[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

SYNTHESIS OF IMIDAZOLINES, DIAZEPINES, TRIAZEPINES, AND IMIDAZOLIDONES FROM A 1,2-DIAMINE AND 1,1-DICARBOXYLIC ESTERS[1]

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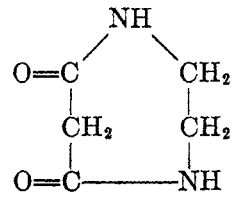
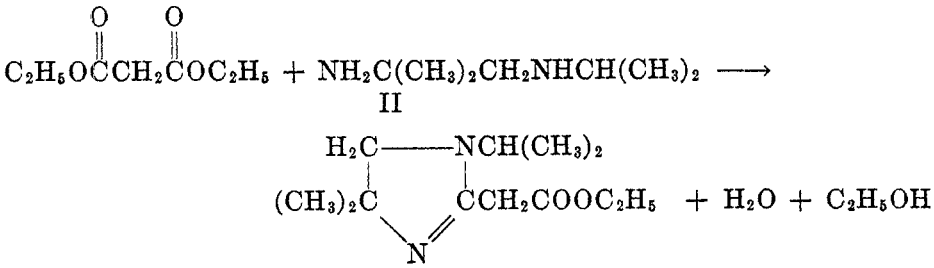
A. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE WITH MALONIC ESTER

Freund (1) heated a mixture of malonic ester and ethylenediamine and obtained a high-melting condensation product with the empirical formula $C_5H_8N_2O_2$. Largely upon the basis of a nitrogen analysis he suggested a formula (I) for this substance and named it ethylenemalonamide. This work was later confirmed by Dox (2).



I

In the present investigation, the main product obtained when malonic ester was heated with N-(2-aminoisobutyl)isopropylamine (II) was a solid crystalline material, which was soluble in alcohol and dilute hydrochloric acid but insoluble in water. The compound formed a picrate and analysis gave results which are in agreement with the structure III.



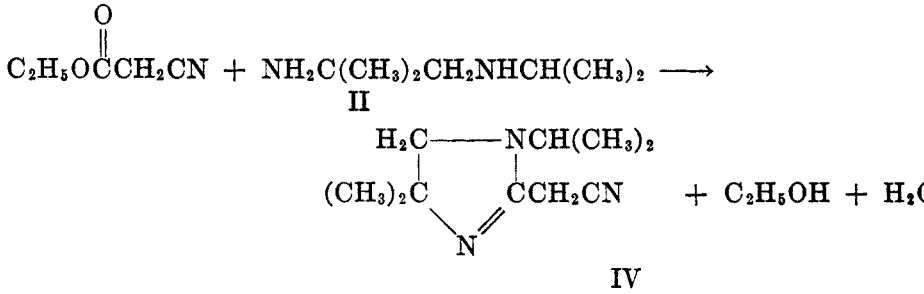
II

III

The proof of structure of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III) was accomplished by an independent synthesis following the method of Copeland and Day (3) who found that *o*-phenylenediamine condenses

[1] This publication was abstracted from the thesis presented by Mr. Pachter to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the M.S. degree. Mr. Pachter's present address is Department of Chemistry, University of Southern California.

with ethyl cyanoacetate to yield 2-cyanomethylbenzimidazole. By a similar reaction between II and ethyl cyanoacetate an analogous product (IV) was obtained.

