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THE SYNTHESIS OF SOME TRIAZOLE DERIVATIVES

By

John M. Collier

A Thesis

In Partial Fulfillment of the

Requirements for the Degree of

Master of Science in Chemistry

The University of New Mexico

1958

This thesis, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

E. A. Castetter
DEAN

11/3/58
DATE

Thesis committee

J. L. Rueborn
CHAIRMAN

Abraham Rosenzweig

Guido H. Daub

Milton Kahn

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DEDICATION

To my wife, Hilma

243249

ACKNOWLEDGMENT

The author wishes to express his deep appreciation to Dr. J. L. Riebsomer for suggesting the original problem and for his advice, encouragement and friendship during the course of this investigation.

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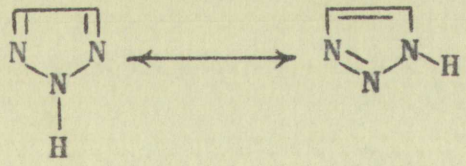
INTRODUCTION

The triazoles have been known since the late 1800's when von Pechmann[1] discovered the ring system during the course of his work with osazones. He first assigned the name "osotriazone" to the parent ring; this was later changed to "osotriazole", a name which is still retained for certain derivatives obtained from the sugar osazones.

The presently accepted names for this series of compounds are 1,2,3,1(2)H-triazole and vicinal or v-triazole. The parent compound (I) is a five-membered, doubly unsaturated molecule containing three nitrogen atoms and two carbon atoms. It exists in two tautomeric forms (I, II).



I II

(1) H. von Pechmann, Ber., 21, 2756 (1888).

From a consideration of dipole moments it has been suggested[2] that the form shown in I predominates.

The parent compound (I) was first synthesized by von Pechmann[1] by the degradation of 2-phenyl-1,2,3,2H-triazol-4-ylcarboxylic acid (III). It has also been obtained[3] as an oxidation product of benzotriazole (IV) and of derivatives of IV. Triazoles can be obtained from the combination of acetylenes with azides[4]. Recently a new synthesis of I was reported[5] utilizing this method. Thus acetylenedicarboxylic acid was combined with benzyl azide to give 1-benzyl-4,5-dicarboxy-1,2,3,1H-triazole (V). The diacid (V) was decarboxylated and then reduced catalytically to I.

Benson and Savell[4] prepared a comprehensive review article discussing in detail the earlier chemistry of the v-triazoles.

The general methods for the preparation of the 2-phenyl-1,2,3,2H-triazoles were described by Sumrell[6].

---

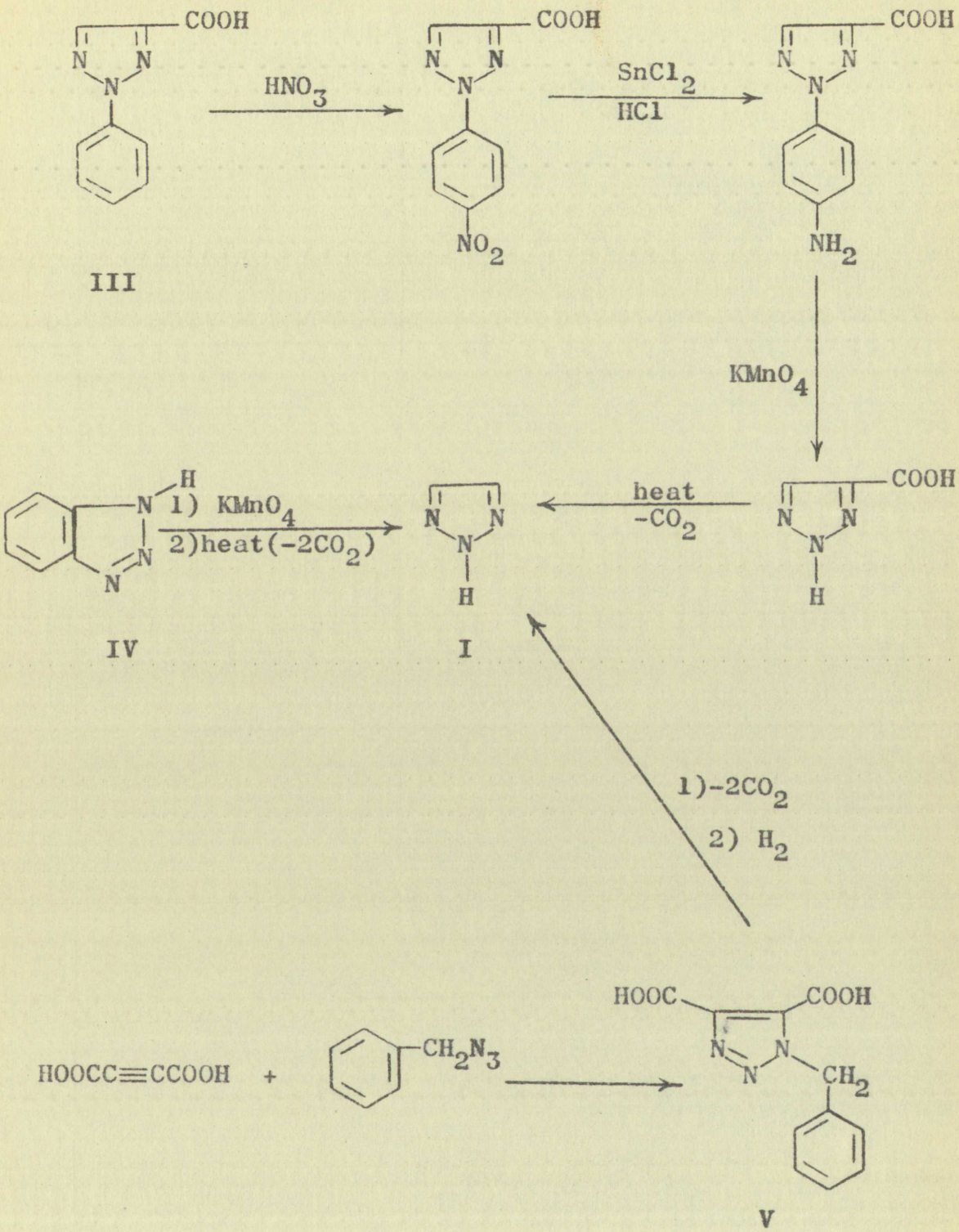
(2) E. Hoggarth, "Chemistry of Carbon Compounds", Vol. IV, Part A, Elsevier Pub. Co., New York, N. Y., 1957, p. 444.

(3) J. A. Bladin, Ber., 26, 545 (1893).

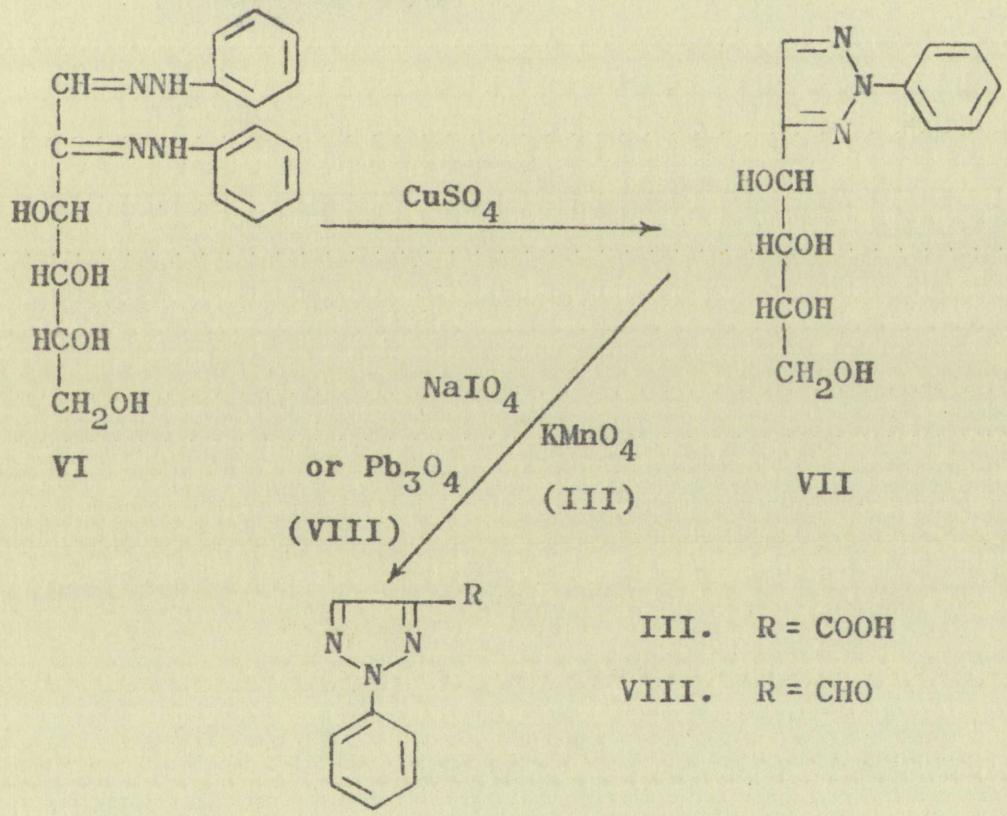
(4) F. R. Benson and W. L. Savell, Chem. Rev., 46, 1 (1950).

(5) R. H. Wiley, K. F. Hussung and J. Moffat, J. Org. Chem., 21, 190 (1956).

(6) G. Sumrell, "Masters Thesis", University of New Mexico, 1948.


COOH
HNO3
NO2
SnCl2
HCl
NH2
III
KMnO4
heat
-CO2
1) KMnO4
2)heat(-2CO2)
IV
I
1)-2CO2
2) H2
HOOCC≡CCOOH
+
CH2N3
HOOC
COOH
CH2
V

The method of Hann and Hudson[7] was used by Sumrell. Thus good yields of the acid (III) and 2-phenyl-1,2,3,2H-triazol-4-ylcarboxaldehyde (VIII) were obtained from D-glucose phenylosazone (VI) by treatment with copper sulfate yielding D-glucose phenylosetriazole (VII), followed by oxidation with potassium permanganate to give III or sodium periodate to give VIII. The aldehyde (VIII) has also been prepared from VII using lead oxide in 25% acetic acid solution[8].



III. R = COOH

VIII. R = CHO

---

(7) R. M. Hann and C. S. Hudson, J. Am. Chem. Soc., 66, 735 (1944).

(8) L. Vargha and M. Remenyi, J. Chem. Soc., 1951, 1068.

The bulk of the recent synthetic work with the triazoles has been confined to the preparation of osotriazoles as aids in the identification of sugars. The phenyl-, p-bromophenyl-, p-tolyl- and β-naphthylosotriazoles of several mono- and disaccharides have been prepared.

Hudson and his associates synthesized the osotriazole derivatives in proving the structures of D-altroheptose[9], L-guloheptulose[10], D-idoheptulose[11] and several higher carbon sugars, for example D-manno-L-mannooctose[12].

Hardegger[13] and his coworkers prepared the p-tolylosotriazoles of several monosaccharides. They also obtained the β-naphthyl- and p-bromophenylosotriazole derivatives of a number of sugars[14]. The

---

(9) D. A. Rosenfeld, N. K. Richtmyer and C. S. Hudson, J. Am. Chem. Soc., 73, 4907 (1951).
(10) L. C. Stewart, N. K. Richtmyer and C. S. Hudson, J. Am. Chem. Soc., 74, 2206 (1952).
(11) J. W. Pratt, N. K. Richtmyer and C. S. Hudson, J. Am. Chem. Soc., 74, 2210 (1952).
(12) J. V. Karabinos, R. M. Hann and C. S. Hudson, J. Am. Chem. Soc., 75, 4320 (1953).
(13) E. Hardegger and H. El Khadem, Helv. Chim. Acta, 30, 1478 (1948).
(14) E. Hardegger, H. El Khadem and E. Schreier, Helv. Chim. Acta, 34, 253 (1951).

phenylosazones of several derivatives of D-psicose were converted to the phenylosotriazoles[15, 16].

Some new carbohydrates and their phenylosotriazole derivatives were reported recently. Hassid[17] and his associates prepared the phenylosotriazole derivative of 3-(α-D-glucopyranosido)-L-arabinose which was biologically synthesized from α-D-glucose-1-phosphate and L-arabinose using pseudomonas saccharophila. Another new disaccharide, 5-(D-glucopyranosyl)-D-fructopyranose, was synthesized and its phenylosotriazole derivative was prepared[18].

