[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEFENSE ACADEMY]

A New Synthesis of Amino Acids. III.[1] The Preparation of *dl*-Glutamic Acid by the Michael Reaction of Acetamidomalonic Acid and Acetamidocyanoacetic Acid Derivative with Acrylic Acid Derivative in Liquid Ammonia

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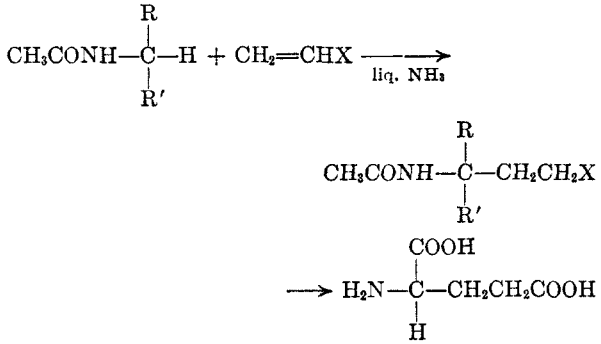
A new synthesis of *dl*-glutamic acid has been devised. It was found that acrylonitrile, acrylic ester, and acrylamide could each be condensed with acetamidomalonic acid and acetamidocyanoacetic acid derivative without any alkaline catalyst in liquid ammonia to give the corresponding Michael-type condensation product. An excellent yield was generally obtained when the reaction was carried out at ordinary pressures below the boiling point of liquid ammonia (−50°). The resulting products, four of them new, were all directly hydrolyzed by boiling with hydrobromic acid to give *dl*-glutamic acid.

Several syntheses for *dl*-glutamic acid from ethyl acetamidomalonate and ethyl acetamidocyanoacetate have been reported. For example, ethyl acetamidomalonate underwent Michael reaction with acrylonitrile,[2] acrylic ester,[3] and acrolein[4,5] in the presence of sodium ethylate to give the corresponding condensation product which could be directly hydrolyzed to *dl*-glutamic acid in acid media. The Michael reaction took place between ethyl acetamidocyanoacetate and acrolein[4] or acrylonitrile[6] in the same manner. The resulting compounds were then degraded to the desired amino acid.

Another approach was recently presented by Kato *et al.*,[7] wherein the condensation product was obtained from an alkali derivative of ethyl acetamidomalonate and β-chloropropionitrile or ethyl β-iodopropionate in anhydrous alcohol. An additional advantage has been reported in our previous work[1,8] in which the intermediates were prepared from acetamidomalonamide, acetamidocyanoacetamide, and ethyl β-bromopropionate with the use of alkali hydroxide in liquid ammonia.

The present investigation is concerned chiefly with the Michael reaction of acetamidomalonic acid and acetamidocyanoacetic acid derivative with acrylic acid derivative in liquid ammonia. We have now found that acrylonitrile, acrylic ester, and acrylamide each condense readily with the malonic acid or the cyanoacetic acid derivative at their α-carbon without any alkaline catalyst in liquid ammonia to give a good yield of the corresponding cyanoethyl carbalkoxyethyl, and carbamoylethyl product, respectively. The reaction has been carried out at room temperature under pressure or at atmospheric pressure below the boiling point of liquid ammonia (−50°). The yield was generally excellent when the reaction was achieved at atmospheric pressure. These results are shown in Table I. Table II gives melting points and analyses of the reaction products. The intermediates thus produced were all converted to *dl*-glutamic acid by boiling with 48% hydrobromic acid for several hours (Table III).



where R, R¹, X = CN, $COOC_2H_5$, $CONH_2$, *etc.*

EXPERIMENTAL

The Michael reaction of acetamidomalonic acid and acetamidocyanoacetic acid derivative with acrylic acid derivative in liquid ammonia. Essentially two methods of the reaction were employed. (A) the use of a pressure vessel at room temperature and (B) the reaction at atmospheric pressure below the boiling point of liquid ammonia (−50°). These are illustrated by the preparation of α-acetamido-α-(β-carbamoylethyl)cyanoacetamide (Method A) and α-acetamido-α-(β-cyanoethyl)malonamide (Method B).

