duction color can be removed only by several crystallizations. If, however, the amino ester is vacuum-distilled with a small amount of zinc dust, a distillate is obtained which, after one crystallization, is colorless and pure. All of the amino esters studied could be distilled without decomposition under a pressure of 2 to 6 mm. with the exception of the *tert.*-butyl. This substance, however, was quite readily purified by crystallization.

Summary

1. A series of alkyl *p*-aminobenzoates consisting of the methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*butyl, *sec.*-butyl, *tert.*-butyl, *n*-amyl and allyl have been prepared.
2. The surface tension effects of these various anesthetics have been determined and their partition coefficients between amyl acetate and water.
3. The anesthetic effects of these substances on goldfish have been quantitatively determined and the results plotted.
4. A comparison of the anesthetic indices, partition coefficients and surface tension effects shows a striking parallelism.
5. From the anesthetic indices, it may be concluded that (a) increase in the length of the carbon chain of the alkyl group increases the anesthetic effect until the *n*-butyl is reached. From that point on, the increased effect will not be so great, probably due to marked insolubility of the esters with further increase in molecular weight; (b) the *n*-alkyl are more effective than the branched-chain alkyl derivatives.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES
V. CARBOXYL DERIVATIVES

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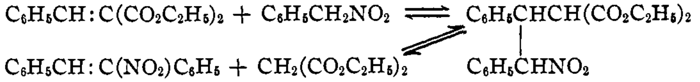
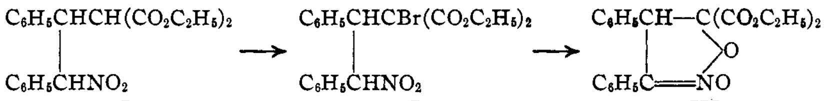
Isoxazoline oxides that have carboxyl groups attached to the ring can be made by a series of reactions similar to those which have been employed for getting all isoxazoline oxides that are known. Thus phenylnitromethane combines with benzal-malonic ester and forms a substance which must be a γ-nitro ester, because it is also formed by the addition of malonic ester to nitrostilbene.



$$\begin{array}{lcl} C_6H_5CH{:}C(CO_2C_2H_5)_2 + C_6H_5CH_2NO_2 & \rightleftharpoons & C_6H_5CHCH(CO_2C_2H_5)_2 \\ & \nearrow & \quad | \\ C_6H_5CH{:}C(NO_2)C_6H_5 + CH_2(CO_2C_2H_5)_2 & & C_6H_5CHNO_2 \end{array}$$

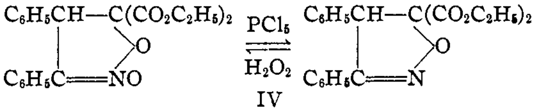
The γ-nitro ester, when brominated, yields an α-bromo-γ-nitro ester and this in turn yields an isoxazoline oxide on elimination of hydrogen bromide.



I II III

This new oxide differs from all others which have been described heretofore in that it has no hydrogen in the 5 position; it, therefore, cannot like these others lose water and form an isoxazole and it is also incapable of undergoing the usual rearrangement to an open-chained oxime. The oxide is in fact a comparatively stable substance, quite unaffected by light and capable of withstanding temperatures up to about 175°. It shows no tendency whatsoever to undergo rearrangement into an open-chained, unsaturated nitro compound.

Like other isoxazoline oxides, and also like furoxanes and azoxy compounds, the new oxide liberates chlorine from phosphorus pentachloride. In this process it is reduced to an isoxazoline derivative from which it can be regenerated by means of the same oxidizers that convert amines into amine oxides and azo into azoxy compounds. This relation between oxidation and reduction product not only furnishes adequate proof of the structure of the substances, but also, in effect, constitutes a new method of synthesis which promises to facilitate the preparation of simpler oxides.