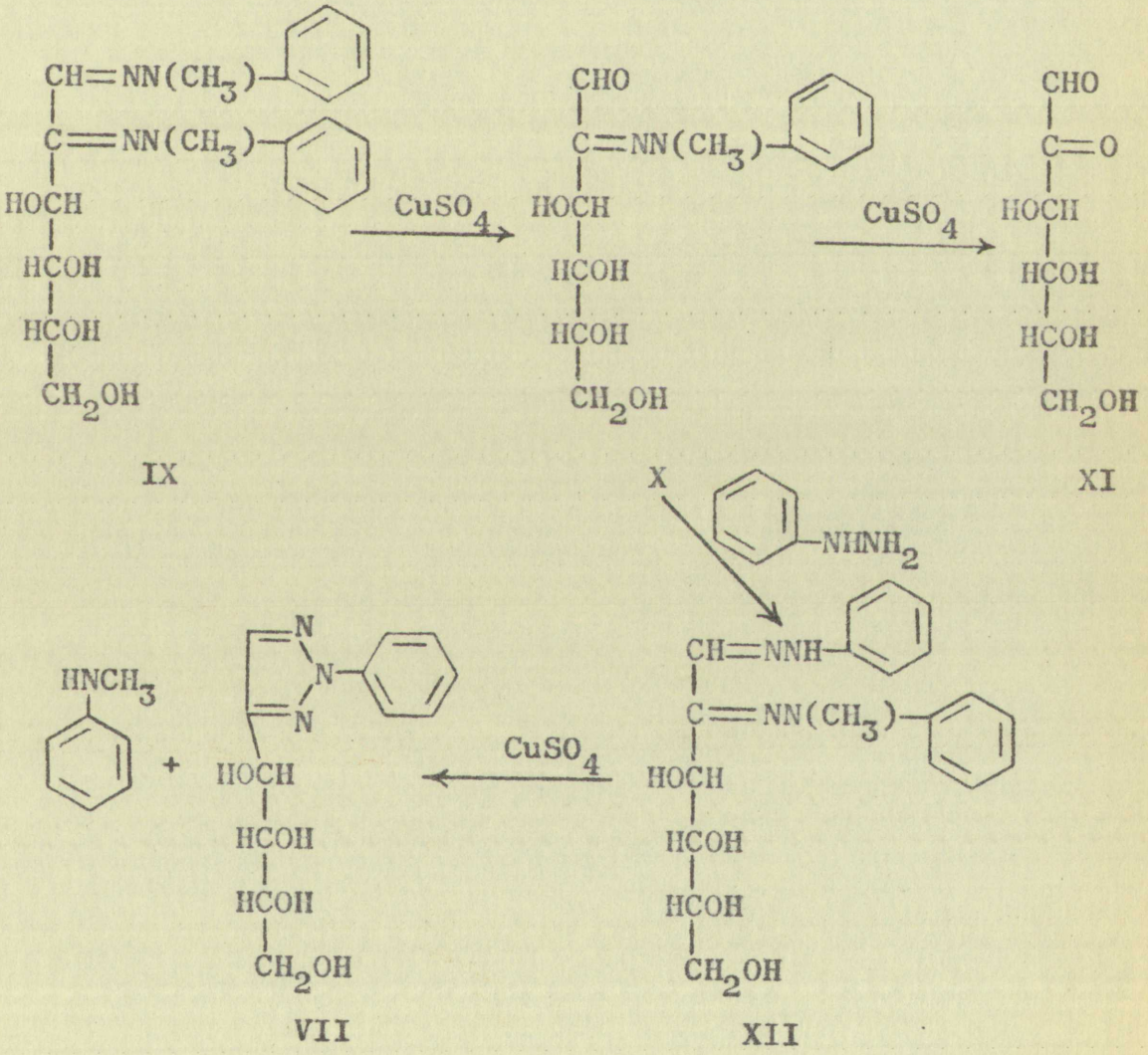
The p-bromophenylosotriazoles were prepared from the p-bromophenylosazones of some sugars labeled with C-14[19], as was the phenylosotriazole from glucose phenylosazone containing tritium on carbon 1 [20].

El Khadem[21] has shown that it is necessary that a hydrogen be attached to the nitrogen of at least one

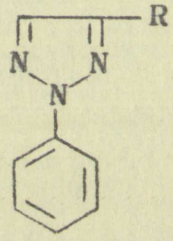
---

(15) E. Hardegger and E. Schreier, Helv. Chim. Acta, 35, 232 (1952).
(16) E. Schreier, G. Stohr and E. Hardegger, Helv. Chim. Acta, 37, 574 (1954).
(17) W. Z. Hassid, M. Doudoroff, A. L. Potter and H. A. Barker, J. Am. Chem. Soc., 70, 306 (1948).
(18) F. H. Stodola, H. J. Koepsell and E. S. Sharpe, J. Am. Chem. Soc., 74, 3202 (1952).
(19) F. Weygand, H. Grisebach, K. Kirchner and M. Haselhorst, Ber., 88, 487 (1955).
(20) F. Friedberg and L. Kaplan, J. Am. Chem. Soc., 79, 2600 (1957).
(21) H. El Khadem, J. Chem. Soc., 1953, 3452.

hydrazone residue in an osazone before osotriazole formation will occur. Thus when the methylphenylosazone (IX) of glucose was treated with copper sulfate the hydrazone (X) was obtained and, upon further treatment with copper sulfate, was converted to the osone (XI). The mixed osazone (XII) was prepared from X with phenylhydrazine and readily formed the phenylosotriazole (VII) with copper sulfate, losing a molecule of methylaniline in the reaction.



The synthesis of 2-phenyl-1,2,3,2H-triazole (XIII) was first reported by von Pechmann[22], who decarboxylated the silver salt of the acid (III). Riebsomer[23] synthesized XIII from glyoxal phenylhydrazone by heating with copper sulfate and reported the preparation of a series of derivatives of XIII containing substituents on the phenyl group. Riebsomer and Stauffer[24] also prepared a



XIII. R = H

XIV. R = CH_3

similar series of derivatives of 4-methyl-2-phenyl-1,2,3,2H-triazole (XIV).

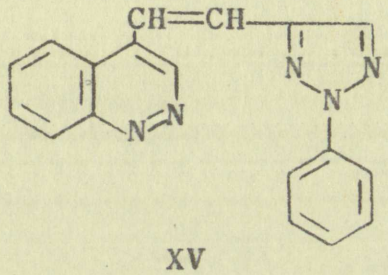
The nitration of the phenyl group in the aldehyde (VIII), resulting in the p-nitro compound, was first reported by Bishop[25].

Castle and Cox[26] effected the condensation of

---

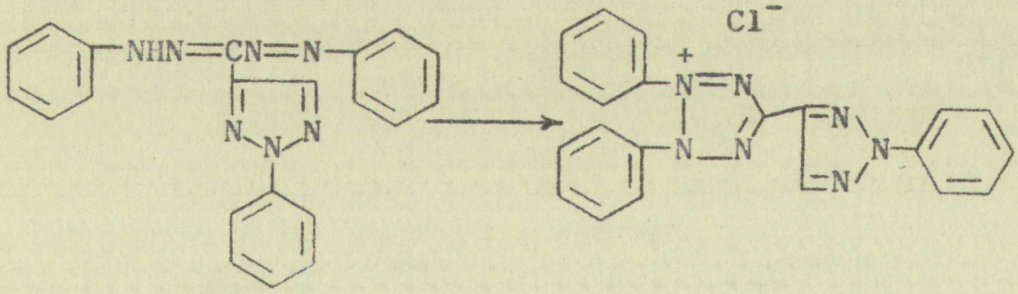
(22) H. von Pechmann, Ann., 266, 292 (1891).
(23) J. L. Riebsomer, J. Org. Chem., 13, 815 (1948).
(24) J. L. Riebsomer and D. A. Stauffer, J. Org. Chem., 16, 1643 (1951).
(25) C. T. Bishop, Science, 117, 715 (1953).
(26) R. N. Castle and D. E. Cox, J. Org. Chem., 18, 1706 (1953).

the aldehyde (VIII) with 4-methylcinnoline, resulting in 1-(4-cinnolyl)-2-[4-(2-phenyl)-1,2,3,2H-triazolyl]-ethene (XV).



XV

Cottrell[27] and his associates condensed the phenylhydrazone of the aldehyde (VIII) with benzenediazonium chloride to form 3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-1,5-diphenylformazan (XVI) which they then cyclized to 1,5-diphenyl-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-tetrazolium chloride (XVII).

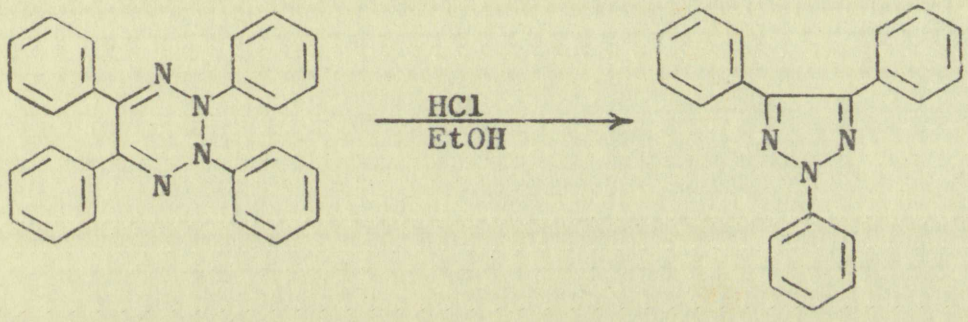


XVI XVII

(27) H. J. Cottrell, D. L. Pain and R. Slack, J. Chem. Soc., 1954, 2968.

Karabinos[28] recently prepared the thiosemicarbazone and the aldazine of the aldehyde (VIII).

2,3,5,6-tetraphenyl-2,3-dihydro-v-tetrazine (XVIII) was converted[29] with hydrogen chloride in boiling ethanol to 2,4,5-triphenyl-1,2,3,2H-triazole (XIX).



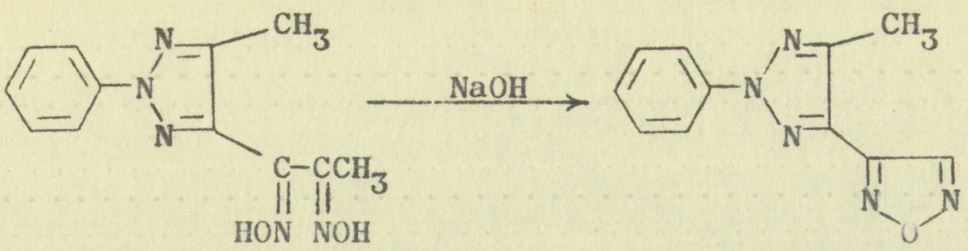
XVIII XIX

Giammanco and Fabia[30] synthesized 4-methyl-3-[5-methyl-2-phenyl-4-(1,2,3,2H-triazolyl)]-furazan (XXI) by boiling 5-methyl-2-phenyl-4-pyruvyl-1,2,3,2H-triazole dioxime (XX) with 30% sodium hydroxide solution. They also synthesized[31] 2,2'-diphenyl-5,5'-dimethyl-4,4'-bitriazole (XXII).

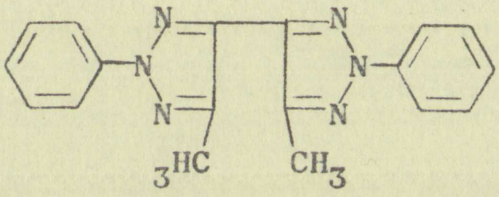
In the present work the author was concerned with

---

(28) J. V. Karabinos, Euclides (Madrid), 16, 279 (1956); C. A., 51, 15508d (1957).
(29) C. A., 47, 2154a (1953).
(30) L. Giammanco and I. Fabia, Gazz. Chim. Ital., 87, 852 (1957); C. A., 52, 4606b (1958).
(31) L. Giammanco and I. Fabia, Gazz. Chim. Ital., 87, 837 (1957); C. A., 52, 4608d (1958).

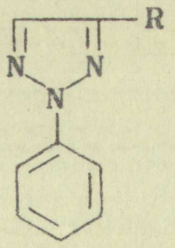


XX XXI



XXII

reactions involving the side chain in the 4-position of 2-phenyl-1,2,3,2H-triazole. A number of investigations have been made in this direction. Sumrell[6] synthesized several derivatives of the aldehyde (VIII). Daub and Castle[32] converted 2-phenyl-1,2,3,2H-triazol-4-ylcarbinol (XXIII) to the iodomethyl compound (XXIV) by treatment with 57% hydriodic acid.

