzoxazolinone was previously synthesized,[3] m.p. 172°. On the basis of our absorption spectra we synthesized the 6-methoxy-2(3)-benzoxazolinone which had been postulated by Virtanen, *et al.*[2]

The procedure we followed involved the acetylation of monomethyl resorcinol, I, to give acetoxy methyl resorcinol, II, b.p. 135–136°/23 mm. Mononitration using nitric acid in glacial acetic acid gave 2-hydroxy-4-methoxynitrobenzene, (III), m.p. 94–95°, which on catalytic reduction gave the corresponding amino compound, IV. This compound on fusion with urea afforded 6-methoxybenzoxazolinone, V.



The product, V, obtained from the synthesis gave no depression in melting point when mixed with factor A and their infrared spectra were superimposable.

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(1) A. I. Virtanen and P. K. Hietala, *Suomen Kemistilehti*, 28B, 165 (1955); *Acta Chem. Scand.*, 9, 1543 (1955).

(2) A. I. Virtanen, P. K. Hietala, and O. Wahlroos, *Suomen Kemistilehti*, 29B, 143 (1956).

(3) W. J. Close, B. D. Tiffany, and M. A. Spielman, *J. Am. Chem. Soc.*, 71, 1265 (1949).

Rearrangement of Dihydroquercetin Tetramethylether with Alkali

CARL ENEBÄCK AND JARL GRIPENBERG

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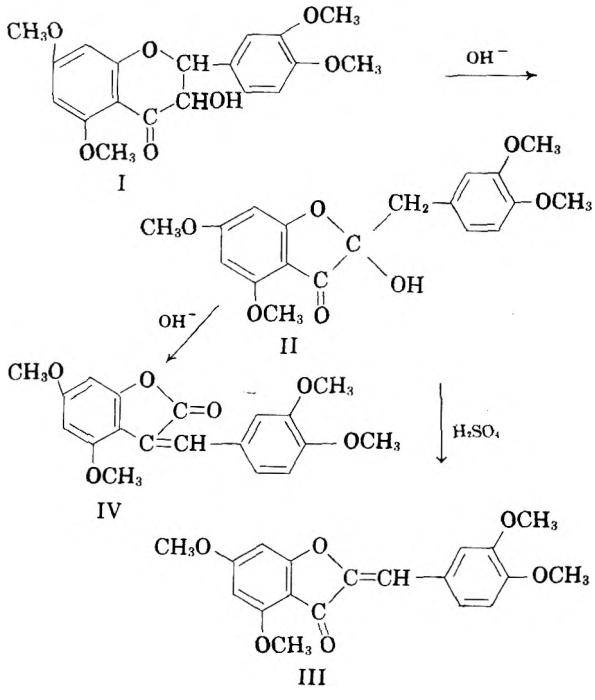
In a recent paper dealing with the methylation of dihydroquercetin (taxifolin) Hergert, Coad and Logan[1] found that methylation under certain conditions led to the formation of 2-(3,4-dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaran-3-one (II). The same compound could also be obtained by treatment of dihydroquercetin-3′,4′,5,7-tetramethylether (I) (Hergert, Coad and Logan[1] use the incorrect name 3′,4′,5,7-tetramethoxydihydroquercetin for this compound) for a few minutes with alkali. When treated with concentrated sulfuric acid II was converted into 2-(3,4-dimethoxybenzylidene)-4,6-dimethoxycoumaran-3-one (III). This is all in accordance with expectations.[2] However, their further statement that prolonged treatment of I or

(1) Hergert, Coad and Logan, *J. Org. Chem.*, 21, 304 (1956).

(2) Gripenberg, *Acta Chem. Scand.*, 7, 1323 (1953).

II with alkali also gives III is contrary to expectations. One would expect that such a treatment should, through a benzilic acid rearrangement, finally lead to 3-(3,4-dimethoxybenzylidene)-4,6-dimethoxycoumaran-2-one (IV), isomeric with III.[3,4,5]



As a matter of fact we synthesized the compound IV, making thereby the remark, that it should be formed from taxifolintetramethylether upon treatment with alkali.[5]

That it is indeed IV that is formed when II, and hence also I, is boiled with alkali has now been confirmed by a direct comparison of the product with synthetic IV, thereby establishing their identity. II was prepared by the method of Kimura[6] and gave, in agreement with Hergert, Coad and Logan,[1] upon treatment with concentrated sulfuric acid, III, identified by comparison with an authentic sample prepared according to Geissman and Fukushima.[7]

The isomeric compounds III and IV have nearly the same melting points, 171.5–172° and 173.5–174°, respectively, but they give a definite depression of melting point in a mixture test. They further differ in their color reactions with concentrated sulfuric acid. III gives a stable crimson-magenta color,[7] whereas IV in sufficient dilution gives a green color, which upon standing turns brown.

(3) Oyamada, *Ann.*, **538**, 44 (1939).
(4) Kotake and Kubota, *Ann.*, **544**, 253 (1940).
(5) Gripenberg and Juselius, *Acta Chem. Scand.*, **8**, 734 (1954).
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EXPERIMENTAL

2-(3,4-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaran-3-one (II). 2'-Hydroxy-3,4,4',6',α-pentamethoxychalcone[6] (1 g.) was dissolved in ethanol (100 ml.). To this was added 2*N* sulfuric acid (20 ml.) and the solution was refluxed for 24 hours. After removing the ethanol the product was taken up in ether. The ether solution was extracted with 1*N* sodium hydroxide. Acidification gave a precipitate, which was taken up in chloroform. Removal of the chloroform and recrystallization once from light petroleum-chloroform and once from methanol gave 0.6 g. white crystals, m.p. 176.5°. (Reported, 176°.[1,6])

3-(3,4-Dimethoxybenzylidene)-4,6-dimethoxycoumaran-2-one (IV). 2-(3,4-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaran-2-one (II) (0.5 g.) was dissolved in 48% ethanol (14 ml.) containing potassium hydroxide (0.5 g.). The solution was refluxed for one hour, acidified, and extracted with ether. The ether was removed and the residue recrystallized from ethanol giving 0.07 g. of yellow crystals, m.p. 173.5–174°, undepressed when mixed with an authentic sample.[5] It dissolved in concentrated sulfuric acid with a green color, slowly turning brown.

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Some 4(or 5)-(2'-Aminopropyl)imidazoles

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The substitution of a 2-aminopropyl group in place of the 2-aminoethyl side chain of phenethylamines was found by Alles[3] to produce but little change in the intensity of their peripheral sympathomimetic activities though the duration of such actions is much prolonged. The effects of corresponding substitution of the 2-aminoethyl side chain of histamine and of its 5(or 4)-methyl derivative that has similar physiological activities was of interest.

