[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in Tetrazole Chemistry. IV. Tetrazolylacetic Acids and Esters[1]

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Received November 17, 1955

A method has been developed for the synthesis of 5-substituted-1-tetrazolylacetic esters and acids and a series of these compounds has been prepared. Several 1-substituted-5-tetrazolylacetic acids have also been prepared by this method but substituted tetrazolylcarboxylates could not be isolated. Some comparative properties of the 1- and 5-tetrazolylacetic acids are briefly discussed.

The first paper in this series[3] reported the synthesis of a series of 1-substituted-5-tetrazolylacetic acids. These acids were prepared by transmetalating tetrazoles containing a hydrogen atom on the α-carbon of the substituent in the 5-position using either phenyllithium or phenylsodium. Carbonation and subsequent hydrolysis of these 1-substituted-5-α-metallotetrazoles gave the desired tetrazolylacetic acids.

Although this synthesis has been found to be generally applicable for the preparation of the 5-acetic acids, it has been previously indicated[4] that the analogous 5-substituted-1-tetrazolylacetic acids cannot be obtained in the same way, the methyl group of 1-methyl-5-phenyltetrazole not being metalated by phenyllithium.

A possible synthetic route to the 1-acetic acids would involve the synthesis of the tetrazole nucleus from starting materials already containing the carboxyl group or a suitable derivative of it, using the method developed by von Braun and Rudolph[5] and extended by Harvill, Herbst, Schreiner, and Roberts.[6] As both the phosphorus pentachloride and the hydrazoic acid used in this synthesis of the tetrazole nucleus would readily attack a free carboxyl group, the ester was taken as the derivative of choice.

The intermediates necessary for the initiation of tetrazole ring closure in this series were the N-acyl derivatives of α-amino acid esters (I) which are, in general, readily available from the corresponding α-amino acids through esterification and acylation. The synthetic route as shown in Figure I has been successfully applied in the preparation of the ten 5-substituted-1-tetrazolylacetic esters (II) given in Table I. The esters were converted into the corresponding acids (III) by hydrolysis in hydrochloric acid-acetic acid solution or by saponification in alcoholic potassium hydroxide. The acids are also listed in Table I.

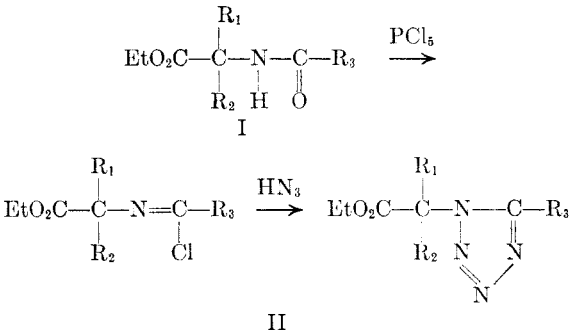


FIGURE I

Five of the esters (IId, e, f, g, i) were isolated as crude oils which underwent gaseous decomposition on attempted distillation. Neither could these oils be made to crystallize. They were converted directly to the acids which were more easily purified. The crude as well as the purified 1-tetrazolylacetic esters also could be readily converted to the corresponding amides. For example, 5-phenyl-1-tetrazolylacetamide was formed as colorless crystals upon allowing the ester to stand in concentrated ammonium hydroxide for 24 hours.

Three attempts to prepare 5-substituted-1-tetrazolylacetic acids by the tetrazole ring closure method have failed to give the desired products. Reactions with both acetyl-*dl*-alanine ethyl ester and isovalerylglycine ethyl ester have been unsuccessful. Application of the ester synthesis to ethyl *dl*-α-acetaminophenylacetate gave a 36% yield of an oil that was found to be 5-ethoxy-2-methyl-4-phenyloxazole through analysis of it and its picrate.