α-Acetamido-α-(β-carbamoylethyl)cyanoacetamide (Method A). To a mixture of 2.8 g. (0.02 mole) of α-acetamidocyanoacetamide and 1.42 g. (0.02 mole) of acrylamide in a glass pressure vessel[9] was added about 15 cc. of liquid ammonia. In a moment considerable heat generated and a lot of white

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TABLE I

THE MICHAEL REACTION OF ACETAMIDOMALONIC ACID AND ACETAMIDOCYANOACETIC ACID DERIVATIVE WITH ACRYLIC ACID DERIVATIVE IN LIQUID AMMONIA

$CH_3CONHCHRR'$		$CH_2{=}CHX$		$CH_3CONHCRR'CH_2CH_2X$			
R	R'	X	Method[a]	R	R'	X	Yield, %
$COOC_2H_5$	$COOC_2H_5$	CN	B	$COOC_2H_5$	$COOC_2H_5$	CN	Quantitative
$COOC_2H_5$	$COOC_2H_5$	CN	A	$COOC_2H_5$	$COOC_2H_5$	CN	63
$COOC_2H_5$	$COOC_2H_5$	$COOCH_3$	A	$COOC_2H_5$	$COOC_2H_5$	$COOCH_3$	72
$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	B	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	Quantitative
$COOC_2H_5$	$COOC_2H_5$	$CONH_2$	A	$CONH_2$	$CONH_2$	$CONH_2$	48[b]
$CONH_2$	$CONH_2$	CN	B	$CONH_2$	$CONH_2$	CN	Quantitative
$CONH_2$	$CONH_2$	CN	A	$CONH_2$	$CONH_2$	CN	73
$CONH_2$	$CONH_2$	$COOC_2H_5$	A	$CONH_2$	$CONH_2$	$CONH_2$	37[b]
$COHN_2$	$CONH_2$	$COOC_2H_5$	B	$CONH_2$	$CONH_2$	$COOC_2H_5$	26
$CONH_2$	$CONH_2$	$CONH_2$	A	$CONH_2$	$CONH_2$	$CONH_2$	70
CN	$COOC_2H_5$	CN	A	CN	$CONH_2$	CN	89[c]
CN	$COOC_2H_5$	CN	B	CN	$CONH_2$	CN	Quantitative[c]
CN	$CONH_2$	CN	A	CN	$CONH_2$	CN	51
CN	$CONH_2$	CN	B	CN	$CONH_2$	CN	96
CN	$CONH_2$	$COOC_2H_5$	A	CN	$CONH_2$	$CONH_2$	66[b]
CN	$CONH_2$	$COOCH_3$	A	CN	$CONH_2$	$CONH_2$	69[b]
CN	$CONH_2$	$CONH_2$	A	CN	$CONH_2$	$CONH_2$	88

[a] See Experimental. [b] After the reaction was completed, 10% ammonium chloride (on a molar basis as compared to $CH_3CONHCHRR'$) was then added to the reaction mixture and kept at room temperature for about 24 hr. in order to cause ammonolysis, and the reaction product was isolated as the corresponding amide. [c] The reaction product was the amide, whereas no esters were obtained.

TABLE II

PHYSICAL PROPERTIES OF $CH_3CONHCRR'CH_2CH_2X$

R	R'	X	M.P.	Reported M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$COOC_2H_5$	$COOC_2H_5$	CN	94–95	92–94[a]	$C_{12}H_{18}N_2O_5$	53.32	53.38	6.71	6.72	10.37	9.96
$COOC_2H_5$	$COOC_2H_5$	$COOCH_3$	65–67[b,f]		$C_{13}H_{21}NO_7$	51.48	51.62	6.98	7.00	4.62	4.97
$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	64–68	63–64[c]	$C_{14}H_{23}NO_7$	52.99	53.00	7.31	7.43	4.41	4.40
$CONH_2$	$CONH_2$	CN	199.5[b,g]		$C_8H_{12}N_4O_3$	45.28	45.25	5.66	5.59	26.41	26.20
$CONH_2$	$CONH_2$	$COOC_2H_5$	217 dec.[b,g]		$C_{10}H_{17}N_3O_5$	46.32	46.20	6.61	6.89	16.21	15.76
$CONH_2$	$CONH_2$	$CONH_2$	233 dec.[g]	233 dec.[d]	$C_8H_{14}N_4O_4$	41.73	41.83	6.13	6.30	24.34	24.41
CN	$CONH_2$	CN	158.5–160[b,h]		$C_8H_{10}N_4O_2$	49.48	49.12	5.15	5.13	28.86	28.27
CN	$CONH_2$	$CONH_2$	234.5 dec.[g]	234.5 dec.[e]	$C_8H_{12}N_4O_3$	45.28	45.23	5.70	5.72	26.41	26.54