It was found that a synthesis of histamine itself could be accomplished from 1,4-diaminobutanone-2, and this synthesis has been recently reported by Fraser and Raphael.[4] The success of this method suggested the possibility of using it for preparing the corresponding 2-aminopropyl imidazole from 1,4-diaminopentanone-2. The preparation of this intermediate from 2-phthalimidobutyryl chloride has been improved over that described by Erne, Ramirez, and Burger.[5] Condensation of the so derived 1,4-diaminopentanone-2 with potassium thiocyanate gave 4(or 5)-(2'-aminopropyl)-2-thiolimid-

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(3) G. A. Alles, *J. Pharmacol.*, **47**, 337 (1933).
(4) M. M. Fraser and R. A. Raphael, *J. Chem. Soc.*, 226 (1952).
(5) M. Erne, F. Ramirez, and A. Burger, *Helv. Chim. Acta*, **34**, 143 (1951).

azole and this on oxidation gave the desired 4(or 5)-(2′-aminopropyl)imidazole. Its picrate and some other salts and derivatives are described.

The plan of synthesis of 5(or 4)-methyl-4(or 5)-(2′-aminopropyl)imidazole reported by Sarasin[6] was followed. The steps involving preparation of isonitroso-allylacetone and of amino-allylacetone had to be modified in our hands to obtain a sufficient amount of the resultant imidazole for pharmacological studies.

Studies of the depressor activities[7] of the 2-aminopropyl-imidazoles here described showed that each was only about one-hundredth as active as the corresponding 2-aminoethyl-imidazole. The 2-aminopropyl-imidazoles were found active in stimulating gastric secretion[8] and were included in some studies on cutaneous anesthesia and pain.[9]

EXPERIMENTAL

1-Chloro-4-phthalimidopentanone-2 (I). 2-Phthalimidobutyric acid was prepared following the procedure of Erne, Ramirez, and Burger,[5] and on drying at 80° under 15 mm. pressure melted at 121.5–122.5°. Its conversion to the acid chloride gave a product which crystallized from benzene, m.p. 85–86°. This was converted into (I) in almost 100% yield as follows: A solution of 2-phthalimidobutyryl chloride (31 g., 0.125 mole) in a liter of dry ether was added dropwise to an ice cold solution of diazomethane (15.5 g., 0.37 mole) in 500 ml. dry ether. After keeping overnight at −5° C. dry hydrogen chloride was passed in for 2 hr. at that temperature. After 12 hr. keeping at −5° removal of ether gave 32.3 g. of (I), m.p. 104°, after recrystallization from acetone, m.p. 105–106°.

1,4-Diphthalimidopentanone-2 (II). Potassium phthalimide (40.4 g., 0.22 mole) and 56.0 g. (0.205 mole) of (I) in 300 ml. dimethyl formamide were heated at 90° with stirring for 90 min. then cooled to 200° and any solid filtered off. To the filtrate 1000 ml. chloroform and 1200 ml. water were added and the heavy layer separated, then washed with 550 ml. of 0.3*N* sodium hydroxide solution and with 200 ml. water. After drying the chloroform extract with anhydrous sodium sulfate the chloroform was distilled at 15 mm. and the residue washed with ether, then recrystallized from benzene to give (II), 50 g. (64%).

Anal. Calcd. for $C_{21}H_{16}N_2O_6$: N, 7.4. Found: N, 7.3.

1,4-Diaminopentanone-2 dihydrochloride (III). Recrystallized II (14 g., 0.037 mole) was refluxed 12 hr. with 500 ml. of 20% hydrochloric acid and, after the addition of 350 ml. more acid, was refluxed 12 hr. more. The cooled solution was filtered and the filtrate evaporated, then cooled and again filtered. After filtering off the phthalic acid, the filtrate was evaporated to dryness and the residue recrystallized several times from ethanol with ether. The white crystalline product melted at 192–193° with effervescence, after browning at 190°. It gave a chlorplatinate crystallizing in orange needles from ethanol which blackened at 180–200° without melting.

Anal. Calcd. for $C_5H_{12}N_2O.H_2PtCl_6$: Pt, 37.1. Found: Pt, 37.6.

The dipicrate in yellow prisms for water darkened at 200–210° without melting. The dibenzoyl derivative after recrystallization from ethanol melted at 184–185°.

4(or 5)-(2′-Aminopropyl)-2-thiolimidazole hydrochloride (IV). Total crude material from a preparation of (III) as above was dissolved in 20 ml. water and filtered, then heated with 3.27 g. potassium thiocyanate (0.024 mole) and after evaporating to a syrup was heated on the steam bath 1 hr. The syrup was then evaporated *in vacuo* and the residue taken up with boiling methanol. Evaporation gave (IV) 4.2 g. (59%).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 37.2; H, 6.2; Cl, 18.3. Found: C, 37.1; H, 6.1; Cl, 18.1.

4(or 5)-(2′-Aminopropyl)imidazole dipicrate (V). A solution of 8.4 g. of (IV) in 150 ml. water with 58.5 g. ferric chloride hexahydrate in 350 ml. water were heated on a steam bath for 1 hr. Then 110 ml. of 20% sodium carbonate solution were added and to the boiling solution 16.5 g. picric acid in 450 ml. water were further added. The crude picrate (18.8 g., 81%) that separated was recrystallized from hot water with charcoal to give bright yellow prisms, m.p. 202–204° (11.2 g., 48%).

Anal. Calcd. for $C_{18}H_{17}N_9O_{14}.H_2O$: C, 35.9; H, 3.2; H_2O loss in weight, 3.1%. Found: C, 36.1; H, 3.3; H_2O, 2.9%.

The dihydrochloride was prepared from the dipicrate but could not be obtained as a crystalline solid. The platinichloride was prepared from a solution of the dihydrochloride as fine orange needles from ethanol and it backened at 250–260° without melting.

Anal. Calcd. for $C_6H_{11}N_3.H_2PtCl_6$: Pt, 36.5. Found: Pt, 36.3.

A hygroscopic dihydrobromide was obtained after crystallization from alcohol with addition of acetone, m.p. 172–273°. It is rapidly deliquescent in air and must be stored in a desiccator.

Anal. Calcd. for $C_6H_{11}N_3.HBr$: C, 25.1; H, 4.6; Br, 55.7. Found: C, 25.3; H, 4.6; Br, 56.3.

The oxalate was prepared by making a solution of the dihydrochloride basic with sodium carbonate, evaporating to dryness, and taking the base into ethanol, then adding oxalic acid. Acetone was further added and the product crystallized in colorless needles, m.p. 120–122°.

Anal. Calcd. for $C_6H_{11}N.H_2C_2O_4.H_2O$: $H_2C_2O_4$, 27.9; N, 13.0. Found: $H_2C_2O_4$, 28.1; N, 13.0.

4(or 5)-(2′-Aminopropyl)imidazole (VI). Twenty-one and two-tenths grams of (V) were treated with 175 ml. 5*N* hydrochloric acid and 800 ml. benzene and the layers separated. Residual picric acid was removed from the aqueous layer with benzene and final treatment with charcoal. Evaporation at 15 ml. to about 10 ml. gave a solution which on addition of sodium hydroxide to *p*H 8 gave a base that was extracted with chloroform or methylene chloride. Drying of the extract with anhydrous sodium sulfate and then distillation gave the base (VI), 2.0 g. (44%) that distilled at 132°/0.01 mm., 158°/0.2 mm., and 182°/4 mm.