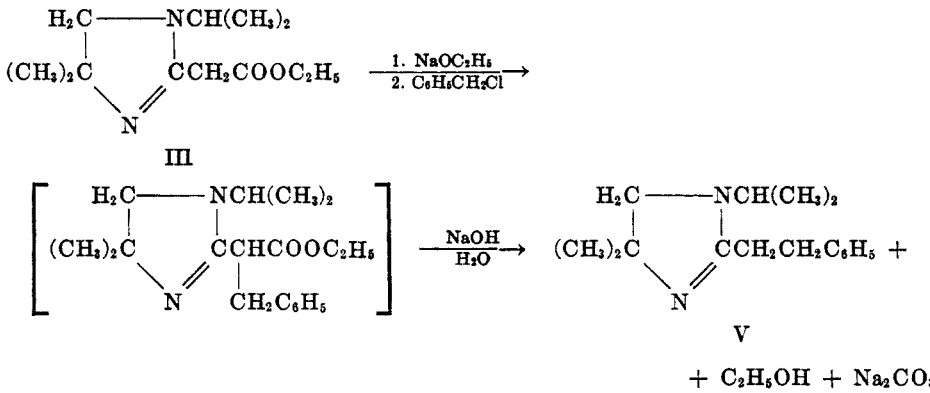


IV

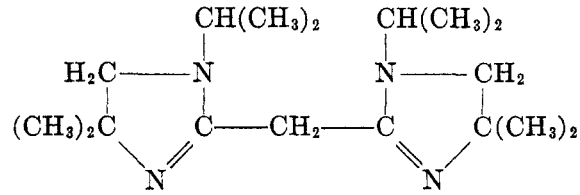
The 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV) was a monoacid base, formed a picrate, and had a neutral equivalent and nitrogen content which conformed to the structural formula presented. When refluxed with alcoholic hydrogen chloride, IV was converted to a compound which was identical in all respects with III.

Neither III nor IV yielded the corresponding acid upon hydrolysis. Only the decarboxylated product 1-isopropyl-2,4,4-trimethyl-2-imidazoline was obtained. This suggested that III might be used in a malonic ester-type synthesis and hence give a useful method for the preparation of the imidazolines.

The sodio derivative of III was found to react with benzyl chloride and upon hydrolysis produced 4,4-dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline (V).

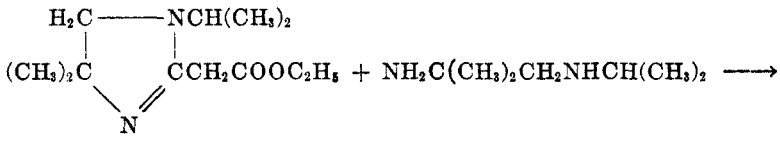


V

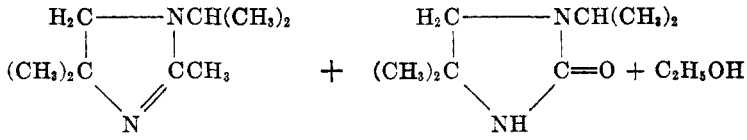


VI

was not formed. Instead, the following reaction occurred.



III II



VII VIII

The properties of the 1-isopropyl-2,4,4-trimethyl-2-imidazoline (VII) were in agreement with those previously found for this compound (5).

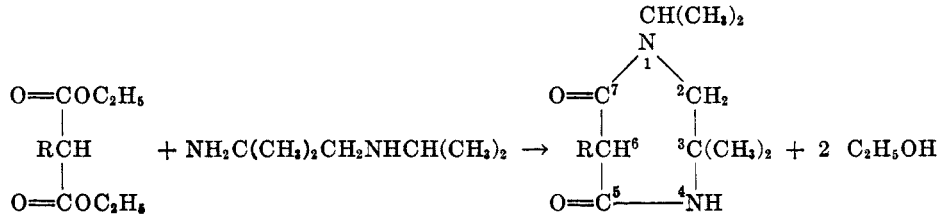
4,4-Dimethyl-1-isopropyl-2-imidazolidone (VIII) was formed in this reaction by a mechanism which at present is unexplained. It was synthesized by heating a mixture of II, chlorocarbonic ester, and anhydrous potassium carbonate. It is believed that a urethan was first produced in this reaction which then formed VIII by losing a molecule of ethanol.

B. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE WITH MONOSUBSTITUTED MALONIC ESTERS

Dox (2) investigated the reactions of monosubstituted alkylmalonic esters with ethylenediamine. He reported that the products were amorphous and colloidal and probably polymeric, that their melting points were high but not sharp, and that decomposition occurred upon melting with darkening in color and evolution of gas.

The reaction of monosubstituted malonic esters with N-(2-aminoisobutyl)-isopropylamine (II) gave compounds which were strikingly different in nature from those mentioned above. They were relatively low-melting solids, formed large crystals, were stable at their melting points and, indeed, were even distilled under reduced pressure at temperatures above 200° without decomposition. Our preparations and those of Dox, in fact, were similar only in analysis. Analysis of the compounds indicated formulas which corresponded to seven-membered rings.