[a] Ref. 2. [b] New compound. [c] Ref. 7. [d] Ref. 8. [e] Ref. 1. [f] Recrystallized from ether-petroleum ether (b.p. 30–50°). [g] Recrystallized from water. [h] Recrystallized from ethanol-water.

TABLE III

HYDROLYSIS OF THE MICHAEL REACTION PRODUCT TO *dl*-GLUTAMIC ACID

$CH_3CONHCRR'CH_2CH_2X$			$H_2NCH(COOH)CH_2CH_2COOH$
R	R'	X	Yield, %
$COOC_2H_5$	$COOC_2H_5$	CN	34
$CONH_2$	$CONH_2$	CN	48
$CONH_2$	$CONH_2$	$CONH_2$	48
CN	$CONH_2$	CN	77
CN	$CONH_2$	$CONH_2$	51

precipitate began to separate. Because of the exothermic character of the reaction external cooling with cold water was necessary until the reaction was complete (for several minutes). The mixture was allowed to stand at room temperature thereafter for about 0.5 hr. Then the ammonia was evaporated. The remaining solids were washed with water; yield, 3.7 g. (88%) of α-acetamido-α-(β-carbamoylethyl)cyanoacetamide. After recrystallization from water it melted at 234.5° dec.

α-Acetamido-α-(β-cyanoethyl)malonamide (Method B). Acrylonitrile 5.3 g. (0.1 mole) was added dropwise to a stirred solution of 15.9 g. (0.1 mole) of α-acetamidomalonamide and 150 cc. of liquid ammonia during the course of 25 min. while maintaining the reaction temperature at −50° by cooling with Dry Ice–alcohol. The mixture was stirred for 2 hr. thereafter; then the ammonia was evaporated and the remaining solids were collected and dried; yield 21.2 g. (quantitative) of α-acetamido-α-(β-cyanoethyl)-malonamide which melted at 193–195°. After repeated recrystallization from water the melting point was raised to 199.5°.

Hydrolysis of the reaction product to dl-glutamic acid. In general, hydrolysis was effected by boiling under reflux the reaction product with 48% hydrobromic acid for several hours. *dl*-Glutamic acid was isolated by method illustrated in the following example.

Hydrolysis of α-acetamido-α-(β-cyanoethyl)malonamide. A solution of 4.6 g. (0.02 mole) of α-acetamido-α-(β-cyanoethyl)malonamide in 10 cc. of 48% hydrobromic acid was refluxed for 4 hr., the solution evaporated, and the residue freed from hydrobromic acid by repeated addition of water and evaporation. The resulting product was dissolved in methanol (48 cc.) and treated with pyridine (3.8 cc.). After cooling for several days in the refrigerator the *dl*-glutamic acid was collected, washed with methanol, and once recrystallized from 50% aqueous ethanol; yield 1.4 g. (48%) m.p. 193–196° dec.

Anal. Calcd. for $C_5H_9NO_4$: N, 9.52. Found: N, 9.72.

Identification of the glutamic acid was obtained by preparing the *N*-benzoyl-*dl*-glutamic acid; m.p. 152–154°, reported 155–157°.[10]

Anal. Calcd. for $C_{12}H_{13}NO_5$: N, 5.58. Found: N, 5.73.