The isolation of an oxazole from this tetrazolylacetic ester synthesis was not entirely unexpected and was also experienced in one of the successful ester preparations. In the synthesis of ethyl α-(5-phenyl-1-tetrazolyl)propionate a 47% yield of 5-ethoxy-4-methyl-2-phenyloxazole was realized. Karrer and his co-workers[7] have reported the preparation of a number of 5-ethoxyoxazoles by the action of phosphorus pentachloride or phosphorus pentoxide on N-acyl-α-amino esters. Similarly,

(1) Taken in part from the Ph. D. Thesis of C. R. Jacobson (1954).

(2) Present address: Bilhuber-Knoll Corp., Crane Street, Orange, New Jersey.

(3) Jacobson and Amstutz, *J. Org. Chem.*, **18**, 1183 (1953).

(4) Jacobson, Master's Thesis, Lehigh University (1952).

(5) von Braun and Rudolph, *Ber.*, **74**, 264 (1941).

(6) Harvill, Herbst, Schreiner, and Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(7) Karrer, Mizamichi, Storm, and Widmer, *Helv. Chim. Acta*, **8**, 205 (1925).

TABLE I

5-SUBSTITUTED-1-TETRAZOLYLACETIC ESTERS AND ACIDS

Ethyl Esters (R = C_2H_5)													Acids (R = H)							
						Analyses											Analyses			
				Yield,	Recryst.	M.P.,	Calc'd		Found			Yield,	Recryst.	M.P.,			Calc'd			Found
No.	R_1	R_2	R_3	%	Solvent	°C.	C	H	C	H	No.	Method[a]	%	Solvent	°C.	C	H	N.E.	C	H	N.E.
IIa	H	H	CH_3	41	CCl_4	73–74	42.4	5.9	42.4	6.0	IIIa	A	85	H_2O	191–192 d.	33.8	4.3	142	33.8	4.3	142
IIb	H	H	C_2H_5	49	—	[d]	45.6	6.6	45.5	6.6	IIIb	A	51	$C_2H_4Cl_2$	132–133	38.5	5.2	156	38.5	5.2	157
IIc	H	H	cycloC_6H_{11}	87	MeOH-H_2O	62–63	55.4	7.6	55.7	7.5	IIIc	B	40	H_2O	131–132	51.4	6.7	210	51.3	6.4	209
IId	H	H	Benzyl	90[b]	—	—	—	—	—	—	IIId	B	48[c]	H_2O	175–176 d.	55.0	4.6	218	55.3	4.9	218
IIe	H	H	C_6H_5	92[b]	—	—	—	—	—	—	IIIe	A	62[c]	H_2O	180–182 d.	52.9	4.0	204	53.2	4.2	204
IIf	CH_3	H	C_6H_5	35[b]	—	—	—	—	—	—	IIIf	A	34[c]	H_2O	189–190 d.	55.0	4.6	218	55.3	4.8	220
IIg	C_2H_5	H	CH_3	99[b]	—	—	—	—	—	—	IIIg	A	40[c]	$CHCl_3$	117–119	42.4	5.9	170	42.5	6.1	170
IIh	C_6H_5	H	C_6H_5	12	EtOH-H_2O	106–107	66.2	5.2	65.9	5.2	IIIh	B	69	EtOH-H_2O	210 d.	64.3	4.3	280	64.0	4.2	280
IIi	CH_3	CH_3	C_6H_5	45	$isoC_3H_7OH$	82–83	60.0	6.2	59.9	6.2	IIIi	A	60	H_2O	188–189 d.	56.9	5.2	232	56.8	5.3	232
IIj	H	H	α-Naph.	51[b]	—	—	—	—	—	—	IIIj	A	16[c]	EtOH-H_2O	222 d.	61.4	4.0	254	61.5	4.2	254

[a] Method A: Hydrolysis in hydrochloric-acetic acid solution. Method B: Saponification in ethanolic potassium hydroxide. [b] Crude yield. Ester could not be purified. [c] Yield from crude ester. [d] B.p. 155–156°/1.0 mm.

Wrede and Feuerriegel,[8] and Wiley[9] have prepared numerous oxazoles from α-amino acids by treatment with acetic anhydride followed by phosphorus pentachloride or concentrated sulfuric acid. Some oxazole formation may have occurred in the synthesis of the other 5-substituted-1-tetrazolylacetic esters but no particular attempts were made to isolate such products if they were present.