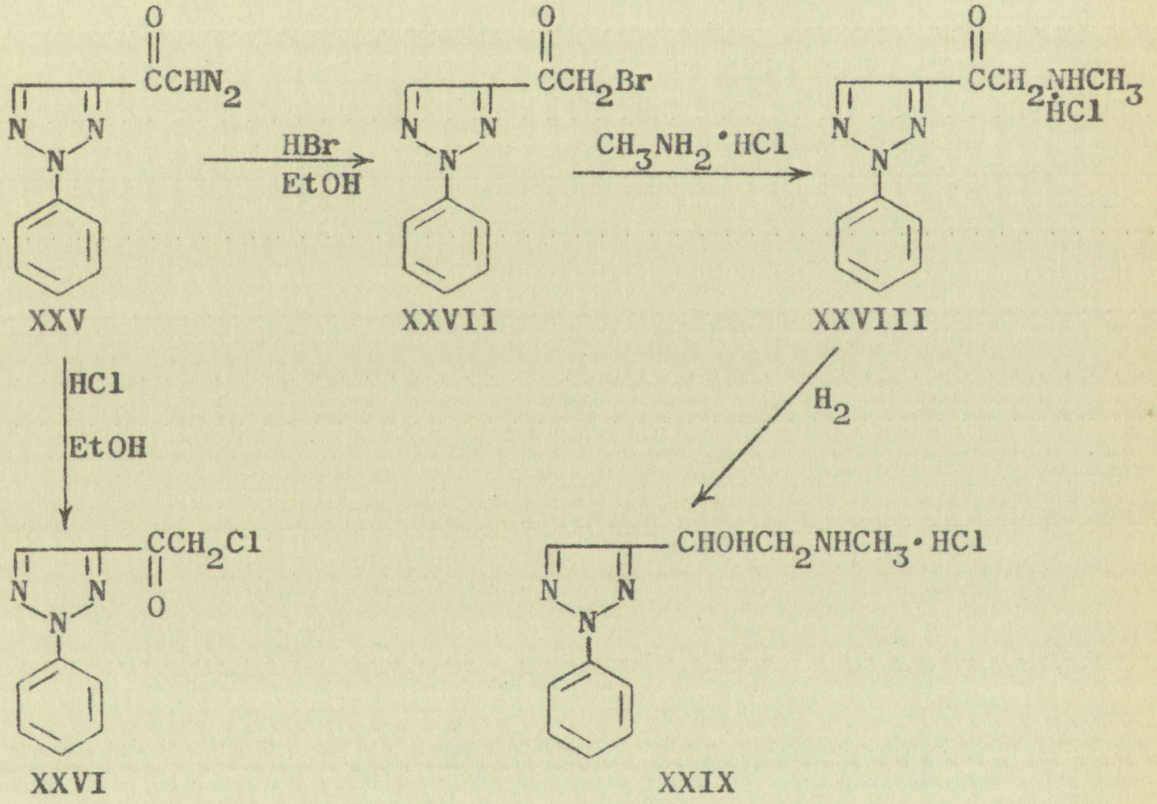


XXIII. R = CH_2OH

XXIV. R = CH_2I

(32) G. H. Daub and R. N. Castle, J. Org. Chem., 19, 1571 (1954).

Stein and D'Antoni[33] carried out a number of reactions with the diazoketone (XXV) obtained from the reaction of the acid chloride of III and diazomethane. They treated XXV with hydrochloric acid in ethanol to obtain the chloroketone (XXVI) and with hydrobromic acid in ethanol which yielded the corresponding bromide (XXVII). The bromide (XXVII) with methylamine gave the salt (XXVIII) which was reduced catalytically to the hydroxy compound (XXIX). The reduced compound (XXIX) was found to have



(33) M. L. Stein and L. D'Antoni, Il Farmaco (Pavia) Ed. Sci., 10, 235 (1955); C. A., 50, 4924a (1956).

mydriatic action.

Triazoles and their derivatives have been used as herbicides[34], growth inhibitors in plants[35], and in the preparation of polymethine dyes[36]. They have also found some use as copolymers with amides in the preparation of yarns[37]. Triazoles have found only very limited pharmacological use.

Castle[38] investigated the optical crystallographic properties of the alcohol (XXIII) and its oxidation products (VIII and III). He found that the three compounds all crystallized in the orthorhombic system but no definite trend in optical properties was evident in this series.

---

(34) C. A., 47, 11538f (1953); C. A., 48, 14085i (1954); C. A., 49, 6528b (1955).

(35) C. A., 47, 12735a (1953); C. A., 50, 12197g (1956).

(36) U. S. Patent 2,503,709 (April 11, 1950); C. A., 44, P5743d (1950).

(37) U. S. Patent 2,658,497 (Aug. 3, 1954); C. A. 48, P14233h (1954).

(38) R. N. Castle, Mikrochim. Acta, 1953, 196.

DISCUSSION

2-Phenyl-1,2,3,2H-triazol-4-ylcarboxylic acid (III) was readily available from sucrose *via* the preparation of the intermediates D-glucose phenylosazone (VI) and D-glucose phenylosotriazole (VII), the latter of which was converted to the acid (III) by oxidation with alkaline potassium permanganate.

Attempts were first made to lengthen the side chain of the acid (III) using the Arndt-Eistert synthesis[39]. The intermediate diazoketone (XXV) was probably formed from the reaction of the acid chloride of III with diazomethane since a positive diazoketone test was obtained by the evolution of nitrogen with strong mineral acid. The rearrangement of the diazoketone (XXV) using 95% ethyl alcohol and silver oxide[40] evolved nitrogen but hydrolysis of the ethyl ester yielded a mixture of acidic material which could not be resolved. Attempts to rearrange XXV at high temperatures (170-190°) with benzyl alcohol and γ-collidine[41], followed by hydrolysis of the resulting benzyl ester also afforded intractable acidic material.

---

(39) F. Arndt and B. Eistert, Ber., 68, 200 (1935).
(40) M. S. Newman and A. S. Hussey, J. Am. Chem. Soc., 69, 3023 (1947).
(41) A. L. Wilds and A. L. Meader, J. Org. Chem., 13, 763 (1948).

The methyl ester (XXX) of III, prepared using methanol and dry hydrogen chloride, was reduced to 2-phenyl-1,2,3,2H-triazol-4-ylcarbinol (XXIII) with lithium aluminum hydride which, in turn, was converted to 2-phenyl-1,2,3,2H-triazol-4-ylmethyl bromide (XXXI) by refluxing with 48% hydrobromic acid.

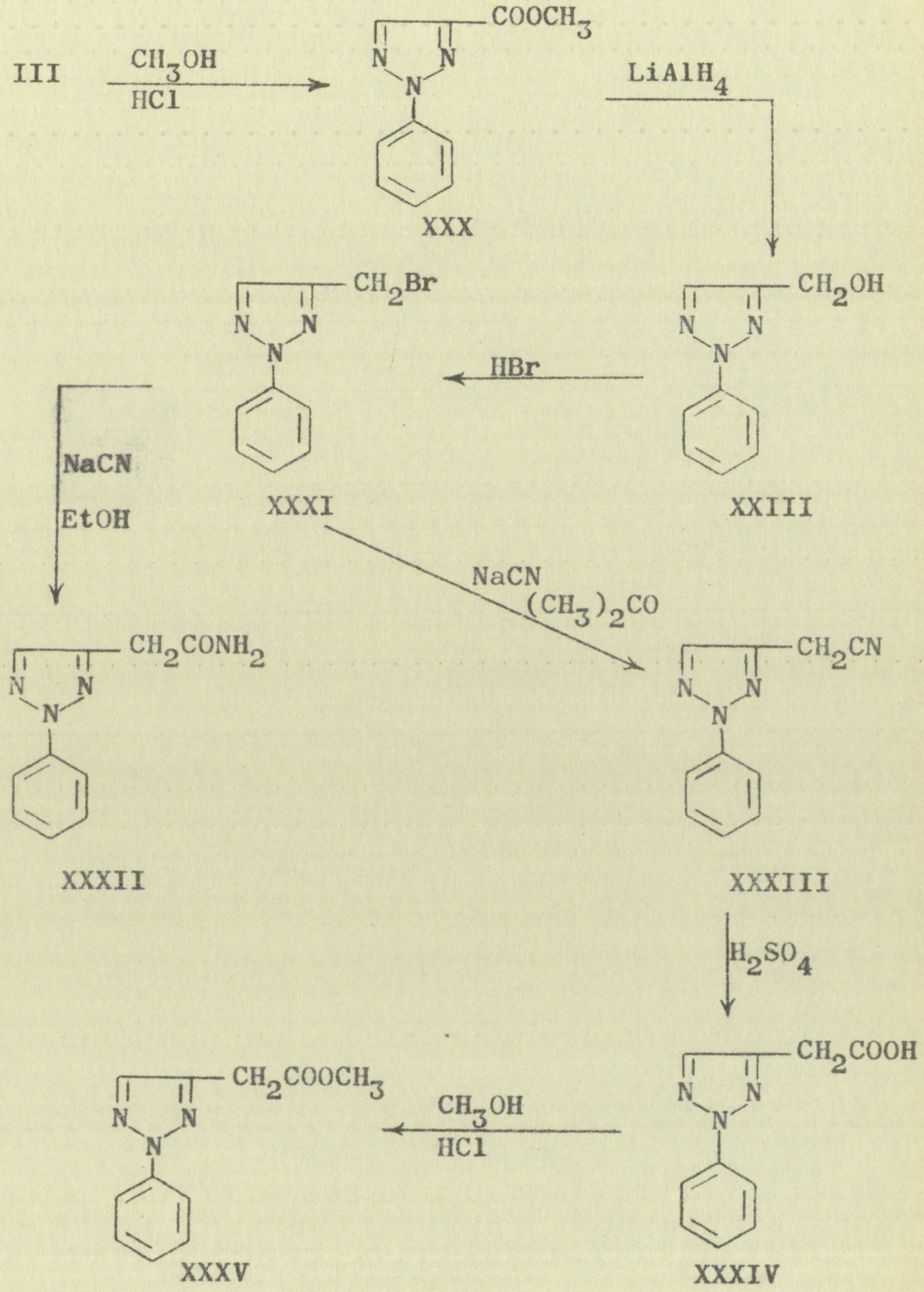
The reaction of XXXI with sodium cyanide in ethyl alcohol and water failed to produce the expected nitrile, instead a low yield of 2-phenyl-1,2,3,2H-triazol-4-ylacetamide (XXXII) was isolated, probably due to the mild hydrolytic conditions of the reaction. Substitution of acetone* for the ethyl alcohol afforded fair yields of 2-phenyl-1,2,3,2H-triazol-4-ylacetonitrile (XXXIII) which was converted to 2-phenyl-1,2,3,2H-triazol-4-ylacetic acid (XXXIV) by hydrolysis with sulfuric acid in 22% over-all yield from the acid (III). Methyl-2-phenyl-1,2,3,2H-triazol-4-ylacetate (XXXV) was obtained by refluxing XXXIV with methyl alcohol saturated with dry hydrogen chloride.

The infra-red absorption spectra** of the above series of compounds were measured for identification purposes. The hydroxyl group in XXIII is indicated by the

---

*S. P. Birkeland, private communication.

**All infra-red absorption spectra in this work were obtained using a Perkin-Elmer (Model 137) infra-red recording spectrophotometer.


III
CH3OH
HCl
COOCH3
XXX
LiAlH4
CH2OH
XXIII
HBr
CH2Br
XXXI
NaCN
EtOH
NaCN
(CH3)2CO
CH2CONH2
XXXII
CH2CN
XXXIII
H2SO4
CH2COOH
XXXIV
CH3OH
HCl
CH2COOCH3
XXXV

peak at 3 μ (Fig. 1). Figure 2 shows the infra-red absorption spectrum of the bromide (XXXI). The characteristic absorption bands of the amide (XXXII) are at 2.9 μ, 3.1 μ and between 6.0 and 6.1 μ (Fig. 3). The nitrile band in XXXIII appears only very weakly at about 4.4 μ (Fig. 4). The bands characteristic of the carbonyl groups in the acid (XXXIV) and the ester (XXXV) are located between 5.7 μ and 5.8 μ (Fig. 5 and 6).

The aldehyde (VIII) was easily obtained from D-glucose phenylosotriazole (VII) by oxidation with sodium periodate at room temperature[6].

Preliminary experiments on the Reformatsky reaction[42] of the aldehyde (VIII) with ethyl bromoacetate indicated that this was not a feasible method to extend the side chain of VIII by two carbons.