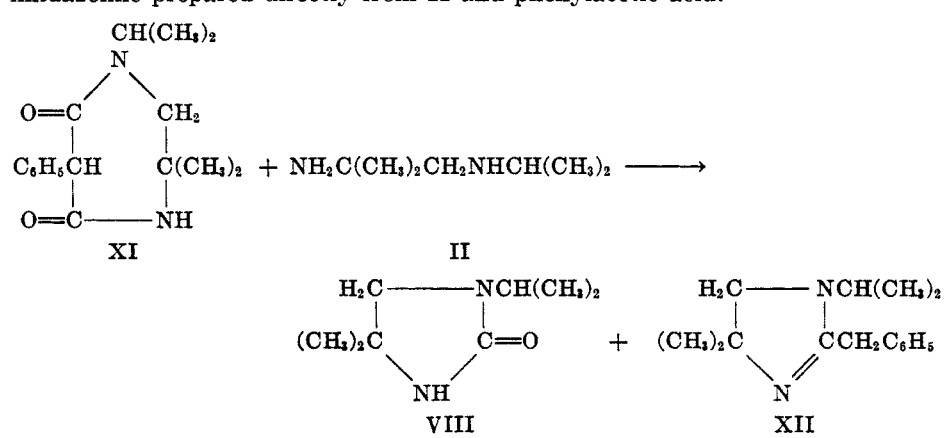
Diethyl-*n*-butyl malonate, diethylbenzyl malonate, and diethylphenyl malonate reacted with one equivalent of II, as indicated by the general equation below, to form 6-*n*-butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (IX), 6-benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (X) and 6 - phenyl - 5,7 - diketo -3,3 - dimethyl - 1 - isopropylhexahydro - 1,4 - diazepine (XI), respectively. These compounds were neutral in character in contrast to the basic products obtained from malonic ester.



II

In the past there has been some contention as to whether seven-membered rings similar to these are actually formed (6) or whether, instead of cyclizing, the molecules polymerize. The fact that definite melting points and boiling points were obtained for compounds (IX) and (X) is rather good evidence against polymerization in these compounds. More conclusive proof for the seven-membered ring structures was obtained from molecular weight determinations by the boiling-point elevation method. For compound (X), molecular weight 288, in benzene solution at a concentration of 0.0508 *M* the molecular weight 350 was obtained. At a concentration of 0.110 *M*, the value found was 405. When concentration was plotted against apparent molecular weight, an extrapolation to zero concentration gave a molecular weight close to the expected value of 288. These data suggest that as the concentration increases, hydrogen bonding between diazepine rings results in a rapid increase in the apparent molecular weight.

When XI was heated with an excess of II, the seven-membered ring opened and reclosed forming the imidazolidone (VIII) and 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline (XII), the latter compound being identical with the imidazoline prepared directly from II and phenylacetic acid.

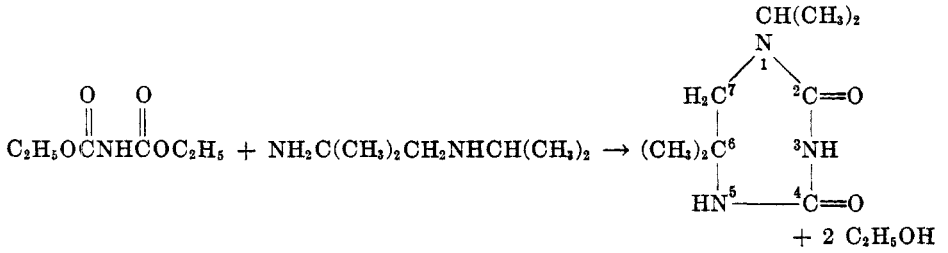


XI II VIII XII

Compounds (VIII) and (XII) were both formed as by-products in the synthesis of XI.