The synthesis of the analogous 1-substituted-5-tetrazolylacetic acids by the same general method was also attempted. The starting materials in this series were N-substituted malonamates prepared from the corresponding malonic esters through saponification to the half acid, conversion to the acid chloride, and interaction with the appropriate amine.

The preparation of the necessary N-substituted malonamates proved to be a major stumbling block in the synthesis of a widely varied series of the 5-acetic esters and acids. However, three accessible N-substituted malonamates were converted into the 1-substituted-5-tetrazolylacetic esters given in Table II. The acids shown in Table II were obtained by saponification of the corresponding esters in alcoholic potassium hydroxide.

The crude esters were isolated as high-boiling oils, one of them, IVc, crystallizing to a low-melting solid after distillation. Ethyl 1-*n*-butyl-5-tetrazolylacetate (IVa) could not be purified by distillation, undergoing gaseous decomposition above 140° at 0.5 mm. pressure. This crude ester was saponified to the acid without purification. Both ethyl 1-phenyl-5-tetrazolylacetate (IVb) and ethyl α-(1-phenyl-5-tetrazolyl)-*n*-butyrate (IVc) were converted into the corresponding amides in good yield by allowing the ester to stand in concentrated ammonium hydroxide until crystallization was complete.

It should be noted that Meyer and Heimann[10] have reported that esters of the general type $ArNHCOCH_2CO_2R$ are readily transformed into chlorinated quinolines by the action of phosphorus pentachloride. However, under the conditions used in the preparation of the ethyl 1-aryl-5-tetrazolylacetates from the ethyl malonanilates the formation of quinolines was not observed.

Both the 1- and 5-tetrazolylacetic acids exhibit properties of typical organic acids. They are slightly stronger than acetic acid and the 1-isomers are likewise slightly stronger acids than the corresponding 5-isomers. For example, the dissociation constant of 5-phenyl-1-tetrazolylacetic acid (IIIe) is 2.0×10^{-3} while that for 1-phenyl-5-tetrazolylacetic acid (Vb) is 7.9×10^{-4}.

All of the known 5-tetrazolylacetic acids undergo

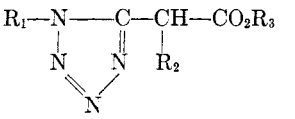
(8) Wrede and Feuerriegel, *Z. physiol. Chem.*, **218**, 129 (1933).

(9) Wiley, *J. Org. Chem.*, **12**, 43 (1947).

(10) Meyer and Heimann, *Compt. rend.*, **204**, 1204 (1937).

TABLE II

1-SUBSTITUTED-5-TETRAZOLYLACETIC ESTERS AND ACIDS



No.	R_1	R_2	R_3	Yield, %	B.P., °C. (M.P.)	Mm.	Analyses Calc'd C	Calc'd H	Calc'd N.E.	Found C	Found H	Found N.E.
IVa	n-C_4H_9	H	C_2H_5	65[a]	—	—	—	—	—	—	—	—
Va	n-C_4H_9	H	H	20[b]	(127–128 d.)[d]	—	45.6	6.6	184	45.3	6.6	184
IVb[f]	C_6H_5	H	C_2H_5	35	160	0.1	56.9	5.2	—	56.8	5.2	—
Vb[c]	C_6H_5	H	H	72	(135–135.5 d.)	—	—	—	—	—	—	—
IVc	C_6H_5	C_2H_5	C_2H_5	37	156–158 (52–53)[e]	0.1	60.0	6.2	—	59.8	6.0	—
Vc	C_6H_5	C_2H_5	H	70	(88–89 d.)[e]	—	56.9	5.2	232	56.7	5.1	232

[a] Crude yield. Ester could not be purified. [b] Yield from crude ester. [c] Ref. 3. [d] Recrystallized from ethylene dichloride. [e] Recrystallized from ether-petr. ether. [f] The boiling-point and analysis of this ester agree with those of the same ester [Jacobson, Kerr, Jr., and Amstutz, *J. Org. Chem.*, **19**, 1909 (1954)] previously prepared from the acid obtained by the metalation procedure.[3]

simple decarboxylation at their melting-points (below 150°) to give the corresponding alkyl derivatives. The 1-acetic acids all undergo gaseous decomposition above 175°, the lower-melting derivatives doing so upon heating the melts above this temperature. However, they not only evolve carbon dioxide but simultaneously undergo further decomposition with the production of dark tarry materials from which it has not been possible to isolate the products of simple decarboxylation. These results are in accord with Benson's statement[11] that tetrazoles which melt above 150° generally do so with decomposition of the tetrazole nucleus.