Bis-N-2,4-dinitrophenyl derivative (VII). Heating (VI) and chloro-2,4-dinitrobenzene in ethanol at 80° for 15 min. followed by the evaporation of the solvent under 15 mm. gave a red glass, which recrystallized from ethanol with acetone gave orange plates, m.p. 159.5–161°.

Anal. Calcd. for $C_{18}H_{15}N_7O_8$: C, 47.3; H, 3.3. Found: C, 47.0; H, 3.3.

As a comparison compound, imidazole was reacted with chloro-2,4-dinitrobenzene in ethanol, then the solution concentrated and crystallized. After recrystallization, light brown rhombic crystals, m.p. 145.5–146.5°, were obtained.

Anal. Calcd. for $C_9H_6O_4N_4$: C, 46.2; H, 2.6; N, 23.9. Found: C, 45.7; H, 2.9; N, 24.6.

5(or 4)-Methyl-4(or 5)-(2′-aminopropyl)imidazole dihydrochloride. Following Sarasin[6] isonitroso-allylacetone was prepared and reduced to amino-allylacetone which was converted into 5(or 4)-methyl-4(or 5)-allyl imidazole. Hydrobromic acid was added and the 2-bromopropyl compound reacted with ammonia. The desired product was obtained as the hydrochloride in colorless needles, m.p. 215–217°.

(6) J. Sarasin, *Helv. Chim. Acta*, **6**, 377 (1923).

(7) G. A. Alles, B. B. Wisegarver, and M. A. Shull, *J. Pharmacol.*, **77**, 54 (1943).

(8) M. I. Grossman, C. Robertson, and C. E. Rosiere, *J. Pharmacol.*, **104**, 277 (1952).

(9) S. R. Rosenthal, *Arch. intern. pharmacodynamie*, **96**, 220 (1953).

Anal. Calcd. for $C_7H_{13}N_3 \cdot 2HCl$: C, 39.6; H, 7.12; Cl, 33.4. Found: C, 40.0; H, 7.5; Cl, 33.4.

The first two steps of this synthesis required modification: *Isonitroso-allylacetone.* Hydrolysis of 50 g. of ethyl allylacetoacetate was carried out by dissolving it in a cold solution of 36 g. potassium hydroxide in 650 ml. of water and allowing to stand 24 hr. Twenty grams of sodium nitrite in concentrated solution were added, the mixture was cooled to 0°, and 88 g. sodium dihydrogen phosphate monohydrate in a little water were added. A cold solution of 52 g. sulfuric acid (96%) in 250 ml. water was slowly added, with the temperature kept below 0°, and the mixture stirred for 15 min. Three extractions with ether and then shaking the ether extracts with 100 ml. 4 *N* sodium hydroxide solution gave an aqueous layer that was acidified with 100 ml. 4*N* sulfuric acid. The separated oil was taken up with ether, dried over potassium carbonate and on evaporating the ether 28.4 g., m.p. 76° (degrees) were obtained.

Amino-allylacetone hydrochloride. Isonitroso-allylacetone (18.5 g.) in small portions was added to a solution of stannous chloride dihydrate in 100 ml. 12*N* hydrochloric acid. The temperature was kept at 20–30° and 34.7 g. mossy tin were added, then the mixture kept at 50° for 15 min. After separating unreacted tin the filtrate was made up to 1400 ml. with water and saturated with hydrogen sulfide. After filtering, the solution was evaporated under reduced pressure. The residue crystallized from ethanol with addition of acetone to give 11.1 g. (51%) of m.p. 153–154°.

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Steroidal Sapogenins. XXXVIII.[1] 5-Pregnene-3β,17α-diol-12,20-dione 3-Acetate

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Received March 16, 1956

In a previous publication[2] we described the preparation and properties of a new 12-keto sapogenin, gentrogenin. In continuation of previously described researches on 12-keto compounds of the C_{21} series[2] we have used gentrogenin as a source of C_{21} compounds containing both the 12-keto group and the 5,6-olefinic bond. It will be recalled that the sapogenin degradation product 5,16-pregnadien-3β-ol-12,20-dione acetate prepared by Marker[3] was reported to melt from 226 to 228°, while our product, I, from gentrogenin melted from 173 to 175°.[2]

In this present note we wish to describe the conversion of our 5,16-pregnadien-3β-ol-12,20-dione acetate, I, of melting point 173–175° to the 16α,17α-epoxide, II, and subsequently to the derived bromohydrin, III, and 17α-hydroxy desbromo compounds, IV. This route for introduction of the 17α-hydroxyl group was first used by Julian, *et al.*[4] Parallels to the present reactions have been described in the hecogenin series[5] and diosgenin series[4]; however, in the present case the analogy could not be followed to the point of introduction of the 21-acetoxy group. We were not able to prepare 3β,21-diacetoxy-5-pregnen-17α-ol-12,20-dione from IV by treatment in sequence with bromine, potassium iodide, and sodium acetate.[6]

EXPERIMENTAL

16α,17α-Epoxy-5-pregnen-3β-ol-12,20-dione Acetate, II. 5,16-Pregnadien-3β-ol-12,20-dione acetate, 0.63 g., was dissolved in 80 ml. of methanol. To the solution cooled in an ice bath was added 5 ml. of 30% hydrogen peroxide followed by 2.3 ml. of 4*N* sodium hydroxide. After storing overnight at 10°, 80 ml. of water and 2.3 ml. of 4*N* hydrochloric acid were added. On concentration of the solution *in vacuo* to 40 ml., a crop of crystalline plates separated and was collected by filtration. A small additional amount of product was isolated by extracting the filtrate with methylene chloride. Acetylation of the product with 60 ml. of 1:1 acetic anhydride-pyridine overnight at room temperature, dilution with water, extraction with ether, washing the organic layer with dilute hydrochloric acid and dilute sodium bicarbonate, drying with sodium sulfate, and concentration to 50 ml. gave a crystalline precipitate of 512 mg. of hexagonal, broad blades, m.p. 235.8–236.3°. Concentration to 7 ml. gave an additional crop of 88 mg., total yield 89%. The analytical sample, recrystallized from ether, showed transition to long spicules, m.p. 238.0–238.2°, $[\alpha]_D^{25}$ +29.4° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.44; H, 7.99.

16β-Bromo-5-pregnene-3β,17α-diol-12,20-dione 3-Acetate, III. A solution of 500 mg. of epoxide in 15 ml. of glacial acetic acid was cooled to 15° and treated with 5 ml. of a solution of 2 ml. of 48% hydrobromic acid dissolved in 12 ml. of acetic acid. After standing 16 hr. at room temperature, the solvents were evaporated at 35° under water-aspiration. The slushy residue was diluted with ether, and the organic layer was washed with water, 2% sodium bicarbonate, and saturated brine, and after drying with sodium sulfate, was concentrated to 30 ml. on the steam bath and allowed to evaporate slowly, depositing 510 mg. of large hexagonal prisms, m.p. 214–217°, yield 86%. Recrystallization was effected by dissolution in a minimal volume of methylene chloride, dilution with ether, and boiling to remove the methylene chloride azeotropically. Repeated crystallization by this procedure gave dense polyhedra undergoing transition over 190° on the Kofler block to hexagonal plates with characteristic degenerate trapezoidal forms having a double melting point within the narrow range 219.2 to 220.5°, $[\alpha]_D^{25}$ −35°. The infrared carbonyl spectrum strongly resembled that of the hecogenin analogue shown in figure 1-A in reference 5 with strong bands at 1734, 1720, and 1695 $cm.^{-1}$.