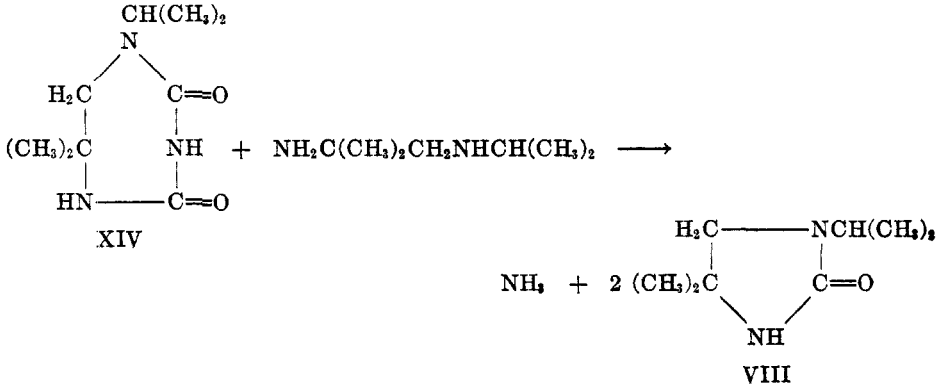
C. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE AND IMIDODICARBOXYLIC ESTER

The condensation of N-(2-aminoisobutyl)isopropylamine (II) and diethyl imidodicarboxylate followed a somewhat different course and the crystalline cyclic diamide 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV) was obtained.



II XIV

With a second equivalent of II, compound (XIV) opened and reclosed to form ammonia and two equivalents of 4,4-dimethyl-1-isopropyl-2-imidazolidone (VIII) in almost quantitative yield.



XIV VIII

EXPERIMENTAL

PART A

All of the following reactions involving N-(2-aminoisobutyl)isopropylamine (II) were carried out under a 4′ × $\frac{5}{8}$″ helix-packed column which was equipped with a decanter still-head. In those reactions in which water was a product, benzene was added to the reaction mixture and, as it distilled, the water formed in the reaction was carried out as an azeotropic mixture. At the still-head the water separated and the benzene returned to the column. In those reactions in which alcohol was the only volatile product, benzene was not usually added and the still-head merely served as a receptable for the alcohol which distilled during the reaction. The absence of benzene in these latter instances did not affect the courses of the reactions since the same results were obtained when the reactions were carried out with benzene added.

Ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III). To 160 g. (1 mole) of malonic ester was added 65 g. (0.5 mole) of II and the mixture was heated for 8 hours between 125° and 145° until no more water-alcohol mixture came over at the top of the column. Benzene was added and the temperature was raised to 165° for one hour.

The reaction mixture was cooled and a half gram of solid material, melting point over 310° was removed. The filtrate was extracted with 45 ml. of concentrated hydrochloric acid in 50 ml. of water. The aqueous layer was made basic and an oil separated which solidified. This product was recrystallized from ethanol and 57 g. (51%) of the ester, m.p. 59–59.3°, was obtained.

Anal. Calc'd for III, $C_{12}H_{22}N_2O_2$: N, 12.4; Neutral equivalent, 226.
Found: N, 12.7; Neutral equivalent, 222.

A *picrate* of III was prepared by adding 1 g. of picric acid dissolved in 5 ml. of ethanol to 1 g. of III in 3 ml. of ethanol and refluxing the solution for a few minutes. Upon cooling, a crystalline solid separated which gave, upon recrystallization from ethanol, the picrate, m.p. 103–104°.

Anal. Calc'd for $C_{17}H_{25}N_5O_9$: N, 15.8. Found: N, 15.4.

2-Cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV). To 65 g. (0.5 mole) of II was added 113 g. (1 mole) of cyanoacetic ester and the mixture was heated to 110° for seven hours. Benzene was then added and the temperature was raised to 160° for two hours. The reaction mixture was cooled and the crystals were filtered and recrystallized from ethanol to give 54 g. (61%) of the nitrile (IV), m.p. 197°.

Anal. Calc'd for IV, $C_{10}H_{17}N_3$: N, 23.4; Neutral equivalent, 179.
Found: N, 23.3; Neutral equivalent, 178.

A *picrate* of IV was prepared by dissolving 1 g. of IV in the least amount of ethanol and adding the solution to a saturated alcoholic solution of 1 g. of picric acid. Yellow crystals formed immediately which were recrystallized from ethanol to give the picrate, m.p. 177–179°.

Anal. Calc'd for $C_{16}H_{20}N_6O_7$: N, 20.6. Found: N, 20.6.