While the free 5-tetrazolylacetic acids are prone to decarboxylate in solution at temperatures below their melting-points, the free 1-isomers appear to be quite stable under similar conditions. The sodium salts in both series are stable to prolonged refluxing indicating stability of the carboxylate ion.

The relative ease of decarboxylation of the 5-acetic acids appears to arise from the ability of the carboxyl hydrogen to form a six-membered chelate ring structure involving one of the nitrogen atoms in the tetrazole nucleus. Loss of carbon dioxide thus probably follows a path similar to that suggested[12] for the facile decarboxylation of the α-pyridylacetic acids, although no quantitative data is presently available to support these conclusions.

A further extension of this synthesis to the preparation of the corresponding 1- and 5-tetrazolylcarboxylic esters was also attempted. The treatment of ethyl oxanilate with phosphorus pentachloride and hydrazoic acid according to the usual procedure for the preparation of 1,5-disubstituted tetrazoles gave none of the desired ethyl 1-phenyl-5-tetrazolylcarboxylate after prolonged refluxing, the starting material being recovered. Neither did the stable imide chloride of ethyl oxanilate react with hydrazoic acid in refluxing benzene solution as evidenced by lack of hydrogen chloride evolution and recovery of ethyl oxanilate after treatment of the residue from the reaction mixture with water. Thus it appears that the chlorine atom of this imide chloride is not capable of being replaced by the azide ion under the conditions used.

The attempted preparation of ethyl 5-methyl-1-tetrazolylcarboxylate by application of this tetrazole synthesis to acetylurethan appeared to proceed normally. However, the crude product reacted vigorously with water accompanied by evolution of hydrazoic acid, some starting material and much resinous matter being recovered. The results suggest that the necessary imide chloride was formed and was subsequently transformed into the intermediate imide azide which did not undergo ring closure to form the tetrazole. In the presence of water the isolated imide azide then decomposed with evolution of hydrazoic acid.

Acknowledgements. The authors wish to express their sincere thanks to E. Bilhuber, Inc. for financial support which made this work possible. They are also indebted to Mr. Anthony D'Adamo of the above firm for the synthesis of one of the tetrazoleacetic acids and to Dr. Velmar B. Fish of Lehigh University for performing some of the analyses.

EXPERIMENTAL[13]

N-ACYL-α-AMINO ACID ESTERS

Acetylglycine ethyl ester was prepared in 89% yield from glycine ethyl ester hydrochloride by the method of Cherbuliez and Plattner.[14]

(11) Benson, *Chem. Revs.*, **41**, 1 (1947).

(12) Doering and Pasternak, *J. Am. Chem. Soc.*, **72**, 143 (1950).

(13) All melting points taken with Anschutz thermometers and together with boiling points are otherwise uncorrected.

(14) Cherbuliez and Plattner, *Helv. Chim. Acta*, **12**, 317 (1929).

Propionylglycine ethyl ester. Glycine ethyl ester hydrochloride (70 g., 0.5 mole), propionic anhydride (130 g., 1.0 mole), and fused sodium acetate (41 g., 0.5 mole) were stirred and heated at 100° for one hour. After concentrating the reaction mixture under reduced pressure the residue was thoroughly washed with four 100-ml. portions of ether. Distillation of the ether from the dried extract followed by fractionation of the residual oil gave 55.0 g. (69%) of colorless oil of b.p. 136–137°/8 mm. The product solidified in the receiving flask to a colorless crystalline solid of m.p. 51.5–53.0°.