Anal. Calcd. for $C_{23}H_{31}BrO_5$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.28; H, 6.92; Br, 17.57.

5-Pregnene-3β,17α-diol-12,20-dione 3-Acetate, IV. The epoxide, 4.8 g. in 144 ml. of glacial acetic acid, and 48 ml. of hydrobromic acid in 200 ml. of acetic acid were mixed and reacted as described above. The solvents were evaporated under reduced pressure (water aspirator). The semi-solid residue in acetone acidified with 3 ml. of acetic acid

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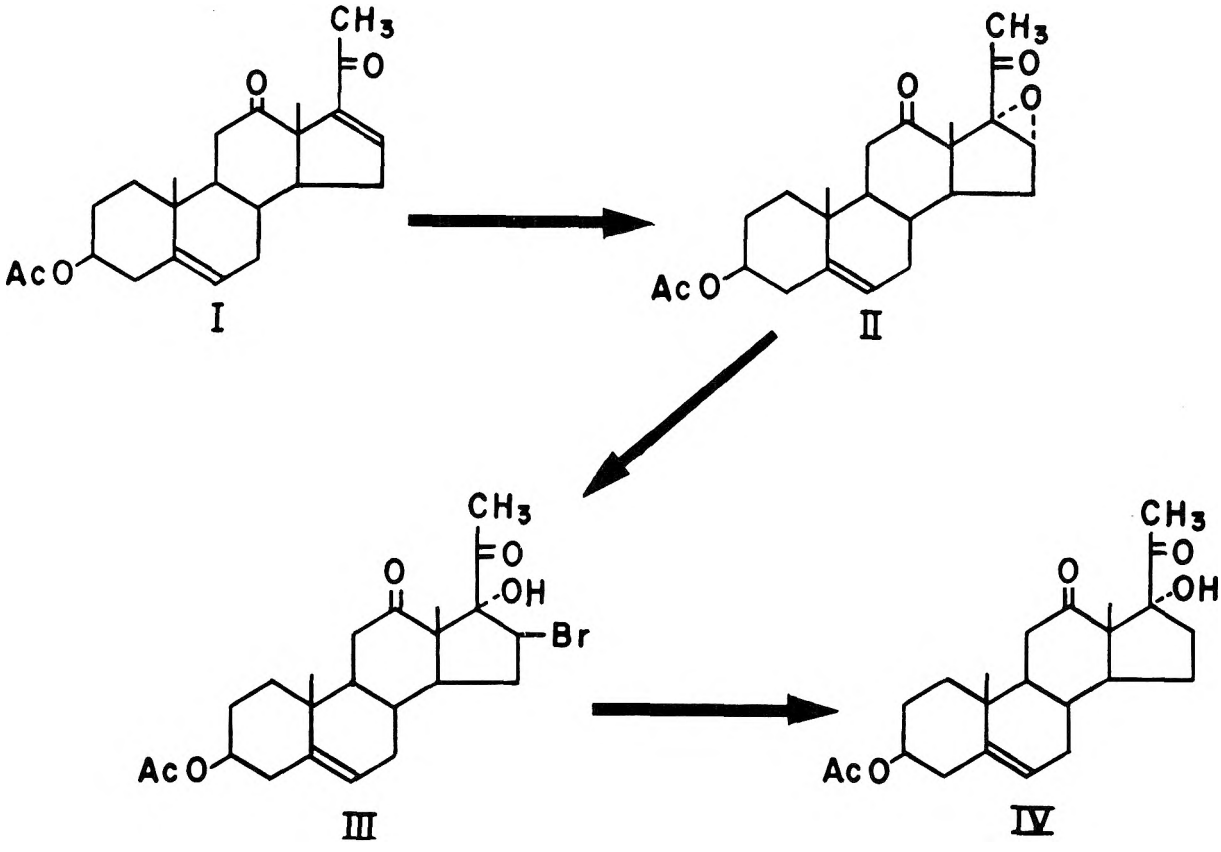
(6) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *J. Am. Chem. Soc.*, **71**, 3574 (1949).



was refluxed 4 hr. with 48 g. of a Raney nickel catalyst. The catalyst was prepared from the alloy using Adkins' directions[7] modified by the acetone inactivation method of Barkley, *et al.*[8] The catalyst was filtered off and the solvents were evaporated. Trituration of the residue with ether gave 4 g. of dense granular polyhedra melting at about 170°, yield 83%. Recrystallization from cyclohexane (dense, granular crystal forms) and from methanol gave needles m.p. 181.0–182.2° with incomplete transition to plates, $[\alpha]_D^{25}$ −23.3°. The carbonyl infrared spectrum strongly resembled that of the hecogenin analog, Figure 1-B in reference 5, showing strong bands at 1735, 1706, and 1694 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.06; H, 8.31. An experiment using highly purified, isolated bromohydrin and a portion of the same Raney nickel catalyst used in the above experiment gave reversion of the bromohydrin to the epoxide.

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(9) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service U. S. Department of Agriculture.

A Note on the Preparation of β-Ionone

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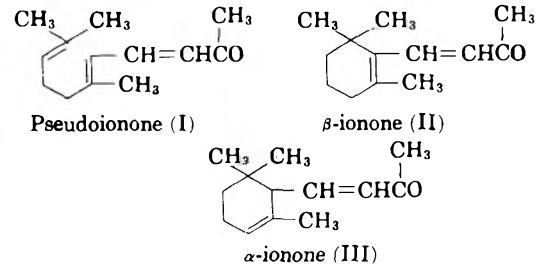
Since 1947, when the first technically feasible synthesis of vitamin A was announced,[1] the preparation of pure β-ionone has assumed considerable importance, as it forms one of the important intermediates in the above synthesis.

β-Ionone (II) is obtained along with the α-isomer (III) by the cyclization of pseudoionone (I) under the influence of acidic reagents.[2,3,4]



The relative proportions of the two compounds

(1) O. Isler and coworkers, *Helv. Chim. Acta*, **30**, 1911 (1947).

(2) Haarman and Reimer, German Patent 133,563, July 22, 1902.

(3) F. Tiemann, *Ber.*, **31**, 808, 867, 1736, 2313 (1898); **32**, 327 (1899); **33**, 3708 (1900).

(4) F. Tiemann and P. Krüger, *Ber.*, **26**, 2692 (1893).

obtained depend on the cyclizing agent used. The two have to be separated by a time-consuming method which depends on the difference in the solubilities of the bisulfite compounds of the two in water in the presence of sodium chloride.[5]

It was, therefore, thought that a method which would give predominantly β-ionone as compared to the yield of its isomer, α-ionone, would be of great interest for the manufacture of Vitamin A. Such a method would make it unnecessary to use the above method of separation.