Conversion of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV) *to ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate* (III). A 10-g. sample of IV was refluxed with 150 ml. of a 10% alcoholic hydrogen chloride solution for 4.5 hours. Ammonium chloride was removed to lessen bumping after the first hour and again after 2.5 hours. The excess alcohol was removed by distillation until 50–75 ml. remained. Again the ammonium chloride was removed and the distillation continued over a water-bath until no more alcohol came over. The residue was neutralized with a saturated solution of sodium bicarbonate. Warming was necessary to decompose the hydrochloride of the ester. The material which separated and solidified was filtered, dried, and recrystallized from ethanol giving 9.7 g. (78%) of III, m.p. 59–59.3°. A mixed m.p. with III prepared previously showed no depression.

A *picrate* of this material was prepared by the usual method. The crystals which formed were recrystallized from ethanol giving the picrate, m.p. 103–104°. A mixed m.p. with the picrate of III, m.p. 103–104° gave no depression.

4,4-Dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline (V). To 2.5 g. of sodium dissolved in 100 ml. of absolute alcohol was added 22.6 g. (0.1 mole) of the ester (III). After the solid dissolved, 12.5 g. (0.15 mole) of benzyl chloride was added slowly with stirring. The mixture was then refluxed with stirring for four hours. The sodium chloride was removed and the filtrate was distilled over a water-bath until no more alcohol came over. The residue was refluxed with 1.5 times the theoretical amount of 10% aqueous sodium hydroxide for two hours. The oily layer was separated and acidified with hydrochloric acid, any insoluble material being discarded. The acid solution was treated with 10% sodium hydroxide and an oil separated. This layer was dried over magnesium sulfate and distilled to give 10.0 g. (41%) of the imidazoline (V), b.p. 168–170° at 15 mm. It was later found that hot alkali results in some disruption of the imidazoline ring. It is possible that the yield would be increased if the hydrolysis were carried out in acid solution.

Anal. Calc'd for V, $C_{16}H_{24}N_2$: N, 11.5; Neutral equivalent, 244.
Found: N, 11.4; Neutral equivalent, 245.

A *picrate* of V was prepared by the usual procedure and when recrystallized from ethanol, it melted at 120–121°. Since the melting point of the picrate was close to that of picric acid (122°), a mixed melting point was taken and found to be 85–115°.

Anal. Calc'd for $C_{22}H_{27}N_5O_7$: N, 14.8. Found: N, 14.7.

4,4-Dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline. Direct synthesis. To 5 g. of β-phenylpropionic acid was added 8 g. of the diamine (II) and the mixture was heated at 140° for 4 hours. Benzene was added and the temperature was gradually raised to 200° over a second 4-hour period. The benzene and unreacted diamine were then removed by distillation and as much as possible of the remaining liquid was dissolved in a 5% solution of hydrochloric acid. The acid solution was extracted with ether and the ether layer was discarded. An excess of concentrated ammonium hydroxide was added and an oil separated. Extracted with ether, dried over calcium chloride, and distilled it gave the imidazoline, b.p. 175° at 20 mm.

Anal. Calc'd for $C_{16}H_{24}N_2$: N, 11.5; Neutral equivalent, 244.

Found: N, 11.2; Neutral equivalent 244.5.

The *picrate* of this imidazoline was prepared, m.p. 120–121°.

Anal. Calc'd for $C_{22}H_{27}N_5O_7$: N, 14.8. Found: N, 14.6.

A mixed melting point of this picrate with the picrate of V showed no depression.

Reaction of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III) *with* II *to yield 1-isopropyl-2,4,4-trimethyl-2-imidazoline* (VII) *and 4,4-dimethyl-1-isopropyl-2-imidazolidone* (VIII). To 22.6 g. (0.1 mole) of III was added 16.2 g. (0.125 mole) of II. The mixture was heated to 140–150° for 5 hours and after that the temperature was raised slowly to 200° over a second 5-hour period. The reaction mixture was cooled in ice overnight. The crystals (VIII) that formed were washed with petroleum ether. The filtrate and the washings were fractionally distilled. After the petroleum ether and unreacted diamine were removed, the product was distilled to give 8 g. of the imidazoline (VII), b.p. 89–90° at 28 mm. From the residue in the distilling flask, an additional small amount of crystals was obtained.

