3. It gives a series of reactions by which it is easy to prepare the esters of benzoylacrylic acid.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.]

THE CONDENSATION OF AMINO COMPOUNDS WITH NITROMALONIC ALDEHYDE.

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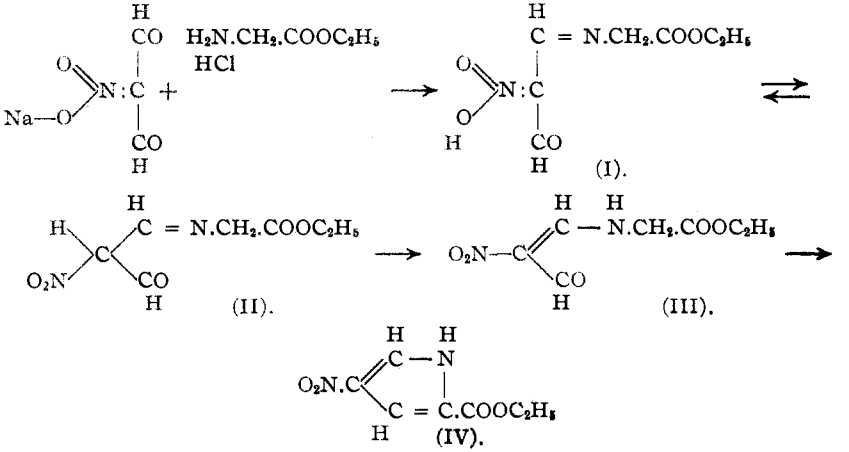
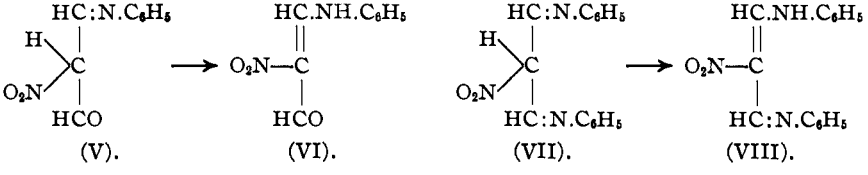
The condensation of aminoacetic esters with nitromalonic aldehyde has been shown by Hale and Hoyt[1] to yield carbopyrrolic esters. As an intermediate step in the production of this pyrrole these authors described briefly an aldehyde of the aliphatic series and assigned thereto the constitution as shown in Formula II. This intermediate product we now find possible of formation in dilute alkaline medium from which it separates readily. The presence of dilute alkali must certainly be expected to hold the isonitro group of nitromalonic aldehyde in its original form and make secure the constitution of Formula I for an alkaline salt of that compound produced in the first stage of the condensation; the free substance, however, actually precipitated from the alkaline solution is not a salt and consequently Formula II as a nitroparaffin, readily tautomeric with the isonitro form in the presence of alkali, cannot represent its constitution. The action of warm alkali easily effects the transformation of this intermediate product to a pyrrole derivative, in which the Hinsberg reaction and also the Liebermann nitrosamine reaction clearly indicated a secondary amine. By reason of the comparative stability of the intermediate product in dilute acid solution the Liebermann nitrosamine



[1] THIS JOURNAL, 37, 2538 (1915).

reaction offered here the only possibility of determining the presence of a secondary amine in the molecule. The constitution of this latter named compound therefore must be assigned a formula as shown in III wherein the tautomeric form of the isonitro compound first produced (II) undergoes an intramolecular arrangement with transfer of the labile hydrogen atom from the central carbon to the nitrogen thus giving rise to a more stable configuration. From this latter type of compound with a methylenic group between the basic imino and acidic carboxyl groups we should expect to find a marked tendency for further condensation with an aldehyde, exactly as reported in the work of Hale and Hoyt (*loc cit.*), to give the carbopyrrolic ester, Formula IV.

The assumption that a compound of Formula II might represent the free intermediate product was based upon the work of Hill and Torrey[1] where a series of products resulting from the condensation of nitromalonic aldehyde with amino compounds was assigned this general type of structure. Thus in the condensation between nitromalonic aldehyde and aniline there result two distinct products called by Hill and Torrey the monanil (V) and the dianil (VII). The presence of a secondary amine identified in each of these compounds now indicates the structure of the first as in Formula VI, a β-phenylamino-α-nitroacrolein, and that of the second as in Formula VIII—a β-phenylamino-α-nitroacrolein anil. Neither of the compounds possesses any tendency toward salt formation, a condition practically demanded by the structure formerly assigned to them. With *p*-toluidine Hill and Torrey obtained similar compounds, and these accordingly must receive exactly analogous formulas. So also the condensation with methylamine and its derivatives are likewise to be interpreted.