The relative proportions of the α- and β-isomers obtained on cyclization of pseudoionone are dependent on the cyclizing agent employed, sulfuric acid giving mainly β-ionone and phosphoric, fumaric and other weaker acids[7] giving mainly the α-isomer. E. E. Royals[8] investigated the several procedures and suggested the use of a mixture of 70 parts of conc. sulphuric acid and 30 parts of glacial acetic acid as the cyclizing agent for the preparation of β-ionone. He claimed, on the basis of a comparison of the refractive index of the final product with that of pure β-ionone obtained by other methods, to have obtained β-ionine (90% purity) in good yield (71% on the basis of the weight of pseudoionone used).

During the course of the present work, it was found that, though the above cyclizing agent could be used for the preparation of pure β-ionone, the procedure adopted by E. E. Royals leads to unsatisfactory results. This was not noticed earlier due to the fact that the refractive index alone was used to evaluate the purity of the β-ionone obtained. It was found that the u.v. absorption spectrum (the measurement of the molecular extinction coefficient at 296 mμ) had also to be employed to verify the same.[9] When the purity of the cyclized product obtained by the procedure of Royals was measured by both the methods, it was found to contain only 50% of β-ionone. This was supported by the preparation of the bisulphite addition product of the ionone when only 50% of the cyclized product went into solution. (The u.v. absorption spectrum of the insoluble part was found not to correspond to that of α-ionone either.)

Y. R. Naves and coworkers[10] have reinvestigated the yields of the products obtained by the cyclization of pseudoionone by the use of several cyclizing agents proposed by Royals, other than the one investigated by us. By means of analytical methods, especially analysis in the infrared region between 12 and 14 microns, they have obtained results which also indicate the unreliability of conclusions based on the measurement of the refractive index of the cyclized product alone.

After a series of experiments, it was found that the yields claimed by Royals[8] could be obtained by modifying his procedure in two ways. (a) The temperature of the reaction mass after cyclization is not allowed to rise to 25°C as given by him but is kept till the end below 15°C. (b) The product of the reaction is poured into a mixture of broken ice and ether with rapid stirring and not into ice water alone without mechanical stirring as suggested in the earlier work. The presence of ether during decomposition facilitates the immediate taking up of the β-ionone formed without allowing it to remain in contact with acid.

The results obtained by us in this way support the theory put forward by E. Royals as to the influence of the strength of the acid on the cyclization of pseudoionone.

EXPERIMENTAL

The pseudoionone used in this experiment was prepared from lemongrass oil (with 75% citral content) by condensation with acetone in the presence of aqueous sodium hydroxide.[5] The steam volatile impurities were removed by steam distillation[8] and the fraction showing n_D^{20} of 1.5230–1.5280 (b.p. 90–100°/0.2 mm.) was taken for use as pseudoionone.

The sulfuric acid and the glacial acetic acid used in these experiments were of the C.P. quality. The concentration of sulphuric acid was checked by density measurements (95% concentration).

Cyclization of pseudoionone to β-ionone. The cyclizing agent [175 g. of conc. H_2SO_4 (95%) and 75 g. of glacial acetic acid] was placed in a 500 ml. three-necked flask with a mechanical stirrer, a dropping funnel, and a thermometer reaching into the reaction mixture. The flask was cooled in an ice bath and the cyclizing agent was vigorously stirred while pseudoionone (50 g.) was added dropwise during 30-45 min.; the rate of addition was adjusted so that the temperature of the reaction mixture did not exceed 10–15°C. When the pseudoionone had all been added, the cooling bath was removed and the stirring continued at 10–15°C. for 5–10 min. The reaction mixture was poured into a mixture of ice water (1 l.) and ether (200–250 ml.) with vigorous stirring. The water layer was again extracted with ether and the combined ether extracts were washed with water, sodium carbonate solution (1%), then to neutral with water and dried over anhydrous sodium sulphate. After the removal of ether from the extracts by distillation, the residue was steam distilled and the ionone passed over in the distillate. The distillate was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and then the ether was removed by distillation. The residue was distilled under reduced pressure from a 250 cc. Claisen flask through an 8 in. column filled with Nichrome rings. β-Ionone (37 g.) was obtained as a pleasant smelling light yellow colored liquid b.p. 105–108°/0.22 m.; n_D^{28} 1.5170; ϵ_{max} (296 mμ) 9500 (in 95% ethanol) corresponding to a β-ionone content of 90%.

The β-ionone obtained by the procedure of Royals was found to give a value in many cases of n_D^{28} 1.5150 but of ϵ_{max} (296 mμ); 5000 corresponding to a β-ionone content of 50%.

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Some Aromatic and Heterocyclic Derivatives of Carbazole[1]

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The simplest N-arylcarbazole, 9-phenylcarbazole, was first mentioned in a German patent[2] as having been obtained in unspecified yield by heating potassium carbazole, bromobenzene, and copper powder in an autoclave at 180–200°. Dunlop and Tucker[3] obtained a 65% yield of the compound by heating carbazole, iodobenzene, potassium carbonate, and copper bronze at 190–200°. The same substances refluxed in nitrobenzene resulted in an 88% yield of 9-phenylcarbazole.[4] Lister[5] states that in Hager's method bromobenzene could be substituted for iodobenzene, and that the nitrobenzene could be replaced by high-boiling petroleum ether. Although the yield drops to between 50 and 60%, the use of petroleum ether is said to facilitate separation of the product from unreacted carbazole as the latter is soluble only with difficulty in the petroleum ether. Other syntheses of 9-phenylcarbazole involve the thermal decarboxylation of 9-*o*-carboxyphenylcarbazole,[6] and the dehydration of 9-phenyltetrahydrocarbazole with chloranil.[7]

Although substituents, as nitro[3,8] and carboxyl,[6,9] have been introduced on the phenyl group, no other aromatic systems have been attached to the 9-position of carbazole. We now wish to report the preparation of 9-*p*-biphenylyl-, 9-2′-pyridyl-, and 9-2′-quinolylcarbazole, as well as 4,4′-*bis*-(9-carbazolyl)-biphenyl and *p*-*bis*-(9-carbazolyl)-benzene. So far attempts to prepare 9-(*p*-dimethylaminophenyl)-carbazole in various solvents, or without a solvent, have been unsuccessful.

Since 2- and 4-halopyridines and quinolines are more reactive than benzenoid halides, attempts were made to synthesize 9-2′-pyridyl- and 9-2′-quinolylcarbazole under less strenuous conditions. 9-Alkylcarbazoles can easily be prepared by refluxing alkyl iodides and carbazole in acetone solution in the presence of potassium hydroxide.[10] We found that neither 2-bromo- nor 2-chloropyridine yielded the desired product by this method. Higher reaction temperatures, obtained by using pyridine as a solvent, likewise failed to give N-substituted carbazoles either with or without added potassium hydroxide. A report by Banks[11] indicates that the amination of certain haloheterocycles may be acid-catalyzed.