IV

Most reducing agents that are capable of reducing amine oxides, also reduce the isoxazoline oxide, but not with the same result; instead of removing oxygen these reducers invariably add hydrogen and transform the substance into an hydroxy-isoxazolidine. This result could be predicted from the behavior of triphenyl-isoxazoline oxide;[1] and the desire to ascertain with certainty whether N-hydroxy-isoxazolidines are acidic was one of the principal reasons for undertaking this investigation. Posner[2] has shown that N-hydroxy-isoxazolidones are capable of forming copper derivatives, but the structure of these is somewhat doubtful. In our earlier paper[3] we showed that an N-hydroxy-isoxazolidine gives some sort of copper derivative but owing to its peculiar physical properties this could not be purified for analysis. The behavior of the new hydroxy isoxazolidine removes all doubt; when an ethereal solution of the substance is shaken with aqueous copper acetate it momentarily turns purple, then deposits a crystalline copper derivative which is easily recrystallized and which has the composition represented by Formula VI. The N-hydroxy-isoxazolidines are, therefore, acids.

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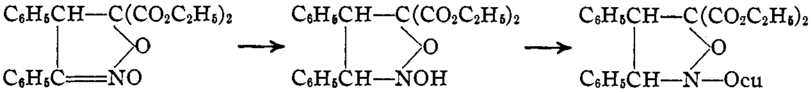
[1] Kohler and Barrett, This Journal, **46,** 2105 (1924).

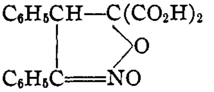
[2] Posner, *Ber.*, **39,** 3515, 3705 (1906).

[3] Ref. 1, p. 2106.

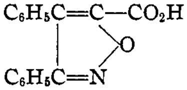


I V VI

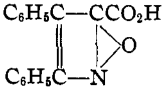
The isoxazoline oxide is very easily hydrolyzed to the corresponding dibasic acid. In contrast with the ester, the acid is extremely unstable. Its solutions in organic solvents rapidly become colored, and in these solutions the acid soon changes into a mixture of highly colored products. In boiling water, the acid slowly loses both water and carbon dioxide and is changed quantitatively into a monobasic isoxazole acid which was identified with the acid described in an earlier paper[4] of this series where its structure (VIII) was established by oxidation with ozone.



VII



VIII



IX

A monobasic acid isomeric with the isoxazole acid (VIII) was at times obtained in small quantities as a by-product in the preparation of the isoxazoline oxide. This isomer is, doubtless, another member of the class of peculiar isoxazole acids discovered by Betti.[5] Like Betti's acids, it melts with decomposition, forms a characteristic yellow copper salt when its ethereal solution is shaken with aqueous copper acetate and is converted into the stable form (VIII) by concd. aqueous potassium hydroxide. All of our attempts to get this acid in larger quantities from the dibasic acid (VII) were unsuccessful. As its origin is unknown, we are unable to add anything to the meager evidence adduced by Betti in favor of a formula like IX for an acid of this class.

Experimental Part

Addition of Phenyl-nitromethane to Benzal-malonic Ester

It is not nearly so easy to add phenyl-nitromethane to benzal-malonic ester as to α,β-unsaturated ketones. In order to avoid transposition of alkyloxyl groups it is necessary to operate in ethyl alcohol. In absolute ethyl alcohol the solubility of sodium phenyl-nitromethane is too small for effective condensation; in 95% alcohol the addition proceeds normally but the reaction is reversible and in the presence of water and the alkaline condensing agent the rate of hydrolysis of benzal-malonic ester into benzaldehyde and malonic ester becomes appreciable. Moreover, since benzaldehyde readily condenses with phenyl-nitromethane, hydrolysis of the unsaturated ester starts a train of condensation and addition reactions

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[4] Kohler, This Journal, **46**, 1733 (1924).

[5] Betti, *Gazz. chim. ital.*, **45**, I, 362, 462; II, 44, 151, 377 (1915); **51**, II, 229 (1921).

which consume most of the phenyl-nitromethane and end with the formation of triphenyl-isoxazoline oxide[6] and triphenyl-isoxazole.

In order to avoid the formation of a mixture of the nitro ester and triphenyl-isoxazoline oxide which it is extremely difficult to separate, it is necessary to use the condensing agent in small quantities and to replace it periodically as it disappears as nitrite or in incidental hydrolysis. It is necessary, also, to remove the addition product at intervals and thus keep its concentration low. The following procedure gave the best and most consistent results.