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Azo Coupling in the Pyrrole System. The Synthesis of Azopyrroles

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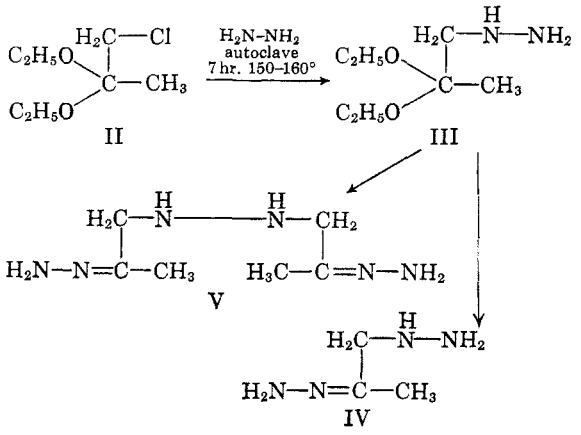
2,5-Diphenylpyrrole-3-diazonium chloride (XIII) has been shown to undergo the azo coupling reaction leading to the new compound class of azopyrroles (I). Coupling of XIII with pyrroles carrying substituents in α-positions furnishes 3,3′-azopyrroles (Ia and Ib), while the coupling products with pyrroles having free α-positions have been assigned the structure of 2,3′-azopyrroles (Ic through Ih). Structure proof of I has been adduced by hydrogenation of the azo group.

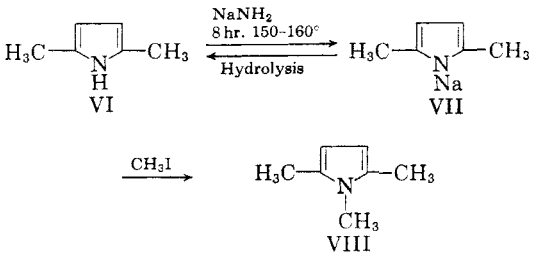
Free azotetrazole is not capable of existence,[2] while azotriazoles are more stable and can be isolated.[3] This tendency toward greater stability when proceeding to azo compounds containing heterocycles with less nitrogen, combined with the fact that the pyrrole ring is stabilized by the amount of 31 kcal.[4] of resonance energy per mole, focussed our attention on the hitherto unknown class of azopyrroles (I).

The synthesis of azopyrroles was first attempted by a modified Knorr synthesis using *N*,*N*′-diphenacetylhydrazine[5] as a carbonyl compound with a methylene group in α-position. However, this compound could not be caused to react with α-amino ketones, *e.g.*, ω-aminoacetophenone. On the assumption that the carbonyl group would gain more ketone character if the hydrazino group were attached to the α-carbon, an attempt was made at synthesizing a simple *N*,*N*′-bisacetoalkylhydrazine, *e.g.*, *N*,*N*′ - bisacetonylhydrazine. As hydrazine reacted violently with 1-chloro-2-propanone, the carbonyl group in the latter compound was protected by acetalization. The 1-chloro-2-propanone diethyl acetal (II) thus obtained, however, was inert toward hydrazine even at reflux temperature. When the reactants were forced to react with each other by heating them in an autoclave, the reaction took a different course resulting in a mixture of products which could be separated and identified as 1-hydrazino-2-propanone hydrazone (IV) and *N*,*N*′-bis(2-hydrazonopropyl)hydrazine (V). Based on the fact that, of the two functional groups in 1-chloro-2-propanone, the chlorine atom is first to react with amines,[6] the formation of IV and V may



then be explained *via* 1-hydrazino-2-propanone (III).

Because of the unexpected course of the reaction and the rather low yields of pure end products, it appeared to be more promising to close the pyrrole ring first and then connect two rings with each other by an azo bridge. Azo coupling, being the most important method for synthesizing azo compounds, would require availability of diazotizable aminopyrroles. However, simple model compounds of this type are not known and Chichibabin's method[7] of aminating heterocycles fails with pyrroles. Thus it was found that in the reaction of sodamide with 2,5-dimethylpyrrole (VI) the sodium atom and not the



(1) Presented at the 138th National Meeting of the American Chemical Society in New York, N. Y., September 1960.

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