The Doebner modification[43] of the Knoevenagel condensation[44], however, afforded a smooth method of accomplishing the extension. Thus when a mixture of VIII and malonic acid was warmed with pyridine containing a trace of piperidine, a good yield of β-2-phenyl-1,2,3,2H-triazol-

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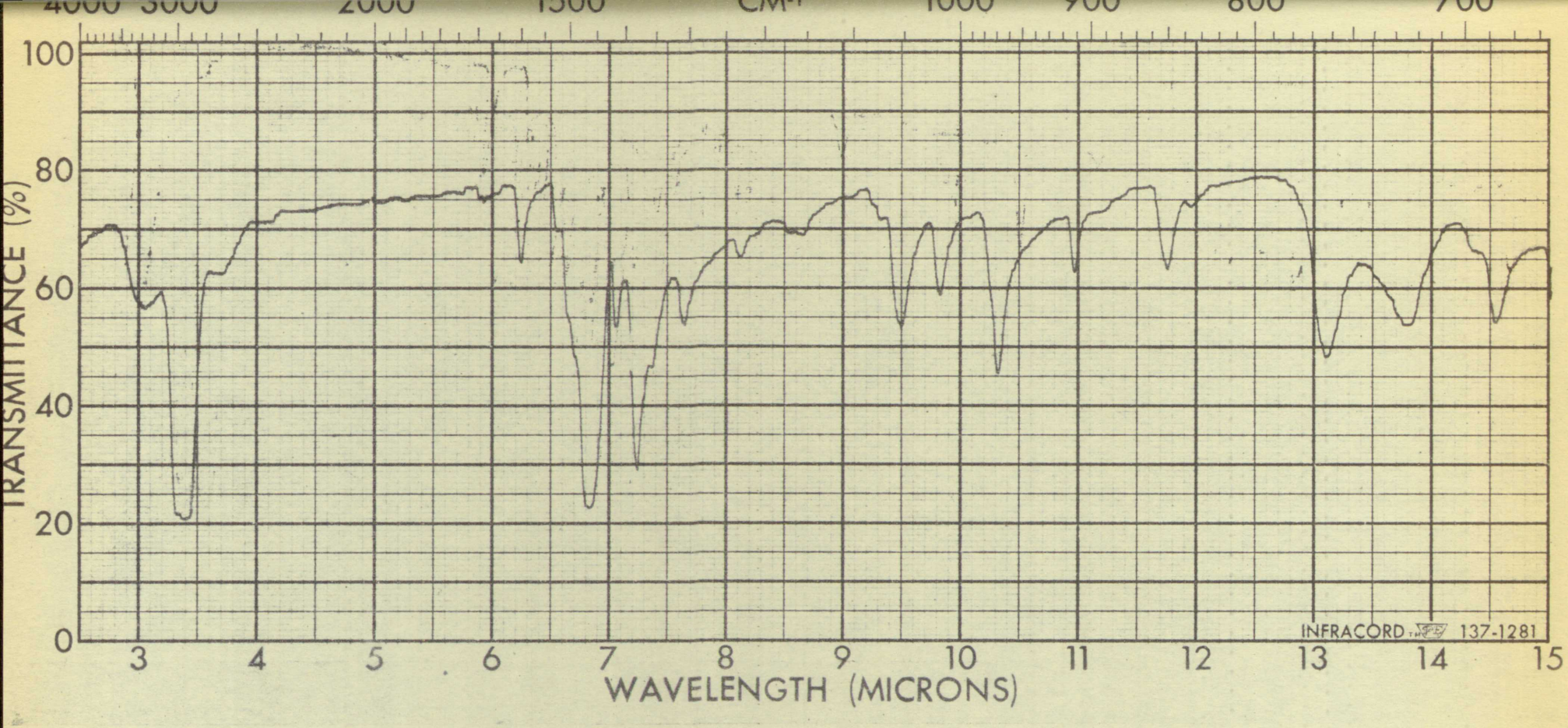
(42) R. L. Shriner, "Organic Reactions", Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 1.
(43) O. Doebner, Ber., 33, 2140 (1900).
(44) E. Knoevenagel, Ber., 31, 2596 (1898).

Figure 1

The Infra-red Absorption Spectrum of 2-Phenyl-1,2,3,2H-triazol-4-ylcarbinol (XXIII).


4000 3000 2000 1500 CM-1 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

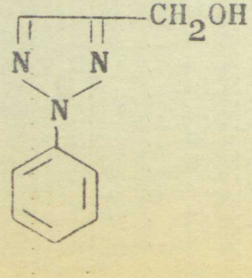
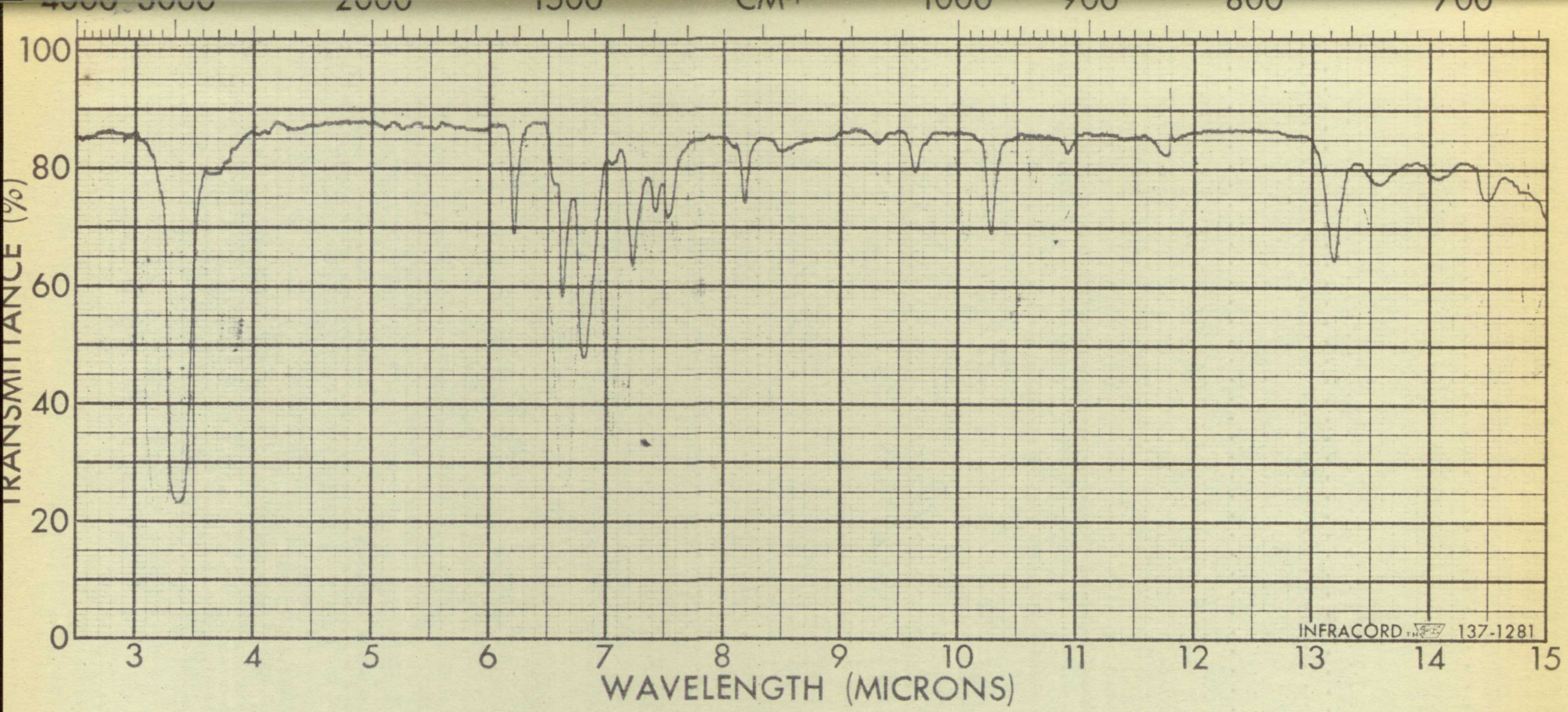

CH2OH
N
N
N

Figure 2

The Infra-red Absorption Spectrum of 2-Phenyl-1,2,3,2H-triazol-4-ylmethyl Bromide (XXXI).


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

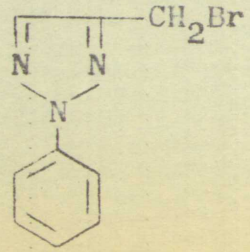
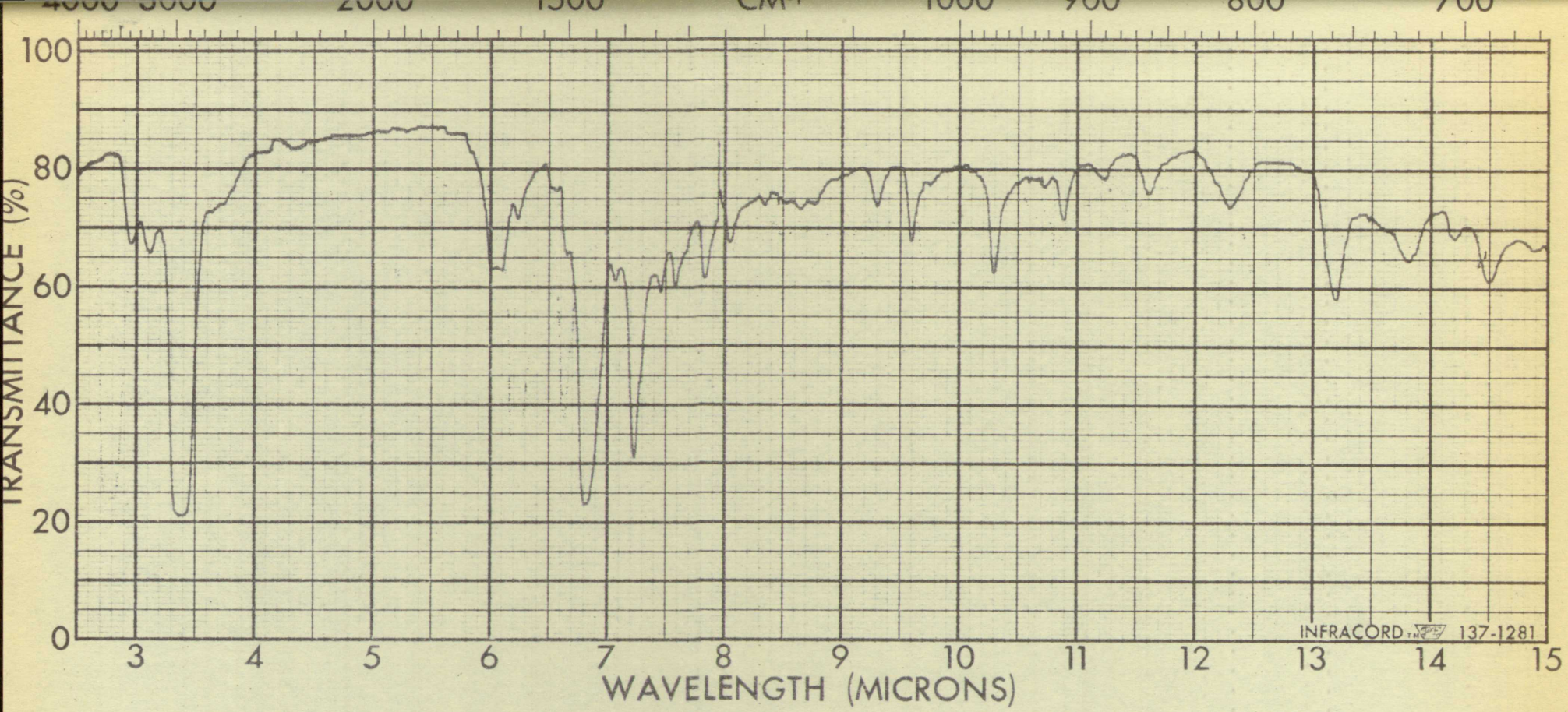

CH2Br
N
N
N

Figure 3

The Infra-red Absorption Spectrum of 2-Phenyl-1,2,3,2H-triazol-4-ylacetamide (XXXII).