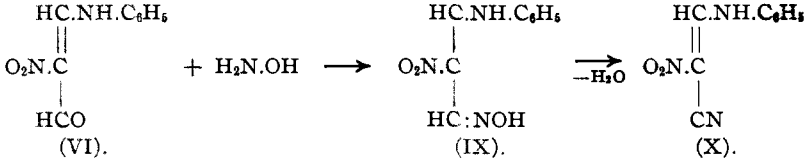
(V). (VI). (VII). (VIII).

The action of phenylhydrazine upon nitromalonic aldehyde led directly to a phenylhydrazone as described by Hill and Torrey. This compound undergoes intramolecular condensation almost immediately to a phenylnitropyrazole and hence its isolation as a more or less stable hydrazino derivative may be doubted. The corresponding diphenylhydrazone described by these authors is stable in alkaline solution and may be isolated as a sodium salt. Its constitution therefore may still be interpreted as that of a true diphenylhydrazone.

In the case of hydroxylamine the condensation with nitromalonic al-

[1] *Am. Chem. J.*, **22**, 99 (1899).

dehyde presented various complexities. By the action of one molecule of hydroxylamine the unstable intermediate product immediately underwent intramolecular condensation to a β-nitro-isoxazole. With excess of hydroxylamine there resulted a dioxime impossible of isolation yet stable in alkaline solution, hence one may still regard it as a true dioxime of a nitroparaffin. The action of aniline hydrochloride upon the sodium salt of this dioxime precipitated at once the anil-oxime described by Hill and Hale[1] a compound resulting also by the action of hydroxylamine upon the so-called monanil (VI). This would indicate the structure, Formula IX, for the compound, a β-phenylamino-α-nitroacrolein oxime. Formula X would then represent the constitution of the so-called nitrile-anil of Hill and Hale, a compound produced by the dehydration of oxime just mentioned, or a β-phenylamino-α-nitro-α-cyanethylene. The formation of this oxime (IX) through the action of aniline hydrochloride upon an alkaline solution of β-nitro-isoxazole, with subsequent dehydration to Formula X, is exactly in accordance with the general reaction of certain amino compounds in opening 5-membered heterocyclic rings. The unaltered oxime of β-phenylamino-α-nitroacrolein (IX) would of course remain stable in alkaline solution whereas it might easily suffer a dehydration into the compound, Formula X, in acid solution. This interpretation easily avoids the apparent contradiction which was noted by Hill and Hale[2] in their earlier explanation of these facts.



The interpretation placed upon the condensation of nitromalonic aldehyde and glycine ester (an α-amino derivative) by Hale and Hoyt[3] should now be modified slightly to accord with the facts just presented. In other words, no final rearrangement in the pyrrole molecule is necessary for condensation when once the transformation of product II into III is proved; the final form of the pyrrole derivative results directly from the intramolecular condensation of III. We have further attempted to involve a β-amino-acid ester in condensation with nitromalonic aldehyde with the hope of throwing some light upon the tendency for this intramolecular condensation of the intermediate product to yield a compound of ring structure. For this purpose we have chosen β-aminopropionic ester or β-alanine ester.

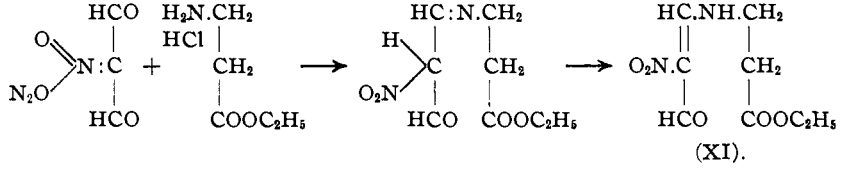
The condensation of nitromalonic aldehyde with β-alanine ethyl

[1] *Am. Chem. J.*, **29**, 269 (1903).

[2] *Loc. cit.*, p. 259.

[3] THIS JOURNAL, **37**, 2542 (1915).

ester proceeded with ease to the formation of a chain compound of Formula XI, a 2-carbethoxy-β-ethylamino-α-nitroacrolein. Though this condensation proceeds best in very slightly alkaline solution it is advisable to employ sodium acetate in place of the free alkali and thus avoid any possible hydrolysis of the ethoxyl group. Neither by the action of more concentrated alkali, not by acids, could a further intramolecular condensation be effected sufficient to make possible the isolation of a pyrrole. The only indication that a pyrrole derivative could be formed from this compound lay in the production of a pyrrole red color upon a pine stick held in the vapor produced when the compound was heated with conc. hydrochloric acid. The temperature and conditions under which this



(XI).

production of a pyrrole was possible rendered negative all of our attempts at its isolation. Its structure naturally would closely resemble that of Formula IV and differs only in that a methylenic group would stand between the carbethoxyl and pyrrole ring.