Anal. Calc'd for $C_7H_{13}NO_3$: C, 52.8; H, 8.2. Found: C, 52.6; H, 8.0.

Hexahydrohippuric acid ethyl ester was prepared by addition during one hour of cyclohexanecarbonyl chloride (58.7 g., 0.4 mole) to a cold (10–15°) stirred solution of glycine ethyl ester hydrochloride (55.8 g., 0.4 mole) and anhydrous potassium carbonate (111 g., 0.8 mole) in 500 ml. of water. After an additional hour's stirring at room temperature the white precipitate was filtered off and washed successively with 100 ml. of water, 200 ml. of 3 *N* hydrochloric acid and 100 ml. of water. Recrystallization of the crude product from 60% ethanol gave 47.0 g. (55%) of the pure ester as small colorless needles, m.p. 83–84°.[15]

Phenaceturic acid ethyl ester was prepared from phenylacetyl chloride, glycine ethyl ester hydrochloride, and anhydrous potassium chloride in the same way as described for the preparation of hexahydrohippuric acid ethyl ester. Recrystallization of the crude product from 50% ethanol gave 61.2 g. (69%) of small colorless needles of the ester, m.p. 79–80.5°. Hotter,[16] who prepared this ester by reaction of the silver salt of the acid with ethyl iodide, reports a m.p. of 79°.

Ethyl hippurate was prepared by esterification of hippuric acid in refluxing 95% ethanol containing 3% concentrated sulfuric acid for six hours. Addition of petr. ether to a solution of the crude ester in ether gave the product in 78% yield; m.p. 58–59°. [Lit. m.p.'s 60.5° (by Fisher esterification of acid),[17] 67.5° (from acid chloride)[18]].

dl-Benzoylalanine ethyl ester. dl-Benzoylalanine was prepared by the method of Fischer[19] and esterified according to the procedure of Brenzinger.[20]

Ethyl dl-α-acetamino-n-butyrate. By Fischer esterification[21] of α-amino-*n*-butyric acid the ethyl ester hydrochloride was isolated in 94% yield; m.p. 142.5–143.5°. (Lit. m.p. 142°).[22]

Ethyl α-amino-*n*-butyrate hydrochloride (50 g., 0.30 mole), fused sodium acetate (50 g., 0.61 mole), and acetic anhydride (100 g., 0.98 mole) were stirred for one hour on a steam-bath and then the excess acetic anhydride and acetic acid were distilled off under reduced pressure. Extraction of the residue with five 100-ml. portions of ether followed by distillation of the ether from the combined dried extracts left a yellow oil that was fractionated under reduced pressure. Yield, 41.1 g. b.p. 105–106°/1 mm. When analysis of the product showed the carbon content to be about 1% below theory, the ester was twice refractionated at 90°/0.2 mm. and 93°/0.4 mm. Analysis after each fractionation continued to give the same carbon content although the hydrogen and nitrogen values checked theory.

Anal. Calc'd for $C_8H_{15}NO_3$: C, 55.5; H, 8.7; N, 8.1. Found: C, 54.3; H, 8.6; N, 8.0.

Ethyl dl-α-acetaminophenylacetate was synthesized from *dl*-α-aminophenylacetic acid by esterification and acetylation according to the procedure of Marvel and Noyes[23] in 58% over-all yield; m.p. 62–64°.

Ethyl dl-α-benzamidophenylacetate. Ethyl *dl*-α-aminophenylacetate was prepared from the corresponding acid in 80% yield by the method of Marvel and Noyes[23] and then was benzoylated in 80% yield according to the procedure of Kossel,[24] m.p. 85–86°.

Ethyl α-benzamidoisobutyrate. α-Benzamidoisobutyric acid was prepared from α-aminoisobutyric acid and benzoyl chloride in 80% yield by the method of Steiger.[25] Esterification of the resulting acid for 24 hours in refluxing 95% ethanol containing 4% concentrated sulfuric acid gave 73% of the ethyl ester after recrystallization from 50% methanol, m.p. 119–121°. (Lit. m.p. 123° with softening at 117° when the ester was prepared from the acid chloride[26]).