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
INFRACORD TM 137-1281

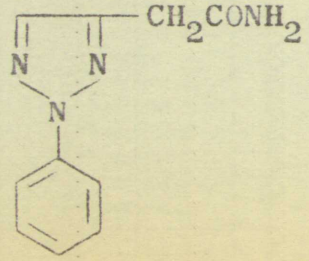
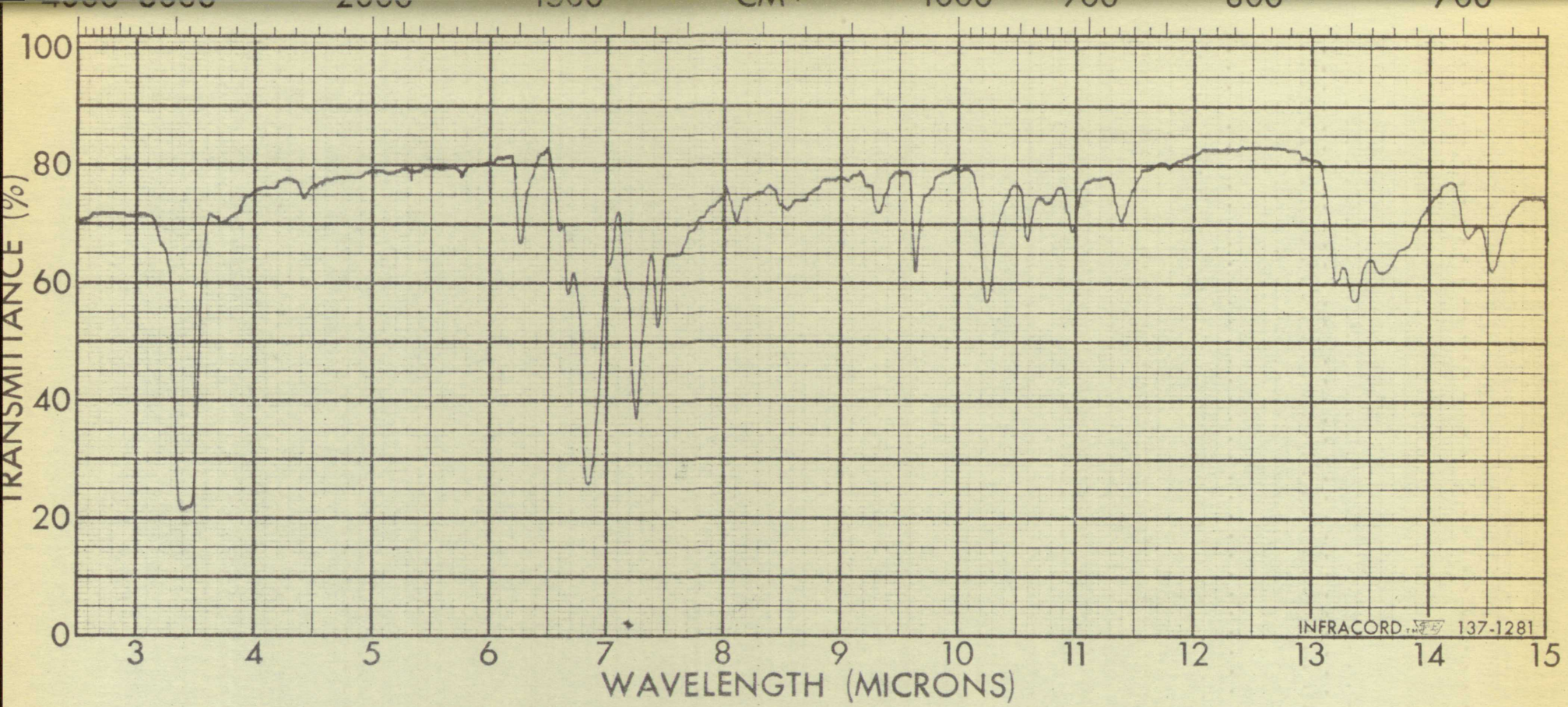

CH2CONH2
N
N
N

Figure 4

The Infra-red Absorption Spectrum of 2-Phenyl-1,2,3,2H-triazol-4-ylacetonitrile (XXXIII).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

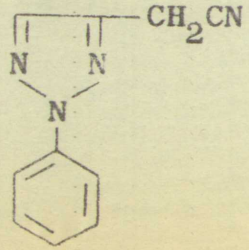
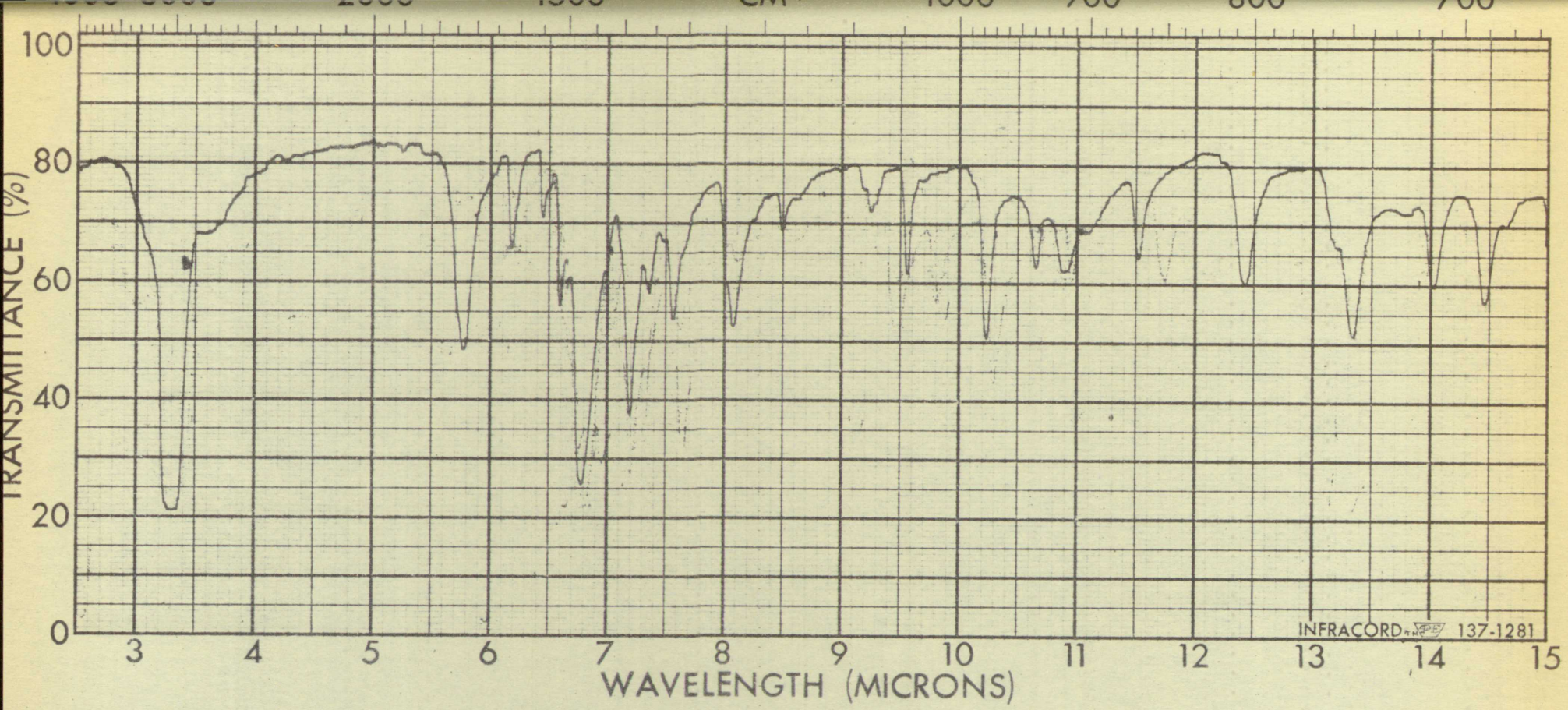

CH2CN
N
N
N

Figure 5

The Infra-red Absorption Spectrum of 2-Phenyl-1,2,3,2H-triazol-4-ylacetic Acid (XXXIV).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

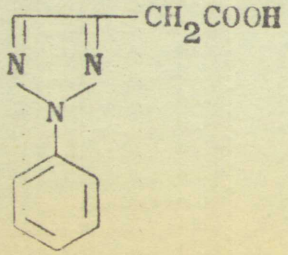
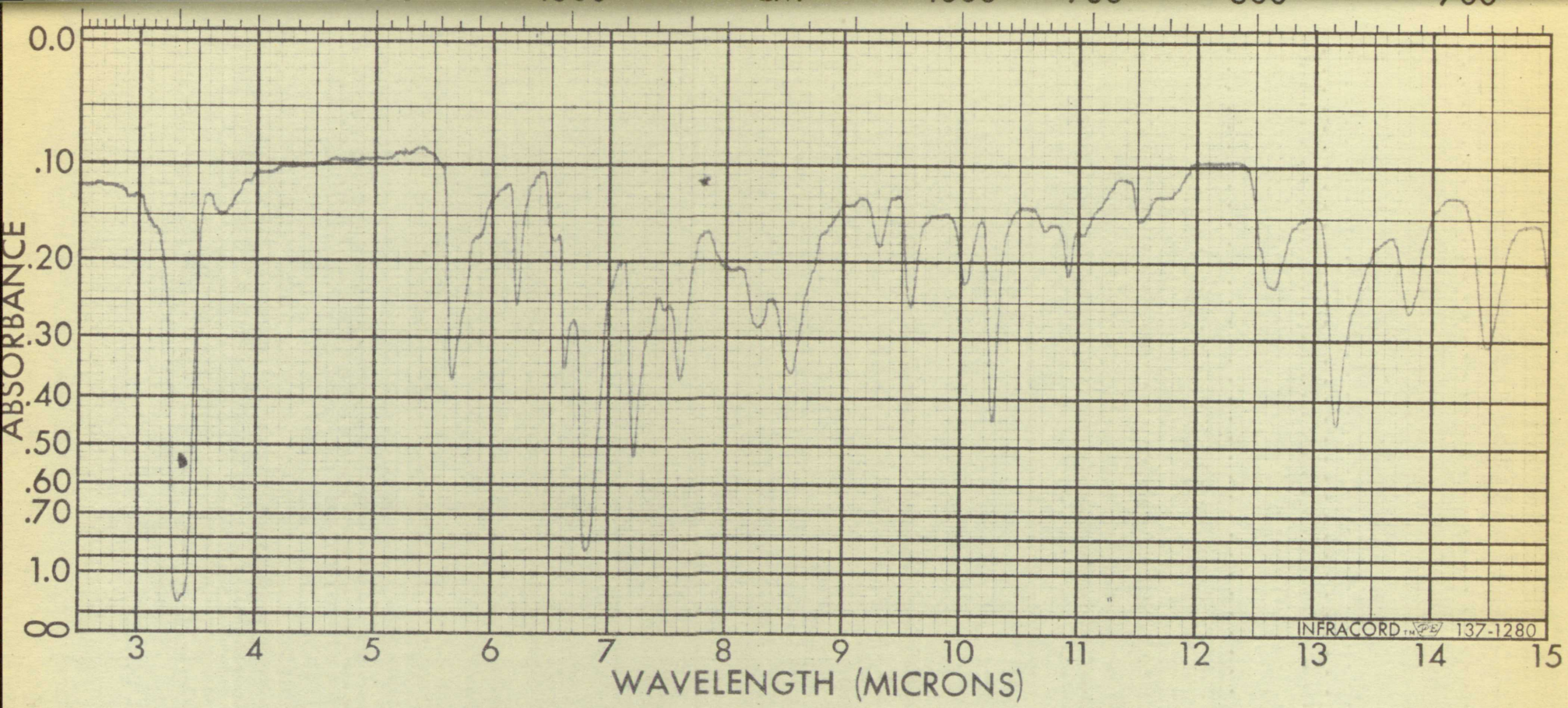
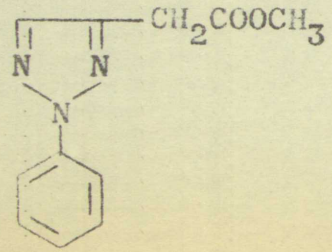