From these results we may conclude that, in aliphatic imino compounds presenting an aldehyde group in such position that its possible interreaction with a methylene group (adjacent to the imino group) may lead to a pyrrole, this condensation is highly favored when this particular methylenic group is attached to a carbethoxyl or other negative component. Were the carbethoxyl replaced by a hydrogen atom we should have at hand a methylamino compound as obtained in the condensation of methylamine and nitromalonic aldehyde. There is here no further tendency for the aldehydic group to condense with the methyl group, a fact in keeping with the statement above. If, on the other hand, the carbethoxyl group is once removed from this particular methylenic group by the interposition of another methylenic group (equivalent to replacement of carbethoxyl by methylene-carbethoxyl, as shown in Formula XI) the influence of this carbethoxyl group becomes so slight that neither the first methylene nor the second methylene show any marked tendency to enter into condensation with the aldehydic group. Were there any tendency for the second methylene to condense with the aldehydic group a dihydropyridine derivative would be obtainable. The isolation of neither pyrrole nor pyridine would seem therefore to indicate the necessity for more strongly negative radicals in juxtaposition to the methylenic groups in these compounds if condensation to cyclic structure is to be made possible.

Experimental Part.

Secondary Amines.—Those compounds mentioned above, and represented by Formulas III, VI, VIII, IX, X and XI, gave only negative results upon application of Hinsberg's reaction for secondary amines. This is due of course to their decomposition in the presence of strong alkali. The Liebermann nitrosamine reaction, however, gave a positive test in each case. To a mixture of each sample with dil. hydrochloric acid a sodium nitrite solution was added. After warming the mixture, extracting the nitrosamine with ether, and treating the residue from ether extract with conc. sulfuric acid and phenol, there appeared a brown-red solution which in turn gave the characteristic blue color with alkali. Attempts to acetylate several of these secondary amines met with little success, any prolonged heating always sufficing for slow decomposition.

Their basic nature may be illustrated in their ability to form double salts with chloroplatinic acid. As an example, β-phenylamino-α-nitroacrolein anil (VIII) gave with chloroplatinic acid a yellow, amorphous pricipitate of the chloroplatinate which by analysis indicated the presence of one secondary aniline group in the original compound.

Calc. for $(C_{15}H_{13}O_2N_2)_2.H_2PtCl_6$: Pt, 20.67. Found: 20.15.

β-Alanine-ethyl-ester Hydrochloride.—The preparation of this compound has offered a number of difficulties, almost all of which have been summarized by Holm[1] and have led him to adopt the general method of Hoogewerff and Van Dorp.[2] Lengfeld and Stieglitz[3] have improved this same method by removing the free alanine hydrochloride directly from the acidified reaction mixture (after its evaporation to dryness) before proceeding with the next step of esterification. We have made one further modification in that an extraction of this dried mass with anhydrous ether suffices for the removal of the chief impurity—succinic acid—and thus makes possible the precipitation of an almost pure alanine ester hydrochloride in the next operation.

32 g. (8 mol.) of sodium hydroxide was dissolved in 300 cc. water cooled to 0°, and 16 g. (1 mol.) bromine slowly added. To this solution 10 g. (1 mol.) of succinimide was added and all well shaken to effect solution. The yellow solution was then heated at 60° for 2 hours, cooled again to 0° and an excess of hydrochloric acid added at this temperature. After filtering, the solution was evaporated to dryness upon a water bath and the residue well dried in a desiccator. This dried residue was now placed in a Soxhlet apparatus and repeatedly extracted with absolute ether to remove all traces of succinic acid, after which the ether was replaced by absolute alcohol and the mass again repeatedly extracted to remove

[1] *Arch. Pharm.*, **242**, 590 (1904).
[2] *Rec. trav. chim.*, **10**, 4 (1893).
[3] *Am. Chem. J.*, **15**, 508 (1893).

the β-alanine hydrochloride. Into this final alcoholic solution, heated under a reflux upon steam bath, a current of dry hydrogen chloride was passed for an hour or more, whereupon all of the alanine was considered as esterified. The solution thus obtained was finally evaporated *in vacuo* to a syrup. This syrup we now dissolved in chloroform and filtered in order to remove any insoluble salt as impurity. The solution was then evaporated to a small volume and dry ether added whereupon the alanine ethyl ester hydrochloride was precipitated as an oil. After decanting the supernatant liquid a little more ether was added in order to remove traces of the chloroform and the oil finally removed to a vacuum desiccator. Crystals of β-alanine-ethyl-ester hydrochloride in fine needles soon appeared and melted at 65.5° as reported by Lengfeld and Stieglitz. The yield was 9.9 g. or 65% of the theoretical.