α-Naphthoylglycine ethyl ester was prepared from α-naphthoyl chloride, glycine ethyl ester hydrochloride, and anhydrous potassium carbonate using the same procedure as described for the preparation of hexahydrohippuric acid ethyl ester. By dissolving the crude product in boiling 95% ethanol (1 g./10 ml.) a 17% yield of α-naphthoic anhydride was separated upon cooling. Dilution of the ethanolic filtrate with water gave the ester as an oil which soon solidified. Further recrystallization of the ester from a large volume of petr. ether (b.p. 60–68°) gave pure product in 47% yield, m.p. 80.5–81.5°.

Anal. Calc'd for $C_{15}H_{15}NO_3$: N, 5.5. Found: N, 5.5.

N-SUBSTITUTED MALONAMATES

Potassium monoethyl malonate was prepared in 66% yield by saponification of diethyl malonate with alcoholic potassium hydroxide according to the procedure of Freund.[27]

Ethyl malonanilate was obtained in 60% yield upon treatment of potassium monoethyl malonate with phosphorus oxychloride followed by aniline, the method of Rugheimer and Hoffmann.[28] The product was isolated as a yellow oil that was not crystallized. A melting-point of 38–39° is reported.[28]

Ethyl N-n-butylmalonamate. A solution of phosphorus oxychloride (30.7 g., 0.2 mole) in 50 ml. of dry benzene was added during 30 minutes to a stirred suspension of ethyl potassium malonate (68.0 g., 0.4 mole) in 350 ml. of dry benzene, the reaction mixture being kept cool in an ice-bath. Reaction was completed by warming the mixture on a steam-bath until a clear solution was obtained.

A solution of *n*-butylamine (58.5 g., 0.8 mole) in 50 ml. of dry benzene was added to the cooled acid chloride solution during 30 minutes, the solution finally thickening to a clear stiff gel that was allowed to stand overnight.

The gel liquified upon washing with two 200-ml. portions of 3 *N* hydrochloric acid followed by two 100-ml. portions of water. Removal of the benzene from the dried benzene solution under reduced pressure left 48 g. of a yellow oil that was distilled under reduced pressure at 118°/1 mm. giving 37.0 g. (49%) of a clear colorless oily liquid.

Anal. Calc'd for $C_9H_{17}NO_3$: C, 57.7; H, 9.2. Found: C, 57.5; H, 9.1.

Ethyl ethylmalonanilate was prepared in 55% over-all yield from diethyl ethylmalonate through the intermediate half acid and acid chloride according to the procedure of Staudinger and Bereza.[29]

(15) Godchot, *Bull. soc. chim.*, [4] **9**, 261 (1911), reports m.p. 75–76° for this compound prepared by acylation of glycine followed by esterification.

(16) Hotter, *J. prakt. Chem.*, [2] **38**, 97 (1888).

(17) Conrad, *J. prakt. Chem.*, [2] **15**, 241 (1877).

(18) Fischer, *Ber.*, **38**, 605 (1905).

(19) Fischer, *Ber.*, **32**, 2451 (1899).

(20) Brenzinger, *Z. physiol. Chem.*, **16**, 552 (1892).

(21) Fischer, *Ber.*, **34**, 433 (1901).

(22) Curtius and Sieber, *Ber.*, **55**, 1543 (1922).

(23) Marvel and Noyes, *J. Am. Chem. Soc.*, **42**, 2259 (1920).

(24) Kossel, *Ber.*, **24**, 4145 (1891).

(25) Steiger, *J. Org. Chem.*, **9**, 396 (1944).

(26) Mohr and Geis, *J. prakt. Chem.*, [2] **81**, 49 (1910).

(27) Freund, *Ber.*, **17**, 780 (1884).

(28) Rugheimer and Hoffmann, *Ber.*, **17**, 739 (1884).

(29) Staudinger and Bereza, *Ber.*, **42**, 4908 (1909).