(*a*) *The liquid fraction* (VII).

Anal. Calc'd for VII, $C_9H_{18}N_2$: N, 18.2; Neutral equivalent 154.

Found: N, 17.9; Neutral equivalent, 152.

A *picrate* of VII was prepared by the usual method which melted at 183° and gave no depression in m.p. when mixed with a specimen of the picrate of 1-isopropyl-2,4,4-trimethyl-2-imidazoline, m.p. 183°.

Anal. Calc'd for $C_{15}H_{21}N_5O_7$: N, 18.3. Found: N, 18.2.

(*b*) *The solid fraction* (VIII). The two crops of crystals were combined and purified by recrystallization from ethanol; yield, 13.9 g. (89%); m.p. 164°.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: N, 17.9. Found: N, 17.9.

Independent synthesis of 4,4-dimethyl-1-isopropyl-2-imidazolidone. To 26 g. (0.2 mole) of II was added 21.6 g. (0.2 mole) of chlorocarbonic ester. The reaction was very vigorous and some cooling was necessary. The resulting warm viscous liquid was mixed with 21 g. of anhydrous potassium carbonate (50% excess) and the mixture was heated under reflux on a metal-bath at 200°. After a few minutes there was a copious evolution of carbon dioxide which continued for a short time. The mixture was then heated at 200° for 5 hours using an air-cooled condenser which permitted water and alcohol to escape at the top. When the reaction was complete, the solid was pulverized and extracted with two 25-ml. portions of ethanol. The ethanol extracts were combined and evaporated to 25 ml. Upon cooling, 13.4 g. (47%) of the 2-imidazolidone crystallized. The product was washed with petroleum ether, and recrystallized from ethanol, m.p. 164°.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9.

Found: C, 61.6; H, 10.7; N, 17.7.

A mixed m.p. with compound (VIII) was 164°, thus establishing the identity of VIII.

PART B

6-n-Butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (IX). A solution of 32.4 g. (0.15 mole) of diethyl *n*-butyl malonate and 26 g. (0.2 mole) of II was heated 8 hours

between 140 and 160°. The reaction mixture was distilled. A forerun consisting of a liquid and a solid distilled up to a temperature of 217° at 4 mm. The main portion distilled at 217 to 226° at 4 mm. and was purified by crystallization from ethanol to give 14 g. (55%) of IX, m.p. 108°.

Anal. Calc'd for IX, $C_{14}H_{26}N_2O_2$: N, 11.0. Found: N, 10.8.

A solid was isolated from the forerun, which upon recrystallization from ethanol, melted at 164° and gave no depression in melting point when mixed with VIII.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: N, 17.9. Found: N, 17.7.

At the time this reaction was run, it was not known that diazepines undergo further reaction with an additional quantity of II (see below), and it is probable that the yields of diazepines may be raised somewhat by using only a small excess of II.

6-Benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (X). A mixture of 50 g. (0.20 mole) of diethylbenzyl malonate and 34 g. (0.25 mole) of II was heated at 140–150° for 5 hours after which the temperature was slowly increased to 200° during a second 5-hour period. After cooling to room temperature, 25 ml. of petroleum ether was added and the mixture was kept at 0° for one hour. The solid was recrystallized from ethanol to give 34.5 g. (60%) of X, m.p. 152°.

Anal. Calc'd for X, $C_{17}H_{24}N_2O_2$: C, 71.2; H, 8.4; N, 9.7.
Found: C, 70.9; H, 8.2; N, 9.8.

The mother liquor from the original crystallization was distilled at reduced pressure and the fraction b.p. 150–185° at 30 mm. was collected. A small additional amount of X remained in the distilling flask. Upon cooling the distilled fraction, 10 g. of a solid crystallized which upon recrystallization from ethanol, melted at 164°. When mixed with an authentic specimen of VIII, it showed no depression in m.p. The remainder of the 150–185° fraction was distilled and 9 g. of a fraction, b.p. 166–170° at 16 mm., was collected which was basic in character and formed a picrate, m.p. 120–121°. The picrate showed no depression in m.p. when admixed with the picrate of 4,4-dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline.