β-Alanine-methyl-ester Hydrochloride.—In order to prepare this product the process as outlined above for the ethyl ester is followed in every particular save that methyl alcohol is substituted for the ethyl alcohol. The yield is practically the same 65%. The hard, granular crystals of this ester melt at 94–5° exactly as reported by Lengfeld and Stieglitz.

2 - Carbethoxy-β-ethylamino - α - nitroacrolein, $C_5H_7O(NO_2).COOC_2H_5$ (XI).—To 5 g. sodium nitromalonic aldehyde and 5 g. of β-alanine ethyl ester hydrochloride dissolved in 50 cc. of 50% alcohol about 0.5 g. of fused sodium acetate was added. The mixture was then heated to 80–90° upon a water bath for 10–15 minutes, after which the mixture, now somewhat cloudy in appearance, was set aside to cool. The yellow crystals which soon separate are readily purified by crystallization from alcohol. The colorless prisms thus obtained melt at 79°. This ethyl ester is readily soluble in benzene, chloroform, acetone or ethyl acetate; fairly soluble in alcohol or water; and only slightly soluble in ether or ligroin.

Subs. 0.1527: CO_2, 0.2500; H_2O, 0.0786; subs. 0.2071.
Moist N_2, 26.4 cc. at 34° and 736.2 mm.
Calc. for $C_8H_{12}O_5N_2$: C, 44.43; H, 5.59; N, 12.96. Found: C, 44.66; H, 5.76; N, 12.99.

The presence of an aldehydic group in this condensation product was indicated by several tests: such for example as the green fluorescence with *m*-phenylenediamine hydrochloride and still more confirmatory, a silver mirror with ammoniacal silver nitrate. The Liebermann nitrosamine reaction gave positive indication of a secondary amine whereas Hinsberg's reaction and others requiring strong alkaline medium could not be employed in this instance. Though dilute alkalies react but slowly upon the compound strong alkalies dissolve it with formation of an insoluble, tarry substance.

2-Carbomethoxy-β-ethylamino-α-nitroacrolein, $C_5H_7O(NO_2).COOCH_3$. —This compound was prepared by condensing sodium nitromalonic aldehyde with β-alanine-methyl-ester hydrochloride. The condensation is carried out in exactly the same manner (with same quantities) as that outlined above for the ethyl ester. The final product however is best purified by crystallization from its concentrated solution in methyl alcohol. The colorless leaflets melt at 66°. The compound is readily soluble in benzene, chloroform, acetone, ethyl acetate or acetic acid; fairly soluble in alcohol; and slightly soluble in ether, ligroin or water.

Subs. 0.1917: CO_2, 0.2913; H_2O, 0.0881.

Subs., 0.2718: moist N_2, 35 cc. at 21° and 727.3 mm.

Calc. for $C_7H_{10}O_5N_2$: C, 41.58; H, 5.00; N, 13.86. Found: C, 41.45; H, 5.14; N, 13.94.

This compound which presents the same general constitution as the preceding naturally gave confirmatory tests for the presence of aldehyde and a secondary amine group.

Attempts at Further Condensation.—By the action of piperidine upon the alcoholic solution of these acrolein derivatives it was thought possible to produce an intramolecular condensation yielding a pyrrole derivative similar in structure to that compound (IV) obtained by Hale and Hoyt[1] and differing only in the presence of one methylenic group situated between the pyrrole nucleus and the carbalkoxyl group. A tarry product resulted in every instance and especially so when free alkali was employed. The nature of the product sought would of course partake more of the characteristics of the regular aliphatic esters and be subject to several types of decomposition, whereas that compound (IV) obtained by Hale and Hoyt partook primarily of those properties associated with a directly substituted pyrrole ring. Conc. hydrochloric acid undoubtedly effected a slight intramolecular condensation as evidenced in the distinct and characteristic red color which appears upon a pine stick when held in the vapors of the hot hydrochloric acid mixture. So far we have not succeeded in isolating the pyrrole. Possibly conditions may be found later for accomplishing this end. The call of the second author to government service necessitated the closing of this work in short time. All of the observations however have been carefully checked by Dr. Edgar C. Britton of this laboratory and for his kindness in this work the authors wish to acknowledge their gratitude.

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[1] *Loc. cit.*