SUBSTITUTED TETRAZOLYLACETIC ESTERS AND ACIDS

As the preparation of the esters listed in Tables I and II and their saponification or hydrolysis to the corresponding acids was accomplished by the same general procedures in each case, only a few examples are given below to illustrate the method used.

Hydrazoic acid was best prepared according to the directions of Garbrecht and Herbst[30] giving benzene solutions which contained about 12% of hydrazoic acid.

Ethyl 5-ethyl-1-tetrazolylacetate (IIb). Phosphorus pentachloride (62.5 g., 0.3 mole) was added in one portion to a stirred solution of *n*-propionylglycine ethyl ester (47.7 g., 0.3 mole) in 500 ml. of dry benzene. The resulting mixture was stirred for 20 minutes accompanied by slight warming, a pale yellow solution resulting. A solution of hydrazoic acid (12.9 g., 0.3 mole) (202 ml. of soln. containing 0.064 g. of HN_3/ml.) then was added during 30 minutes keeping the solution near room temperature by cooling in a cold water-bath. The resulting solution was stirred for 30 minutes and it then was slowly heated to reflux during $1^1/_2$ hours accompanied by evolution of hydrogen chloride. When vigorous reflux had been attained hydrogen chloride evolution had ceased and the dark reaction mixture was cooled and concentrated under reduced pressure.

The oily residue was treated with 200 ml. of water, heated just to reflux and again cooled. Extraction of the mixture with ether followed by removal of the ether from the dried extract left 34.0 g. of a dark oil that was fractionated under reduced pressure to yield 27.1 g. (49%) of a pale yellow oil boiling at 155–156°/1 mm.

5-Ethyl-1-tetrazolylacetic acid (IIIb), (Method A). A 5.0-g. (0.027 mole) portion of the ester (IIb) was refluxed for four hours with 25 ml. of glacial acetic acid, 5 ml. of concentrated hydrochloric acid, and 10 ml. of water. Removal of the solvents under reduced pressure left an oil that solidified to an almost colorless solid. Recrystallization from ethylene dichloride gave colorless needles of m.p. 132–133°, yield, 2.2 g. (51%).

The crude esters in this series usually could be hydrolyzed to give the acids in over-all yields as good as or better than those obtained where the ester was first purified. In this case it was frequently desirable to put the crude acid through a preliminary purification with sodium bicarbonate before recrystallization.

The 5-substituted-1-tetrazolylacetic acids prepared by saponification of the esters (Method B) were obtained through the procedure illustrated below by the preparation of 1-phenyl-5-tetrazolylacetic acid (Vb).

Ethyl 1-phenyl-5-tetrazolylacetate (IVb). To a solution of ethyl malonanilate (39.6 g., 0.19 mole) in 400 ml. of dry benzene was added under cooling in a cold water-bath phosphorus pentachloride (39.8 g., 0.19 mole) the solution immediately becoming clear yellow. After stirring for 30 minutes, a benzene solution of hydrazoic acid (8.2 g., 0.19 mole/147 ml. containing 0.056 g. of HN_3/ml.) was added during 30 minutes with continued cooling. The solution then was slowly heated over one hour to a bath temperature of 80° at which time the evolution of hydrogen chloride had ceased and the solution had darkened. Upon removal of the benzene under reduced pressure, the residual oil was shaken with 200 ml. of cold water, the oil was separated, and the aqueous layer was extracted with three 50-ml. portions of ether. The combined oil and ether extracts were dried and removal of the ether left 38.0 g. of a dark oil. Careful distillation of this oil under reduced pressure gave 15.4 g. (35%) of colorless oily ester boiling at 160°/0.1 mm. A large quantity of tarry residue was not distillable.