Sodium ethylate from 0.3 g. of sodium is added to a solution of 25 g. of benzal-malonic ester and 14 g. of phenyl-nitromethane in 100 cc. of 95% alcohol. The solution is boiled for one-half to three-quarters of an hour, then chilled and filtered. The first crop, after washing with alcohol, is almost pure nitro ester. Ethylate from 0.2 g. of sodium is added to the filtrate which is then boiled for another half-hour and again chilled; the second crop obtained in this way is likewise nearly pure nitro ester. The filtrate is now concentrated to half its volume, treated with more ethylate, and boiled as before. This gives a third crop which is less pure. The total yield of solid product is 30 g. of which perhaps 2 to 3 g. of the last crop is triphenyl-isoxazole.

The effect of leaving the nitro ester in the solution throughout the operation may be seen from the results of an experiment in which a solution containing 25 g. of phenyl-nitromethane and half an equivalent of benzal-malonic ester was heated for five hours, during all of which the alkalinity maintained was slight. The product contained 5.5 g. of nitro ester, 12.5 g. triphenyl-isoxazoline oxide, a considerable quantity of triphenyl-isoxazole, and a small quantity of stilbene.

Addition of Malonic Esters to Nitrostilbene

Although this addition reaction like that of the nitro compound to the unsaturated ester is reversible, it was possible to reduce the formation of by-products to a minimum by operating in absolute alcohol and in the presence of an excess of malonic ester. The procedure was as follows.

Sodium methylate from 1 g. of sodium was added to a boiling solution of 75 g. of nitrostilbene and 55 g. of dimethyl malonate in 250 cc. of absolute methyl alcohol. The mixture was boiled for half an hour, then chilled and filtered. The filtrate, which was still slightly alkaline, was boiled for another hour during which its volume was allowed to decrease to one-third. It deposited a second crop of solid which, like the first, was almost pure nitro ester. The filtrate from this on further concentration deposited a small quantity of a mixture of triphenyl-isoxazoline oxide and unchanged nitrostilbene. The yield of recrystallized nitro ester was 102 g.—about 85%.

Diethyl β,γ-Diphenyl-γ-nitro-ethyl-malonate (I).—The nitro ester and triphenyl-isoxazoline oxide have nearly the same solubility in all solvents. From such a mixture of the two as is frequently obtained in the preparation from benzal-malonic ester, the bulk of the nitro ester may be obtained free from oxide by recrystallization from alcohol, from which the oxide separates much more slowly than the nitro compound. When the mixture contains but little of the latter it is best to recrystallize from aqueous acetone. The ester crystallizes from alcohol in stout needles melting at 132°. It is readily soluble in benzene and in acetone, moderately so in ether and in hot alcohol. sparingly in cold alcohol.

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[6] Ref. 1, p. 2109.

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.4; H, 6.0. Found: C, 65.5; H, 6.0.

Dimethyl β,γ-Diphenyl-γ-nitro-ethyl-malonate, C_6H_5—$CHNO_2CH(C_6H_5)CH(CO_2CH_3)_2$.—The dimethyl ester was purified by recrystallization from boiling methyl alcohol in which it is moderately soluble. It separated in fine needles melting at 140°.

Anal. Calcd. for $C_{19}H_{19}O_6N$: C, 63.6; H, 5.3. Found: C, 63.4; H, 5.6.

Bromination of the Nitro Esters

The bromination of these esters was difficult. It was not only, as is frequently the case, difficult to start the process, but it also required prolonged boiling with excess of bromine to complete it, and in some cases small quantities of impurities in the ester inhibited it completely. In the case of the ethyl ester the best results were obtained when solutions in carbon tetrachloride which contained hydrogen bromide from previous brominations were heated for several days with an excess of bromine in direct sunlight. The bromination even then was generally incomplete and the product remained oily for a long time unless solid was available for inoculation. The methyl ester, which was more readily obtained in a perfectly pure state, could always be brominated by boiling its solution in chloroform with excess of bromine; the process was complete after continuous boiling for 16 hours, and the bromo compound solidified promptly.