The compounds described at this time were prepared incidental to a study concerned with organic liquid solution scintillators. Evaluation of the compounds for this purpose is being made by Dr. Wright H. Langham, F. N. Hayes, and D. G. Ott of the Los Alamos Laboratories who will report the results later.

EXPERIMENTAL[12]

9-p-Biphenylylcarbazole. In a 1-l., 3-necked flask equipped with a thermometer, mechanical stirrer, and a moisture trap with attached air condenser, a mixture of 16.7 g. (0.1 mole) of carbazole, 23.3 g. (0.1 mole) of *p*-bromobiphenyl, 13.8 g. (0.1 mole) of anhydrous potassium carbonate, 0.2 g. of copper bronze, and 250 ml. of petroleum ether (b.p. 190–210°) was stirred and refluxed for 12 hr. The solvent was removed by steam distillation and the residue extracted with two 100-ml. portions of hot benzene and two 50-ml. portions. The benzene was evaporated to yield a yellowish brown solid which was dissolved in 300 ml. of a 2:1 mixture of benzene-petroleum ether (b.p. 60–70°) then chromatographed on alumina using 1:1 benzene-petroleum ether (b.p. 60–70°) as eluant. The largest fraction (m.p. 81–165°) was extracted with ethanol to remove any *p*-bromobiphenyl and the residue recrystallized from a mixture of petroleum ether (b.p. 60–70°) and benzene to yield 3.1 g. (10%) of colorless 9-*p*-biphenylylcarbazole, melting at 224–226°. The infrared spectrum indicated both *o*- and *p*-disubstitution, and no N—H band.

Anal. Calcd. for $C_{24}H_{17}N$: N, 4.39. Found: N, 4.24, 4.23.

p-Bis-(9-carbazoyl)-benzene. Refluxing a mixture of 10 g. (0.0598 mole) of carbazole, 8.3 g. (0.025 mole) of *p*-diiodobenzene, 13.8 g. (0.1 mole) of anhydrous potassium carbonate, 1.0 g. of copper bronze, and 200 ml. of petroleum ether (b.p. 190–210°) for 24 hr., steam distilling the product, and extracting the residue with hot benzene gave a dark solution which was treated with Norit-A and cooled to give 4.0 g. (39%) of white product, m.p. 320–322°. Subsequent recrystallization did not raise the melting point. Evaporation of the mother liquor gave a dark solid which was washed with hot ethanol, and then recrystallized from benzene-petroleum ether (b.p. 60–70°) to yield an additional 1.5 g. (15%) of product, m.p. 319–321°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.20; H, 4.94. Found: C, 88.51, 88.44; H, 4.74, 4.83.

4,4′-Bis-(9-carbazolyl)-biphenyl. In an apparatus similar to that described above, but without a moisture trap, a mixture of 18.4 g. (0.11 mole) of carbazole, 15.6 g. (0.05 mole) of 4,4′-dibromobiphenyl, 15.2 g. (0.11 mole) of potas-

(1) This work was supported by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

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(11) C. K. Banks, *J. Am. Chem. Soc.*, 66, 1127 (1944).

(12) All melting points are uncorrected.

sium carbonate, 1.0 g. of copper bronze, 2.7 g. (0.011 mole) of iodine, and 250 ml. of nitrobenzene was refluxed for 24 hr. The product was steam distilled and the residue extracted with hot benzene. The cooled extract deposited 5 g. of white solid which yielded, after repeated alternate recrystallizations from benzene or toluene and extractions with hot ethanol, 3.2 g. (13%) of transparent crystals, m.p. 282.5–284°. The infrared spectrum indicated both *ortho-* and *para*-disubstituted benzene rings.

Anal. Calcd. for $C_{36}H_{24}N_2$: C, 89.00; H, 5.10. Found: C, 89.13, 89.04; H, 5.18, 5.45.

9-2′-Pyridylcarbazole. A mixture of 8.35 g. (0.05 mole) of carbazole, 7.25 ml. (11.8 g., 0.075 mole) of 2-bromopyridine, 10.4 g. (0.075 mole) of potassium carbonate, 1.0 g. of copper bronze, 1.9 g. (0.0075 mole) of iodine, and 200 ml. of petroleum ether (b.p. 190–210°) was stirred and refluxed for 24 hr. The product was steam distilled and the residue extracted with hot benzene. The cooled extract was evaporated in an air stream to give a heterogeneous solid which was recrystallized twice from ethanol and three times from petroleum ether (b.p. 60–70°) to yield 1.5 g. (13%) of colorless crystals, m.p. 93–95°. The infrared spectrum has a C=N band and lacks a N—H band.

Anal. Calcd. for $C_{17}H_{12}N_2$: N, 11.47. Found: N, 11.36, 11.51.

9-2′-Quinolylcarbazole. Refluxing a mixture of 16.7 g. (0.1 mole) of carbazole, 24.5 g. (0.15 mole) of 2-chloroquinoline, 20.7 g. (0.15 mole) of potassium carbonate, 2.0 g. of copper bronze, and 3.8 g. (0.015 mole) of iodine for 48 hr. yielded a dark product which was extracted with hot benzene. Evaporation of the extract, dissolution of the residue in hot ethanol (Norit-A), filtration, and cooling gave a dark tar and a yellow solution. The solution was decanted into an equal volume of cold water. The resulting oil slowly crystallized. Successive recrystallizations from ethanol, petroleum ether (b.p. 77–115°) and petroleum ether (b.p. 60–70°) yielded 1.5 g. (10%) of colorless crystals, m.p. 93–94°. This compound, in contrast to the pyridyl analog, showed a very troublesome tendency to form an oil at every stage of purification. The infrared spectrum indicated the presence of a C=N bond and an absence of a N—H bond.

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.56; H, 4.79. Found: C, 85.52, 85.38; H, 4.97, 5.07.

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New Synthesis of Trichocereine

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During the course of investigation of the alkaloids present in *Trichocereous terscheckii* (Parmentier), Reti[3] isolated a new phenethylamine base, trichocereine, which is peculiar to this species of cactus. The structure of trichocereine was shown by degradation to be N,N-dimethyl-3,4,5-trimethoxy-β-phenethylamine. Reti gives a cursory description of his synthesis of the base, in unstated yield, from the reaction of 3,4,5-trimethoxy-β-phenethyl chloride with dimethylamine; the phenethyl chloride was obtained by subjecting an aqueous solution of mescaline hydrochloride to the action of nitrous acid. Banholzer, Campbell, and Schmid[4] describe the synthesis of trichocereine (28% yield as the picrate) from 3,4,5-trimethoxybenzoyl chloride *via* the diazo ketone.

A more direct route has been found for the synthesis of trichocereine hydrochloride from 3,4,5-trimethoxyphenylacetic acid[5] in an over-all yield of 47%. The acid was converted to 3,4,5-trimethoxyphenylacetyl chloride by treatment with thionyl chloride in the presence of catalytic amounts of pyridine. Reaction of the resulting acid chloride with dimethylamine afforded N,N-dimethyl-3,4,5-trimethoxyphenylacetamide, which was subsequently reduced to trichocereine with lithium aluminum hydride.