1-Phenyl-5-tetrazolylacetic acid (Vb). A solution of ethyl 1-phenyl-5-tetrazolylacetate (11.6 g., 0.05 mole) in 50 ml. of absolute ethanol was added to a cooled solution of potassium hydroxide (2.8 g., 0.05 mole) in 50 ml. of absolute ethanol. The solution warmed slightly and a fine colorless precipitate quickly formed. After intermittent shaking for three hours, the precipitate was filtered off, washed with a small quantity of absolute ethanol, and dried. This potassium salt was dissolved in 50 ml. of water and the basic solution was acidified to below *p*H 2 with concentrated hydrochloric acid, 1-phenyl-5-tetrazolylacetic acid separating as almost colorless, flocculent crystals that were recrystallized from hot (80°) water to give colorless crystals of m.p. 132.5–133.5°d. Yield, 7.3 g. (72%). Further recrystallization gave product of m.p. 135.0–135.5°d.

If the acid is the desired product in this synthesis, it is more expedient to saponify the crude ester, approximately the same over-all yield being obtained. In this case, it was found to be better to acidify the alcoholic suspension of the potassium salt and filter off the resulting potassium chloride. After evaporating the solvent from the filtrate the residue was suspended in water and extracted into ether. The ether solution then was extracted with saturated sodium bicarbonate solution and the acid was obtained by acidification. This method was used when the crude ester could not be purified.

MISCELLANEOUS PRODUCTS

5-Phenyl-1-tetrazolylacetamide. Crude ethyl 5-phenyl-1-tetrazolylacetate (Theor., 2.32 g., 0.01 mole) was allowed to stand overnight in 10 ml. of concentrated ammonium hydroxide and the resulting colorless crystals were filtered off and washed with a small quantity of water. Dilution of the original filtrate produced a small additional crop of amide. Total yield, 1.05 g. (50%), m.p. 166–167°. Recrystallization from water gave needles of m.p. 166.5–167.5°.

Anal. Calc'd for $C_9H_9N_5O$: C, 53.2; H, 4.5. Found: C, 53.0; H, 4.4.

1-Phenyl-5-tetrazolylacetamide was isolated as above from the corresponding ester in concentrated ammonium hydroxide for 24 hours. Colorless needles of m.p. 176–177° from water. Yield, 90%.[31]

α-(1-Phenyl-5-tetrazolyl)-n-butyramide was obtained in 61% yield and recrystallized from dilute ethanol to give amide of m.p. 126.5–127.5°.

Anal. Calc'd for $C_{11}H_{13}N_5O$: C, 57.1; H, 5.7. Found: C, 57.0; H, 5.6.

5-Ethoxy-2-methyl-4-phenyloxazole. From the attempted preparation of ethyl α-(5-methyl-1-tetrazolyl)phenylacetate in 0.18-mole quantity according to the above described procedure was isolated 40.7 g. of a crude red oil. Distillation gave 16.0 g. (36%) of the oxazole boiling at 128–131°/3.5 mm. From the large quantity of undistillable oily residue that remained, no acid could be isolated upon attempted acid hydrolysis. Refractionation of the oxazole gave a pale yellow distillate boiling at 123–124°/2 mm.

Anal. Calc'd for $C_{12}H_{13}NO_2$: N, 6.9. Found: N, 7.1.

The *picrate* had a melting point of 104–105° after two recrystallizations from 95% ethanol.

Anal. Calc'd for $C_{18}H_{16}N_4O_9$: N, 13.0. Found: N, 13.0.

5-Ethoxy-4-methyl-2-phenyloxazole. Distillation of the crude red oil (19.6 g.) obtained in the preparation of ethyl α-(5-phenyl-1-tetrazolyl)propionate in 0.086-mole quantity, gave 10.2 g. (47%) of colorless, oily oxazole boiling at 116–120°/1.5 mm. The dark, oily, undistillable residue (7.5 g.) was hydrolyzed to α-(5-phenyl-1-tetrazolyl)propionic acid (IIIf). Refractionation of the oxazole gave a colorless distillate boiling at 111–113°/0.8 mm.

Anal. Calc'd for $C_{12}H_{13}NO_2$: N, 6.9. Found: N, 7.0.

The *picrate* had a melting point of 121–122° after recrystallization from 95% ethanol. A 12° melting-point depression was observed in a mixture melting point with picric acid (m.p. 121–122°).

Anal. Calc'd for $C_{18}H_{16}N_4O_9$: N, 13.0. Found: N, 12.9.

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