Diethyl α-Bromo-β,γ-diphenyl-γ-nitro-ethyl-malonate (II).—The bromo compound is readily soluble in carbon tetrachloride, and in boiling alcohol, sparingly soluble in cold alcohol. It was purified by recrystallization from alcohol from which it separated in stout needles; m. p., 74–75°.

Anal. Calcd. for $C_{21}H_{22}O_6NBr$: Br, 17.2. Found: 17.0.

Dimethyl α-Bromo-β,γ-diphenyl-γ-nitro-ethyl-malonate, $C_6H_5CHNO_2CH(C_6H_5)CBr(CO_2CH_3)_2$.—The bromine derivative of the dimethyl ester was purified by recrystallization from methyl alcohol. It separated in transparent prisms or tables; m. p., 125°.

Anal. Calcd. for $C_{19}H_{18}O_6NBr$: C, 52.3; H, 4.1. Found: C, 52.0; H, 4.2.

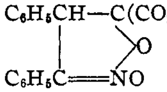
The Isoxazoline Oxides

From the pure bromo compounds the isoxazoline oxides are obtained easily by the usual treatment with potassium acetate. In the case of the ethyl ester, where it was difficult to secure a pure bromine compound, the oxide was usually made from the crude mixture of brominated and unbrominated ester that was left after evaporating the solvent in which the ester had been boiled with bromine. From the absolute alcoholic solution obtained by boiling this residue for an hour with excess of fused potassium acetate, the unbrominated ester could generally be separated almost completely before any of the oxide began to crystallize. At times it was found advantageous to make use of the fact that the oxide crystallizes from ether in large plates which are easily separated by hand from the needles of the unbrominated ester.

Diethyl 3,4-Diphenyl-isoxazoline-oxide-dicarboxylate (III).—A solution of 58 g. of the bromo compound and an equal weight of fused potassium acetate in 30 cc. of absolute alcohol was boiled for an hour. From the cooled solution the oxide separated gradually in stubby needles. It was purified by recrystallization from alcohol; yield, 36.5 g., or about 90%; m. p., 107–108°.

Anal. Calcd. for $C_{21}H_{21}O_6N$: C, 65.8; H, 5.5. Found: C, 65.9; H, 5.6.

Dimethyl 3,4-Diphenyl-isoxazoline-oxide-dicarboxylate,



.—The dimethyl ester crystallizes from methyl alcohol in flattened needles. It is moderately soluble in ether and in methyl alcohol; m. p., 144°.

Anal. Calcd. for $C_{19}H_{17}O_6N$: C, 64.2; H, 4.8. Found: C, 64.4; H, 4.8.

Hydrolysis.—Both the ethyl and methyl esters are hydrolyzed with the utmost ease. When a solution of sodium ethylate containing slightly more than two equivalents is added to a solution of the ester in 95% alcohol, it immediately precipitates a voluminous sodium salt which gradually changes to compact crystals of the disodium salt. These are collected on a filter and washed with absolute alcohol and ether. The salt is not quite stable in solution. Its neutral aqueous solution very slowly becomes alkaline on boiling and in the end it contains only the sodium salt of the isoxazole acid (VIII). Neither the monobasic isoxazoline oxide acid nor the peculiar isoxazole acid (IX) can be obtained in this manner.

3,4-Diphenyl-isoxazoline-oxide-dicarboxylic Acid (VII).—Aqueous solutions of the disodium salt, when they are acidified, deposit a colorless acid that is very difficult to handle. It can be recrystallized from boiling water, but separates in mossy crystals that have variable quantities of water. Its solutions in organic solvents soon turn orange or red. The best specimens were obtained by dissolving the acid in alcohol-free ether, drying this solution rapidly with calcium chloride, concentrating it by evaporation at a low temperature, and then adding benzene in which the acid is very sparingly soluble. It was thus obtained in fine, colorless needles which melted and decomposed at about 130°.

Anal. Calcd. for $C_{17}H_{13}O_6N.H_2O$: C, 59.1; H, 4.0. Found: C, 60.0; H, 4.5.