EXPERIMENTAL

N,N-Dimethyl-3,4,5-trimethoxyphenylacetamide. A slurry of 3,4,5-trimethoxyphenylacetic acid (11.3 g.) in 50 ml. of dry ether was treated with 7.3 ml. of thionyl chloride and then 2 drops of dry pyridine were added to the mixture. After standing at room temperature overnight, the ethereal solution of the acid chloride was filtered free of suspended pyridine hydrochloride and the ether removed at diminished pressure. The residual acid chloride was purified by distillation; b.p. 150–152°/1.5 mm.; yield, 9.1 g. (74%).

A solution of 3,4,5-trimethoxyphenylacetyl chloride (9.1 g.) in 20 ml. of dry ether was first cooled and then slowly added to an ice-cold ethereal solution of 7 ml. of dimethylamine in 30 ml. of dry ether. After the vigorous reaction had subsided, the reaction mixture was filtered free of the precipitated dimethylamine hydrochloride and the clear filtrate evaporated to an oily residue at reduced pressure. Distillation of the residue *in vacuo* afforded 6.7 g. (72%) of N,N-dimethyl-3,4,5-trimethoxyphenylacetamide, b.p. 173–175°/0.4 mm. as a light yellow oil. The amide was crystallized by cooling an ether-petroleum ether solution in a dry-ice bath; colorless prisms, m.p. 49–50.5°. Literature,[4] m.p. 50–51°.

Trichocereine Hydrochloride. Reduction of 8.2 g. of N,N-dimethyl-3,4,5-trimethoxyphenylacetamide was carried out with 1.3 g. of lithium aluminum hydride in 100 ml. of dry ether. The resulting ethereal suspension of the intermediate complex was hydrolyzed by the careful addition of water, and the ether solution was decanted from the solid lithium *meta* aluminate. The ether solution of the reaction product was dried over anhydrous magnesium sulphate, filtered, and treated with a slight excess of an ice-cold solution of hydrogen chloride in dry ether. The crude trichocereine hydrochloride which precipitated was collected and washed with additional dry ether; yield 7.8 g. (88%); m.p. 199–201°. Recrystallization from ethanol containing a small amount of dry ether gave the pure base hydrochloride (6.4 g.) as colorless prisms; m.p. 207–208°. Literature,[3] m.p. 205°.

(1) Battelle Memorial Institute.
(2) Fels Research Institute.
(3) Reti and Castrillon, *J. Am. Chem. Soc.*, **73**, 1767 (1951).
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(5) This compound is available from the Aldrich Chemical Company, Milwaukee, Wis.

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Improved Synthesis of DL-Carnitine Hydrochloride[1]

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We have recently been interested in studying the radiation sensitivity of DL-carnitine hydrochloride, $[(CH_3)_3NCH_2CH(OH)CH_2CO_2H]^+Cl^-$. The first synthetic route to carnitine, involving a Gabriel-type synthesis, was described by Tomita[3]—however, the yields were poor. Another synthesis, based on an oxazolidine intermediate of Bergmann's,[4] has been described by Carter.[5] A final procedure, recently published by Strack, Röhnert and Lorenz[6] involves the preparation of the mononitrile from $ClCH_2CH(OH)CH_2Cl$, followed by treating the chloronitrile with trimethylamine, and finally hydrolyzing the cyano group to carboxyl. This latter procedure was of little interest to us as the over-all yields were also low and because we wished to introduce C^{14} into the carnitine molecule, via $C^{14}H_3I$, at the last step of a reaction sequence. We therefore turned our attention to the Bergmann-Carter synthesis. It is carried out in six steps: (1) epichlorohydrin is treated with benzaldehyde and ammonia to give 5-chloromethyl-2-phenyloxazolidine; (2) the product is treated successively with benzoyl chloride and concentrated HCl to form 3-benzoylamino-1-chloro-2-hydroxypropane; (3) the chloro group is converted to cyano by reaction with KCN to give the corresponding benzoylaminonitrile; (4) the nitrile is hydrolyzed and esterified to the benzoylamino ethyl ester; (5) the ester and benzoylamino groups are simultaneously hydrolyzed to give the free amino acid; and (6) carnitine is formed by quaternization with methyl iodide and KOH.

We have found that this reaction sequence can be simplified by going directly from the benzoylaminonitrile to the amino acid in a single step.[7] The final step in the sequence, the methylation of the amino acid, is very troublesome. The best methylation procedure now available[5] is hard to apply, particularly for a small-scale preparation with C^{14}, because it involves successive extractions with phenol, countercurrent washings with water, and final washings of aqueous extracts with ether. Our experiments have shown that the use of barium hydroxide as the base in the methylation, removal of barium with H_2SO_4, and exchange of other anions for hydroxide on an ion exchange column, leads to an 88% yield of recrystallized DL-carnitine hydrochloride from the amino acid. The experimental conditions for the improved synthesis are described below. (All melting points are uncorrected.)

EXPERIMENTAL

5-Chloromethyl-2-phenyloxazolidine. The directions given by Carter[5] were followed. It is desirable to use freshly purified benzaldehyde and epichlorohydrin, and to add the epichlorohydrin very slowly (to decrease polymerization). We have obtained a yield of 85% of impure 5-chloromethyl-2-phenyloxazolidine by this procedure and, after crystallization, the analytically pure compound was obtained in 76% yield; m.p. 71°.

3-Benzoylamino-1-chloro-2-hydroxypropane. This is a modification of the procedure given by Bergmann, Randt and Brand.[8] To a solution of 40 g. (0.2 mole) of the pure oxazolidine in 150 ml. of chloroform was added 16 g. (0.2 mole) of pyridine. The solution was cooled to −40° in a dry ice-isopropyl alcohol bath, removed from the bath, and 28 g. (0.2 mole) of benzoyl chloride was added dropwise, with stirring. During this addition the temperature of the reaction mixture reached a maximum of 0°. The mixture was then left overnight at room temperature; however, another experiment indicated that the overnight standing was unnecessary.

Concentrated HCl (200 ml.) was then added and the mixture stirred for 5 min. Finally, 500 ml. of water and 500 ml. of petroleum ether (b.p. 60–70°) were added and the flask was placed in a refrigerator. Crystals soon appeared in the upper (pet. ether) phase and the crystallization was complete in 1–2 hours. The yield of crystallized benzoylamino chlorohydroxypropane was 26.8 g. (yield 79%); m.p. 108°.

3-Benzoylamino-1-cyano-2-hydroxypropane. Ten grams (0.047 mole) of crystallized benzoylaminochlorohydroxypropane was dissolved in 60 ml. of 67% ethanol and 5 g. (0.077 mole) of KCN and 50 mg. of KI were added. The solution was left at room temperature for 72 hr. The alcohol and water were removed by evaporation at reduced pressure, and the crystalline residue was washed with ice water, filtered, re-washed with ice water, and dried. It was recrystallized from acetone-petroleum ether giving 7.7 g. (yield 80%) of pure nitrile, m.p. 126°.