CH2COOH
N
N
N

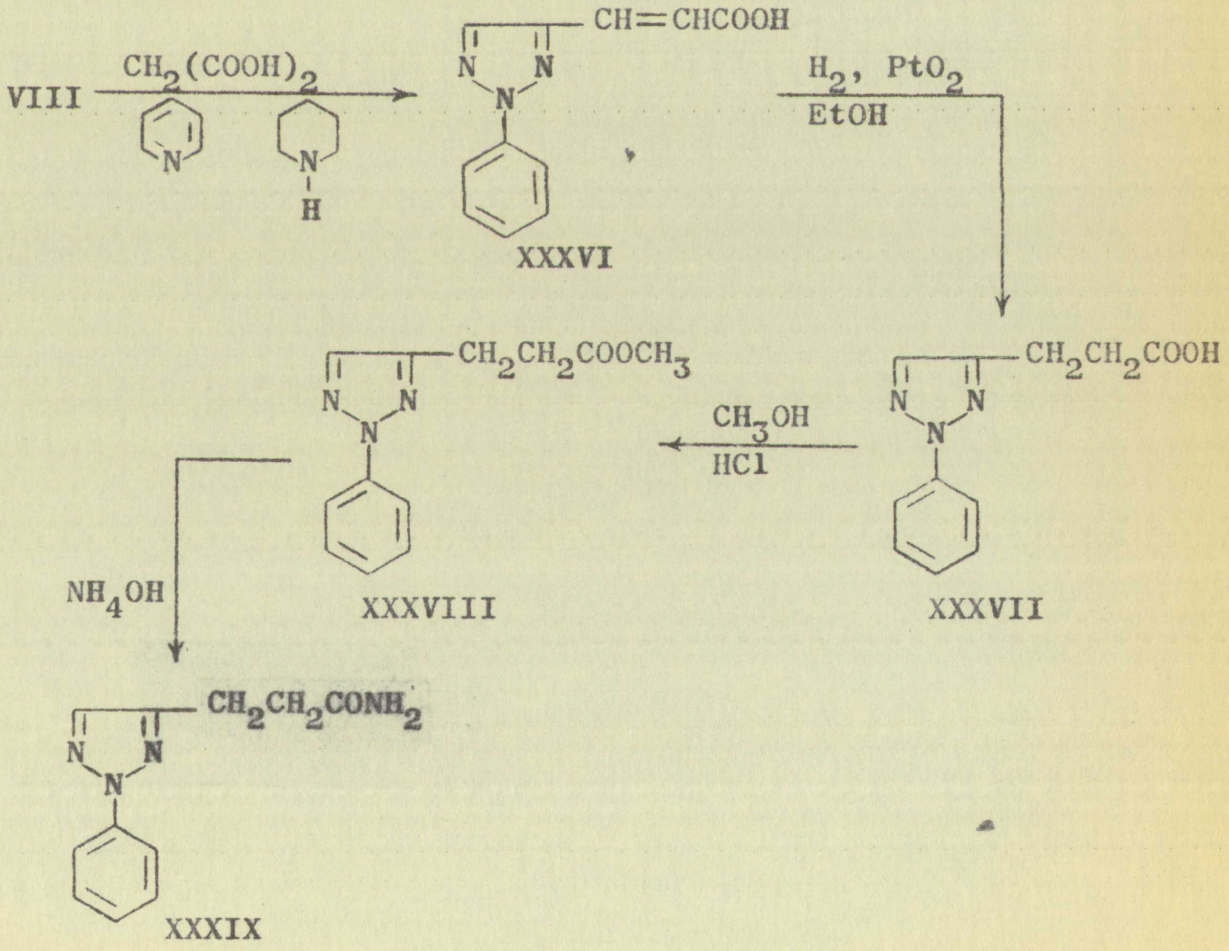
Figure 6

The Infra-red Absorption Spectrum of Methyl-2-phenyl-1,2,3,2H-triazol-4-ylacetate (XXXV).


0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1280


CH2COOCH3
N
N
N

4-ylacrylic acid (XXXVI) was obtained. The acid (XXXVI) was readily reduced at atmospheric pressure in the presence of Adams catalyst to β-2-phenyl-1,2,3,2H-triazol-4-yl-propionic acid (XXXVII). The over-all yield from VIII was 76%. Methyl-β-2-phenyl-1,2,3,2H-triazol-4-ylpropionate (XXXVIII) was prepared from XXXVII as before with methyl alcohol and dry hydrogen chloride. The ester (XXXVIII) was easily converted to β-2-phenyl-1,2,3,2H-triazol-4-ylpropionamide (XXXIX) by shaking with concentrated ammonium hydroxide.



The infra-red absorption spectra of the two acids (XXXVI and XXXVII), the ester (XXXVIII) and the amide (XXXIX) were determined. The characteristic bands for the isolated double bond and the carbonyl group in XXXVI are located at about 6.1 μ and 5.9 μ respectively (Fig. 7). The band for the carbonyl group in XXXVII is at 5.8 μ (Fig. 8). The ester (XXXVIII) and the amide (XXXIX) have characteristic absorption peaks at 5.7 μ (Fig. 9) and at 2.9-3.1 μ and 5.9-6.1 μ (Fig. 10) respectively.

In order to lengthen the side chain of the aldehyde (VIII) by three carbons, the Stobbe condensation[45] was employed using potassium t-butoxide and diethyl succinate. The condensation itself was successful resulting in the isolation of β-carbethoxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic acid (XL). All attempts to decarbethoxylate XL, however, failed. The only material isolated was β-carboxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic acid (XLI). Attempts to decarboxylate XLI also failed, possibly due to the resonance through the conjugated system stabilizing the β-carboxyl group.

The infra-red absorption spectra of the half ester

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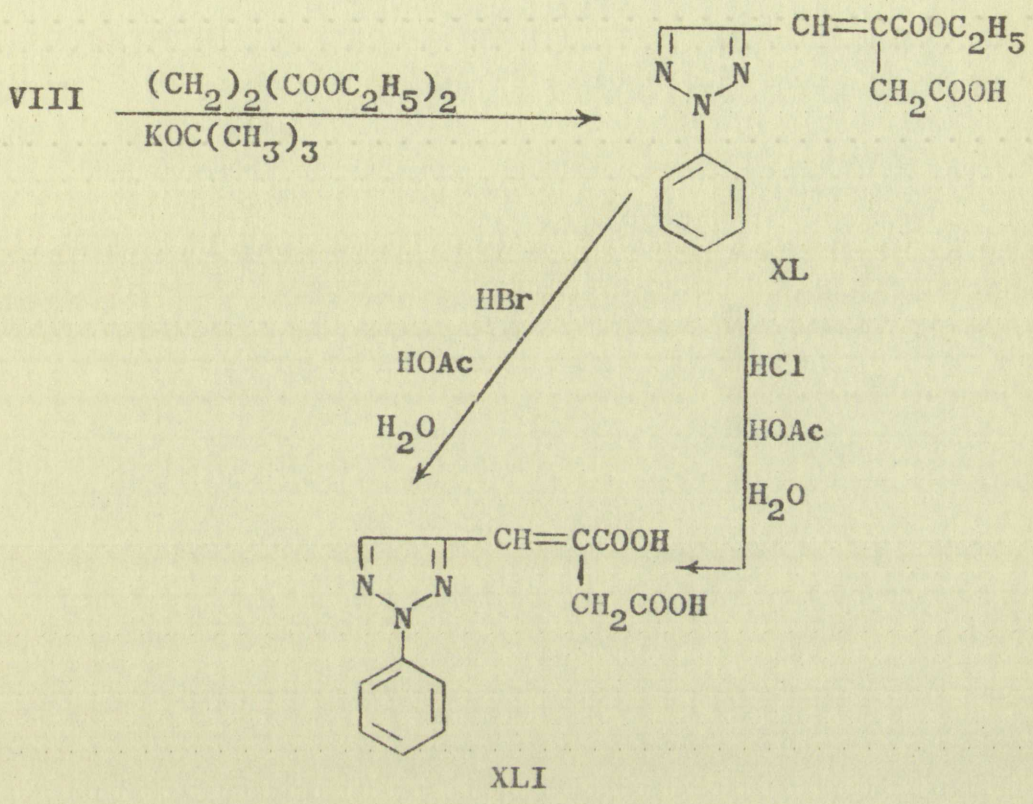
(45) W. S. Johnson and G. H. Daub, "Organic Reactions", Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 1.



(XL) and the diacid (XLI) were determined. The carbonyl groups and the double bond in XL appear at 5.9 μ and 6.2 μ respectively (Fig. 11). The band for the carbonyl groups in XLI is located at about 5.9 μ (Fig. 12).

Since it has been shown[46] that the aldehyde (VIII) reacts readily under conditions of the Perkin reaction[47],

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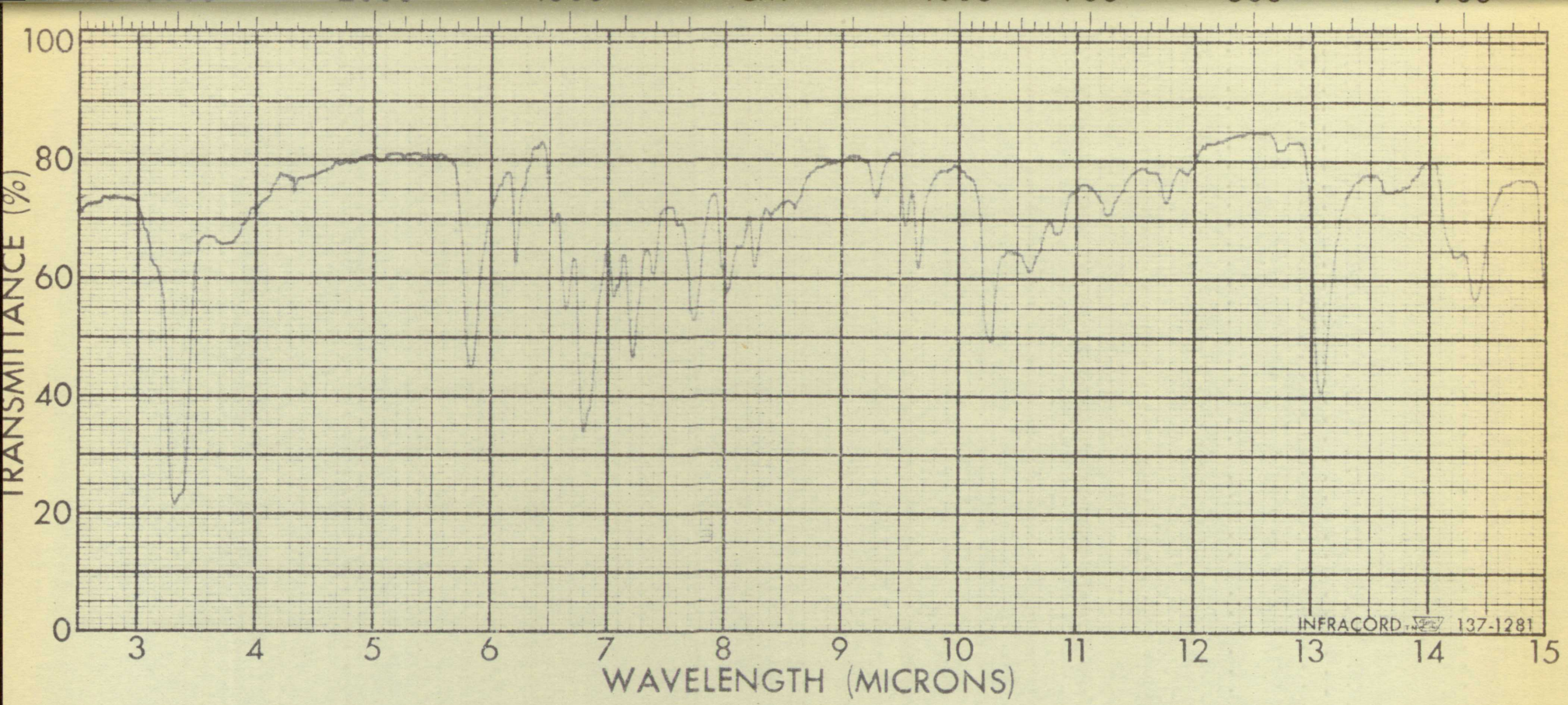
(46) J. L. Riebsomer and G. Sumrell, J. Org. Chem., 13, 807 (1948).

(47) J. R. Johnson, "Organic Reactions", Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 210.

Figure 7

The Infra-red Absorption Spectrum of β-2-Phenyl-1,2,3,2H-triazol-4-ylacrylic Acid (XXXVI).