6-Phenyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (XI). Forty-six g. (0.20 mole) of diethylphenyl malonate was heated with 30 g. (0.23 mole) of II for 6 hours at 150 to 170°. Upon cooling, crystals of XI formed. These crystals were recrystallized from ethanol to give 34 g. (62%) of XI, m.p. 222°.

Anal. Calc'd for XI, $C_{16}H_{22}N_2O_2$: N, 10.0. Found: N, 10.0.

The mother liquor from the main product was distilled and after a small low-boiling forerun, a fraction of 11 g., b.p. 140–170° at 18 mm., was collected. When this fraction was cooled, 2.5 g. of a solid, m.p. 161°, was isolated. It presumably was VIII but this was not established. The remainder of the 140–170° fraction was redistilled and a 7-g. fraction was collected at 156–159° at 18 mm. It formed a picrate, m.p. 146°. The picrate prepared from 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline was prepared and found to melt at 147°.

Anal. Calc'd for $C_{21}H_{25}N_5O_7$: N, 15.3. Found: N, 15.2.

A mixed melting point of this picrate with the picrate prepared from the above 7-g. fraction (b.p. 156–159° at 18 mm.) was 146–147°. Hence the identity of this fraction was established.

Reaction of 6-phenyl-5,7-diketo-4,4-dimethyl-1-isopropylhexahydro-1,4-diazepine (XI) *with* II. To 13.7 g. (0.05 mole) of XI was added 9.0 g. (0.075 mole) of II and the mixture was heated at 150° for 6 hours after which the temperature was raised gradually to 210° during a second 6-hour period. The reaction mixture was cooled and filtered (the mother liquor was saved) and the solid obtained was recrystallized from ethanol to give 7.5 g. (96%) of VIII, m.p. 164°. A mixed melting point with an authentic specimen of VIII gave no depression.

The mother liquor from above was distilled at 17 mm. and the main fraction of 4 g. was collected at 156–159°. This compound (XII) was basic in character and its boiling point suggested that it might be 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline. A *picrate* was prepared of the latter compound as well as from a sample of XII by the usual method. Each picrate had m.p. 147°. A mixed melting point showed no depression.

Anal. Calc'd for $C_{21}H_{25}N_5O_7$: N, 15.3. Found: N, 15.2.

PART C

2,4-Diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV). To 24.2 g. (0.15 mole) of imidodicarboxylic ester was added 26 g. (0.20 mole) of N-(2-aminoisobutyl)isopropylamine (II) and the mixture was heated for four hours at 120–140°. Upon cooling, the mass solidified and upon recrystallization from alcohol gave 25 g. (84%) of XIV, m.p. 206°.

Anal. Calc'd for $C_9H_{17}N_3O_2$: C, 54.3; H, 8.6; N, 21.1.

Found: C, 54.0; H, 8.4; N, 21.0.

Reaction of 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV) *with* II *to yield 4,4-dimethyl-1-isopropyl-2-imidazolidone* (VIII). To 17 g. (0.075 mole) of XIV was added 20 g. (0.15 mole) of II and the mixture was heated for five hours with the temperature gradually being raised from 140° to 200°. When cooled, the product solidified and upon recrystallization from ethanol gave 21.2 g. (91.5%) of VIII, m.p. 164°. A mixed melting point of this compound with an authentic specimen of VIII showed no depression.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9.

Found: C, 61.5; H, 10.2; N, 17.9.

ACKNOWLEDGEMENT

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SUMMARY

1. N-(2-aminoisobutyl)isopropylamine (II) reacts with ethyl malonate to produce ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III), which upon reaction with an excess of (II) produces 1-isopropyl-2,4,4-trimethyl-2-imidazoline and 4,4-dimethyl-1-isopropyl-2-imidazolidone.

2. Monosubstituted malonic esters react with (II) to produce diazepines which upon reaction with excess of (II) form imidazolines and imidazolidones.

3. Imidodicarboxylic ester reacts with (II) to form 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine which reacts with an excess of (II) to produce ammonia and 4,4-dimethyl-1-isopropyl-2-imidazolidone.

ALBUQUERQUE, NEW MEXICO

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