γ-Amino-β-hydroxybutyric acid. The cyano group was hydrolyzed to carboxyl, and the benzoyl group was simultaneously removed, as follows:

To 1.60 g. (7.8 mmoles) of the pure benzoylaminonitrile was added 10 ml. of reagent-grade 48% aqueous HBr and the solution was refluxed for 45 min.; shorter (10, 20 or 30 min.) and longer (1 or 3 hr.) times led to lesser yields. The benzoic acid freed by the hydrolysis was filtered off, washed

(1) The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

(2) U. S. Foreign Operations Administration Fellow, 1954–1956.

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(5) H. E. Carter and P. K. Bhattacharyya, *J. Am. Chem. Soc.*, **75**, 2503 (1953).

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(7) We are grateful to Dr. P. K. Bhattacharyya of the National Chemical Laboratory, Poona, India, for suggesting this possibility.

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with a few ml. of water which was added to the reaction mixture, and the remainder of the benzoic acid in solution was extracted by ether. Gaseous ethylene oxide was then passed into the solution until a final pH of about 6 was reached. Two-thirds of the water was removed under reduced pressure and 25 ml. of ethanol was added to give an ethanol:-water ratio of about 3:1. A few drops of conc. NH_4OH were added to bring the pH to 7; this causes crystallization of the amino acid. The product was washed with 30 ml. of 3:1 ethanol-water and recrystallized from the same solvent mixture. The yield was 0.70 g. (75%) of amino acid with a melting point of 212°, dec.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.33; H, 7.62. Found: C, 40.11; H, 7.64.

DL-*Carnitine hydrochloride.* To a suspension of 6.6 g. (70 meq.) of $Ba(OH)_2.H_2O$ in 20 ml. of water was added 1.0 g. (8.4 mmoles) of recrystallized amino acid. Ten g. (70 mmoles) of methyl iodide was added and brought into the solution with the addition of 100 ml. of methanol. The reaction flask was tightly stoppered and stirred overnight at room temperature. Seventy meq. of H_2SO_4 (11.6 ml. of 6*N*) was added and the barium sulfate removed by centrifugation. The supernatant liquid and washings, containing carnitine, iodide, and sulfate ions, was then passed into 50 ml. of Dowex 1-X anion exchange resin in the hydroxide form. The column was washed with about 25 ml. of distilled water (until aliquot portions of the effluent gave, after removal of the methanol, negative reineckate[9] tests for carnitine) and the effluent was then made acid with a slight excess of dilute HCl. This solution was evaporated to dryness and the carnitine hydrochloride was recrystallized from methanol-ether solution to give 1.46 g. (yield 88%). The over-all yield from epichlorohydrin to carnitine hydrochloride was 32%.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 42.51; H, 8.16. Found: C, 42.60; H, 8.01.

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(9) D. Glick, *J. Biol. Chem.*, **156**, 643 (1944).

Communications TO THE EDITOR

Dibenzo[*a,e*]tropylium and 5-Phenyldibenzo[*a,e*]tropylium Cations

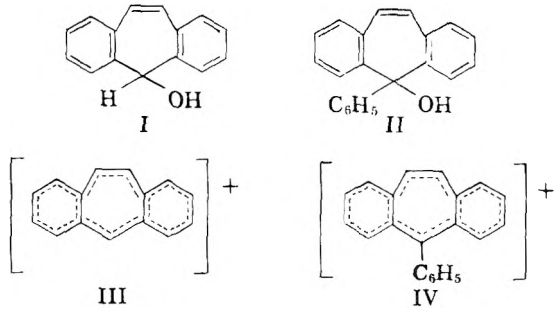
Sir:

In order to get further information on the properties of compounds presenting the tropylium structure, dibenzo[*a,e*]cycloheptatrien-5-ol (I, m.p. 120°. *Anal.* Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.29; H, 5.80) was prepared by sodium borohydride reduction of dibenzo[*a,e*]cycloheptatrienone. (The product, m.p. 98°, previously reported[1] as I, was found to be a mixture of I with a large amount of 5-ethoxydibenzo[*a,e*]cycloheptatriene, m.p. 100°. *Anal.* Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.27; H, 6.85.) Both I and its 5-phenyl derivative[1] II gave deep red colors when treated with sulfuric, perchloric, or formic acid. The solutions in sulfuric acid had rather similar absorption spectra (see Table I), which can be assumed to be due to the ions *III* and *IV*.

TABLE I

ABSORPTION MAXIMA IN 98% SULFURIC ACID

Ion	λ	Log ε	λ	Log ε	λ	Log ε	λ	Log ε	λ	Log ε	λ	Log ε	λ	Log ε
III	236	4.16	270	3.84	306	5.09	380	4.02	398	3.95	508	3.52	540	3.51
IV	240	4.26	268	4.10	312	5.01	384	3.76	414	3.70	528	3.65	564	3.69



Compound I was transformed by thionyl chloride into a covalent chloride (m.p. 123–125°. *Anal.* Calcd. for $C_{15}H_{11}Cl$: C, 79.45; H, 4.89; Cl, 15.66. Found: C, 79.00; H, 5.20; Cl, 15.63), which with silver perchlorate gave a dark red salt, dec. p. 135°. *Anal.* Calcd. for $C_{15}H_{11}^{+}\ ClO_4^{-}$: ClO_4, 34.2. Found: ClO_4, 34.5.

As a measure for the stability of the ions the values of pK_{R^+} were determined in aqueous sulfuric acid by the method of Deno, Jaruzelski and Schriesheim[2]: found for III, −3.7; for IV, −5.7. These data, when compared with those for the tropylium (pK_{R^+}, 4.75)[3] and the benzotropylium (pK_{R^+}, 1.6)[4] ions,[5] show that the fusion of a second benzene ring to the tropylium cation further strongly decreases its stability, probably because of the many high-energy non-Kekulè structures involved in the resonance of the ions of the benzohomologs. On the other hand, the comparison of the value of pK_{R^+} of III with those of the diphenylcarbonium ion (pK_{R^+}, −13.3) and the fluorenylium ion (pK_{R^+}, −14.0)[2] clearly shows that the former ion is much more stable. This should be due to a partial persistence of the peculiar stability of the tropylium system, even when it is fused to two aromatic rings, although another factor may be quite important: the passage from the tetragonal configuration of the carbinol to the trigonal one of the ion diminishes the strain in the seven-membered ring of ion III, but increases it in the five-membered one of the fluorenylium ion.

The decrease in stability of IV compared to III is quite interesting, as it is in net contrast with the large increase produced by the introduction of a third phenyl group into the diphenylcarbonium ion. This could be explained by assuming that the phenyl group in IV is very far from achieving coplanarity with the conjugated system and therefore cannot have much influence on the resonance stabilization of the ion, while the electron-attracting properties of the aromatic group play a major role in diminishing the strength of the secondary base II. This gives a further proof of the intrinsic electronegativity of the phenyl group, for which evidence is so far rather scarce.[6,7]

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(2) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3047 (1955).

(3) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).

(4) H. H. Rennhard, E. Heilbronner, and E. Eschenmoser, *Chemistry & Industry*, 415 (1955).

(5) These data may not be exactly comparable, as they were obtained by different methods, but certainly hold for a qualitative differentiation.

(6) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1955, p. 365.

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