TRANSMITTANCE (%)
100
80
60
40
20
0
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

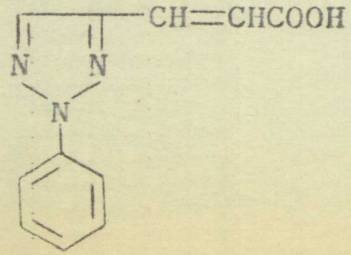
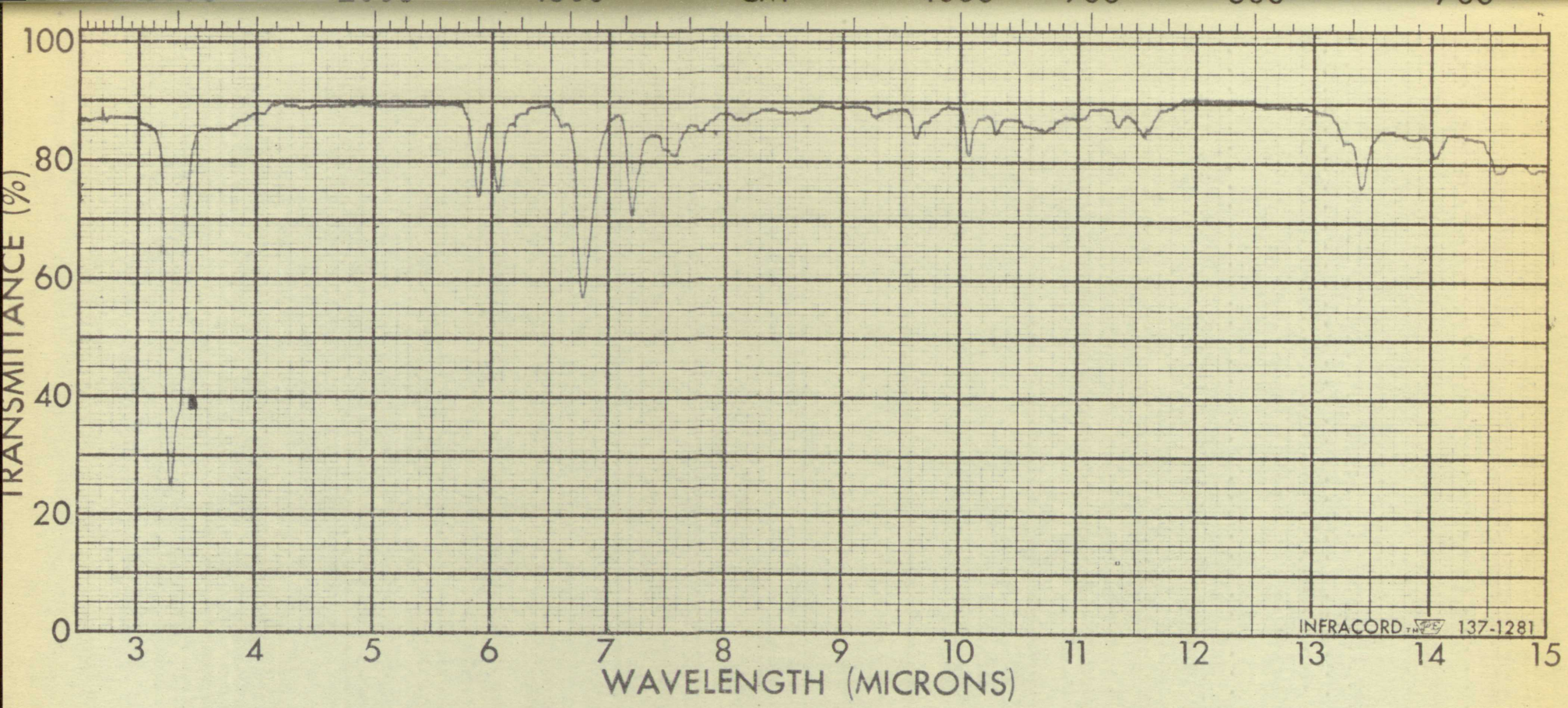

CH=CHCOOH
N
N
N

Figure 8

The Infra-red Absorption Spectrum of β-2-Phenyl-1,2,3,2H-triazol-4-ylpropionic Acid (XXXVII).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD TM 137-1281

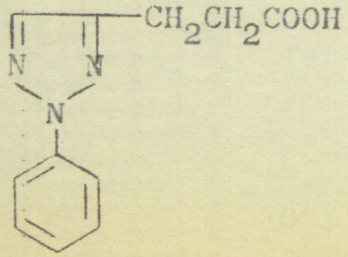
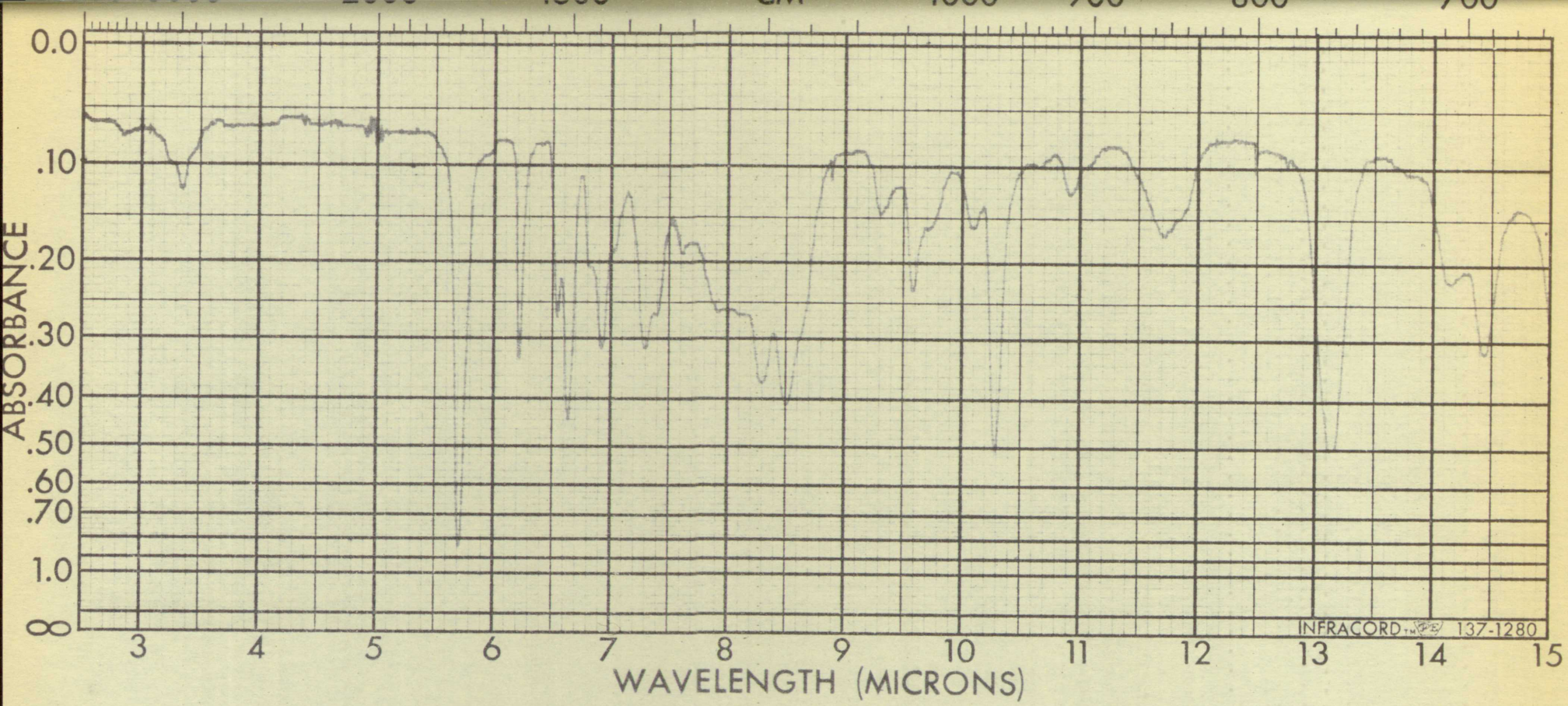

CH2CH2COOH
N
N
N

Figure 9

The Infra-red Absorption Spectrum of Methyl-β-2-phenyl-1,2,3,2H-triazol-4-ylpropionate (XXXVIII).


0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1280

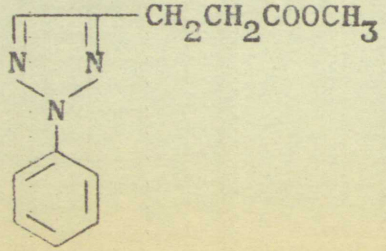
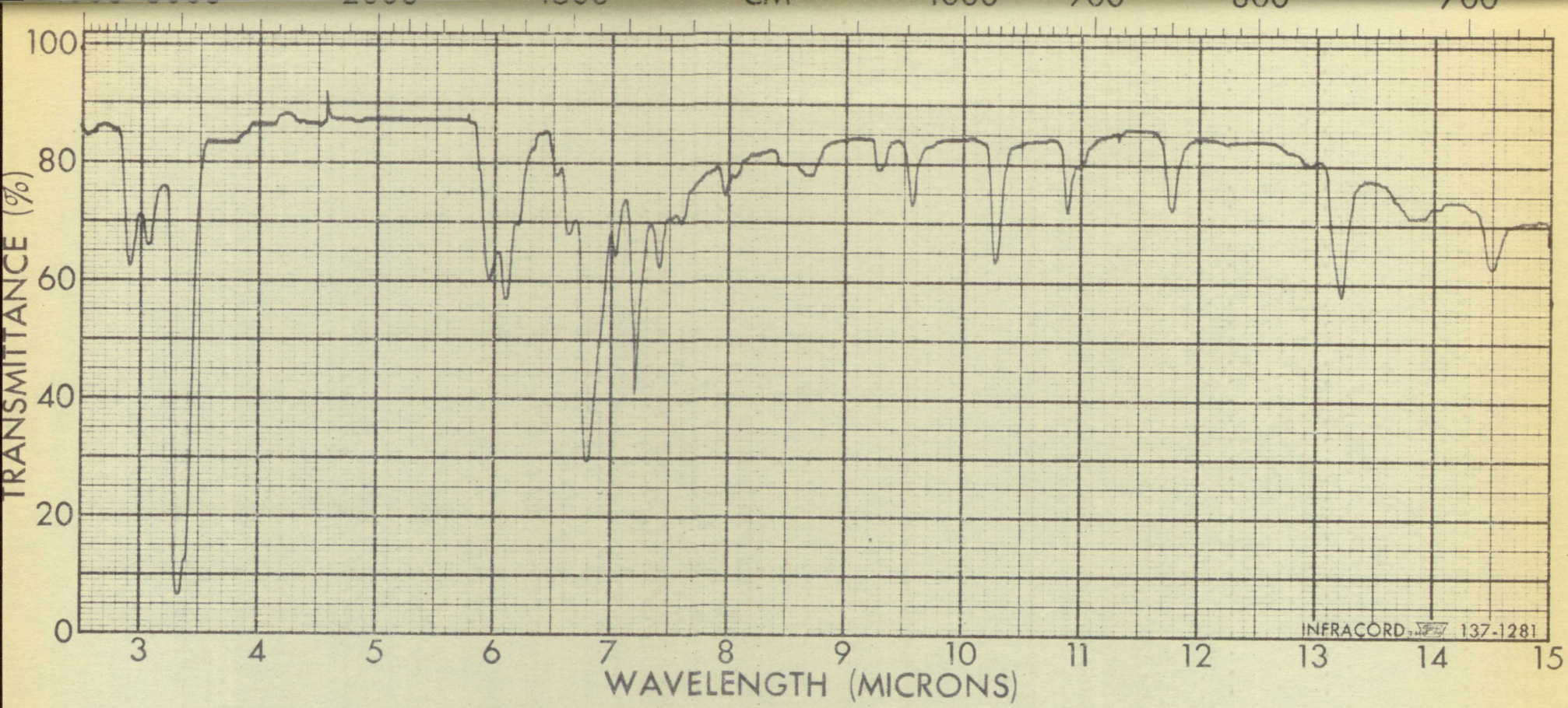

CH2CH2COOCH3
N
N
N

Figure 10

The Infra-red Absorption Spectrum of β-2-Phenyl-1,2,3,2H, triazol-4-ylpropionamide (XXXIX).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