The composition corresponds most nearly to an acid holding one molecule of water. Since more satisfactory analyses were not obtainable, the acid was turned into the silver salt and by way of this into the ethyl and methyl esters. These were found to be identical with the corresponding esters from which the acid had been obtained. At its melting point the acid decomposes into an indifferent red oil and a mixture of colorless acids from which it was possible to isolate the isoxazole acid (VIII), and a small quantity of an unidentified acid that melts without decomposition at 158°. The same decomposition occurs when a suspension of the acid in benzene is subjected to prolonged boiling. Aqueous solutions of the acid, on the other hand, remain colorless and prolonged boiling results in a quantitative transformation into the isoxazole acid (VIII). There is apparently no way in which the acid can be changed into the peculiar acid (IX).

The Isomeric Monobasic Acid (IX).—In one experiment in which the crude bromoethyl ester was heated with potassium acetate in ordinary instead of absolute ethyl alcohol, the reaction gave a large quantity of oily product. From this oil a small quantity of an acid was isolated by dissolving the oil in ether, extracting the ethereal solution with sodium carbonate, and acidifying the carbonate solution. The acid is easily recrystallized from alcohol from which it separates in needles. It is colorless when pure but has a tendency to carry out of the solution a coloring matter which gives it a black hue. It melts with decomposition at about 172°.

Anal. Calcd. for $C_{16}H_{11}O_3N$: C, 72.45; H, 4.15. Found: C, 72.5; H, 4.0.

When an ethereal solution of the acid is shaken with aqueous copper acetate the ethereal layer first assumes a bright yellow color, then deposits a crystalline yellow copper salt from which the acid is regenerated by mineral acids. With potassium hydroxide the acid forms a sparingly soluble potassium salt. When a suspension of this salt in concd. aqueous potassium hydroxide was kept at the ordinary temperature for several days and then acidified, it gave only the isoxazole acid (VIII) which forms a pale green copper salt and melts without decomposition at 169–170°.

Reaction between the Esters and Phosphorus Pentachloride.—The temperature of an intimate mixture of the methyl ester and a slight excess of phosphorus pentachloride was slowly raised until the mixture began to liquefy at about 75°. The reaction was allowed to proceed without further application of heat; it was accompanied by evolution of gas which was passed through potassium iodide solution and thus identified as a mixture of chlorine and nitrosyl chloride. The yellow paste that remained after the reaction had stopped was stirred into ice water which changed it to a colorless oil. This was extracted with ether. The ethereal solution deposited most of the product as a colorless crystalline solid, which was purified by recrystallization from methyl alcohol.

Dimethyl 3,4-Diphenyl-isoxazoline-5,5-dicarboxylate (IV).—This substance, the product of the reaction between the oxide and phosphorus pentachloride, crystallizes in thick lustrous plates; m. p., 158°. It is readily soluble in acetone, moderately soluble in methyl alcohol, sparingly soluble in ether; yield, 4.1 g. from 5 g. of oxide.

Anal. Calcd. for $C_{19}H_{17}O_5N$: C, 67.2; H, 5.0. Found: C, 67.3; H, 5.40.

3,4-Diphenyl-isoxazoline-5,5-dicarboxylic Acid.—The dimethyl ester was easily hydrolyzed, the procedure being the same that was employed with esters of the oxide. The resulting dibasic acid is readily soluble in boiling water but the solutions soon turn red, and the product which separates from them is discolored. The acid is extremely soluble in ether. Solutions in ordinary ether, when diluted to incipient cloudiness, first deposit needles containing water of crystallization then, as the solution becomes drier, colorless tables containing ether. In capillary tubes both forms melt and effervesce at about 120° if the temperature is raised rapidly enough, then resolidify, turn red at about 155°, and finally melt with decomposition at about 166°—the melting point of the anhydrous form. Both ether and water can be removed by heating at 90° in a vacuum.

Anal. Calcd. for $C_{17}H_{13}O_5N$: C, 65.6; H, 4.2. Found: C, 65.8; H, 4.5.

Regeneration of the Isoxazoline Oxide from the Isoxazoline.—To a solution of 3 g. of the isoxazoline in 100 cc. of glacial acetic acid 30% hydrogen peroxide was added in 10cc. portions at intervals of about eight hours. The solution was kept in a bath that was maintained at a nearly constant temperature of 35°. It gradually turned yellow, doubtless owing to slow hydrolysis to the unstable isoxazoline acid. After 30 hours the solutions began to deposit a crystalline solid when inoculated with the oxide. After 40 hours the operation was stopped, the solid collected on a filter, washed and recrystallized from methyl alcohol. It gave 0.6 g. of pure oxide.

Reduction of the Oxide with Zinc and Acetic Acid.—A solution of the diethyl ester in hot glacial acetic acid was diluted with 10% of water, then treated with excess of zinc dust. The mixture was shaken vigorously and kept hot for five minutes, after which more water was added. Reduction was complete in 15 minutes. After removing the unused zinc, the solution was diluted with much water and extracted with ether. The ethereal extract was freed from acetic acid, dried, concentrated and mixed with petroleum ether. Most of the reduction product separated from this mixture in fine, colorless needles; the remainder was isolated by means of the insoluble copper derivative.

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.5; H, 6.0. Found: C, 65.5; H, 6.0.

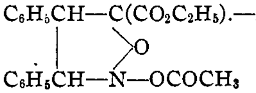
The Hydroxy-isoxazolidine (V).—The hydroxy-isoxazolidine (V) crystallizes in two forms which are mutually convertible. From a mixture of ether and petroleum ether it always separates in fine needles that melt at 140°; from alcohol it crystallizes in much stouter needles that melt at 125°. A mixture of the two forms melts at 137–

139°. When an ethereal solution of either form is shaken with aqueous copper acetate, the ethereal layer assumes for a moment an intensely violet color, then deposits a violet copper derivative.

THE COPPER DERIVATIVE (VI).—The copper derivative (VI) of the hydroxy-isoxazolidine is readily soluble in benzene and chloroform, insoluble in ether. It crystallizes from a mixture of benzene and ether in slender violet needles, and melts with decomposition at about 225°.

Anal. Calcd. for $C_{21}H_{22}O_6NCu^1/_2$: C, 60.6; H, 5.3; Cu, 7.9. Found: C, 60.4; H, 5.3; Cu, 7.5.

THE ACETATE,



$$\begin{array}{l} C_6H_5CH—C(CO_2C_2H_5) \\ \quad | \qquad\quad \rangle O \\ C_6H_5CH—N—OCOCH_3 \end{array}$$

—A solution of hydroxy-isoxazolidine in acetic anhydride was warmed on a steam-bath for five minutes, then diluted with water and warmed again to decompose the excess of anhydride. The acetate crystallized slowly from the cooled solution. As it is readily soluble in organic solvents it is most easily purified by recrystallization from dilute acetic acid from which it separates in small, colorless prisms; m. p., 86–87°.

Anal. Calcd. for $C_{23}H_{25}O_7N$: C, 64.6; H, 5.8. Found: C, 64.5; H, 5.9.

Reduction of the Oxide with Sodium Iodide and Acetic Acid.—A solution of 2 g. of sodium iodide was added to a similar solution of 1 g. of the oxide. The solution turned yellow at the ordinary temperature but the process was extremely slow. The mixture was warmed on a steam-bath for an hour, then cooled and gradually diluted with a solution of bisulfite. It deposited a pale yellow solid which was almost pure hydroxy-isoxazolidine but was contaminated with a small quantity of a yellow by-product. This was most easily removed by shaking an ethereal solution of the solid with copper acetate, recrystallizing the copper compound and regenerating the hydroxy-isoxazolidine. The yield of pure reduction product was 0.7 g.

Summary

1. By means of reactions similar to those which have been employed heretofore, it is possible to prepare isoxazoline oxide acids and esters that have two carboxyl groups in the 5 position.

2. Isoxazoline oxides which have no hydrogen in the 5 position are relatively stable substances. They resemble amine oxides and azoxy compounds in their behavior towards phosphorus pentachloride, but on reduction add hydrogen instead of losing oxygen.

3. The N-hydroxy-isoxazolidines which are formed by addition of hydrogen to the isoxazoline oxides are sufficiently acidic to form well-defined, crystalline copper derivatives.

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