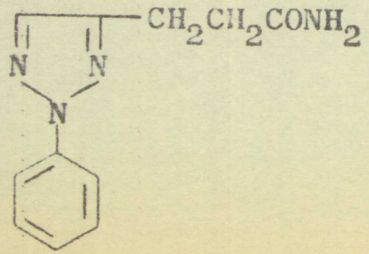
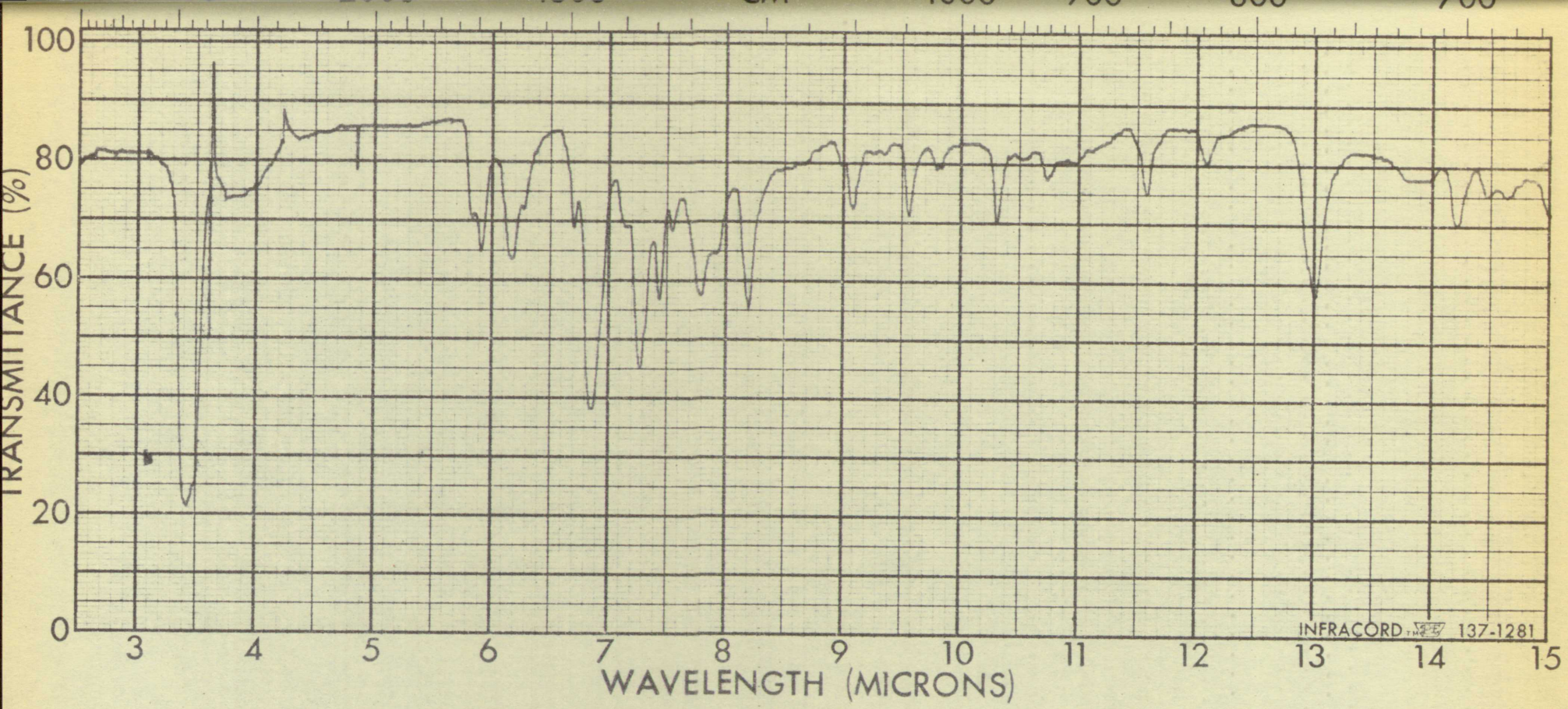

CH2CH2CONH2
N
N
N

Figure 11

The Infra-red Absorption Spectrum of β-Carbethoxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic Acid (XL).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1281

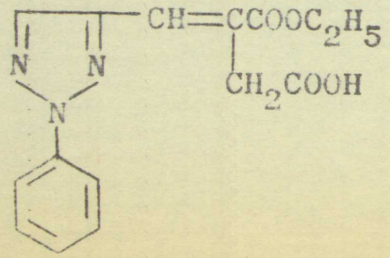
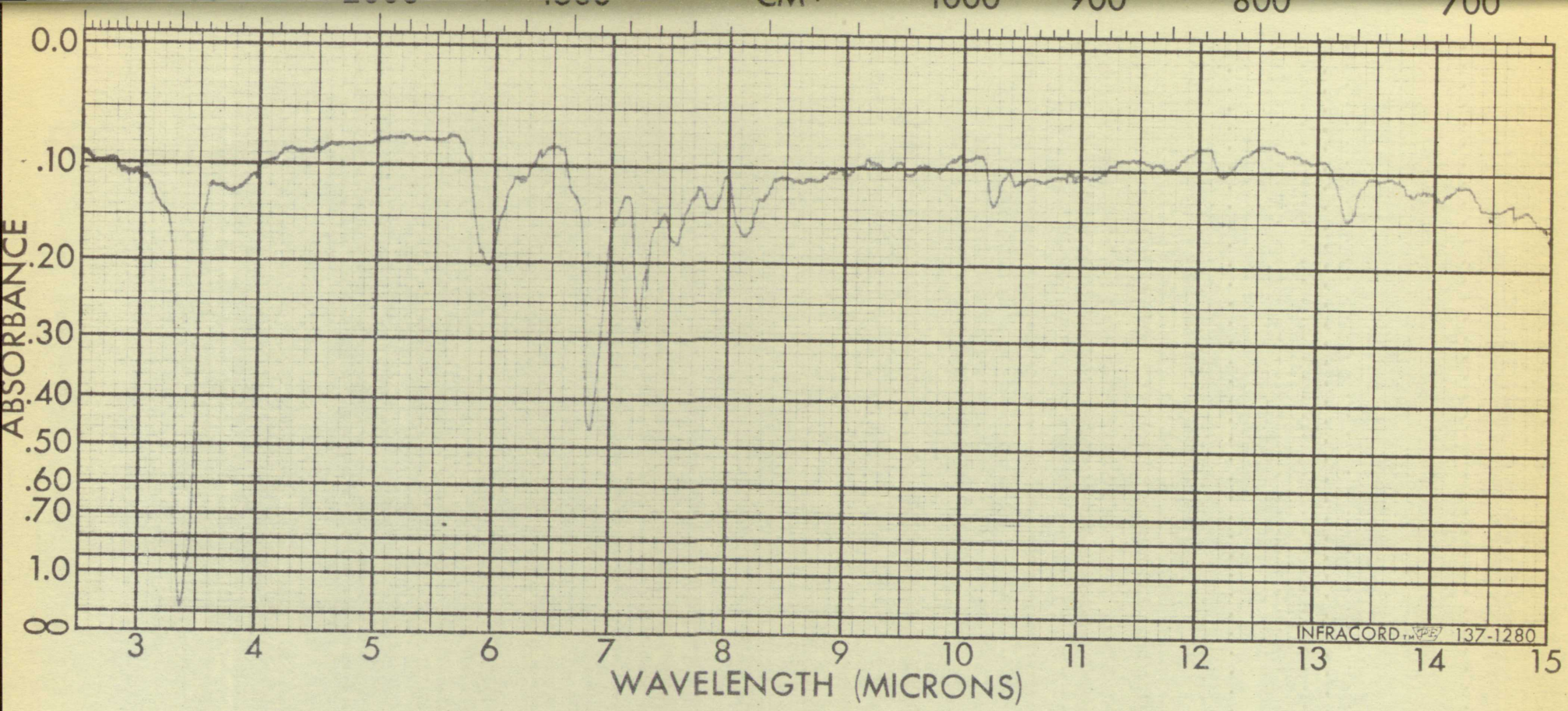
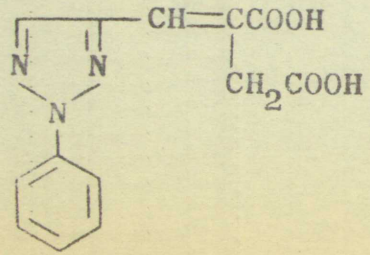

CH=CCOOC2H5
CH2COOH
N
N
N

Figure 12

The Infra-red Absorption Spectrum of β-Carboxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic Acid (XLI).


ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD TM 137-1280

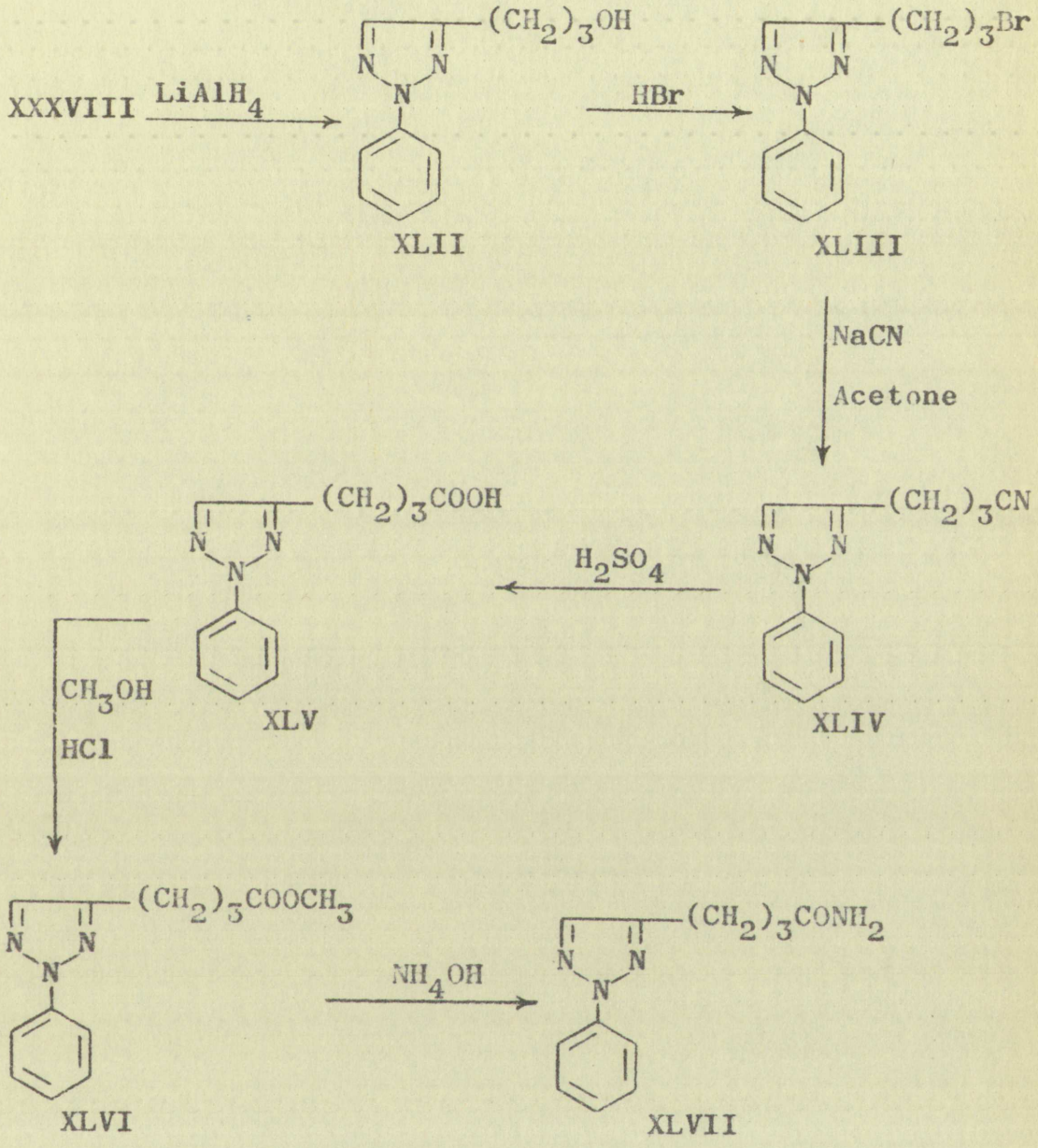

CH=CCOOH
CH2COOH
N
N
N

it was thought that this might afford a route to the extension mentioned above. However, when VIII was allowed to react under these conditions with sodium succinate and acetic anhydride, a tarry liquid mixture was obtained that could not be separated.

The synthesis of the butyric acid derivative was achieved through the reduction of the ester (XXXVIII) with lithium aluminum hydride to 1-hydroxy-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLII), followed by the bromination of XLII with 48% hydrobromic acid yielding 1-bromo-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLIII). The bromide (XLIII) was converted to γ-2-phenyl-1,2,3,2H-triazol-4-yl-n-butyronitrile (XLIV) with sodium cyanide in acetone and water. Hydrolysis of XLIV with sulfuric acid resulted in γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyric acid (XLV) in 76% over-all yield from XXXVIII.

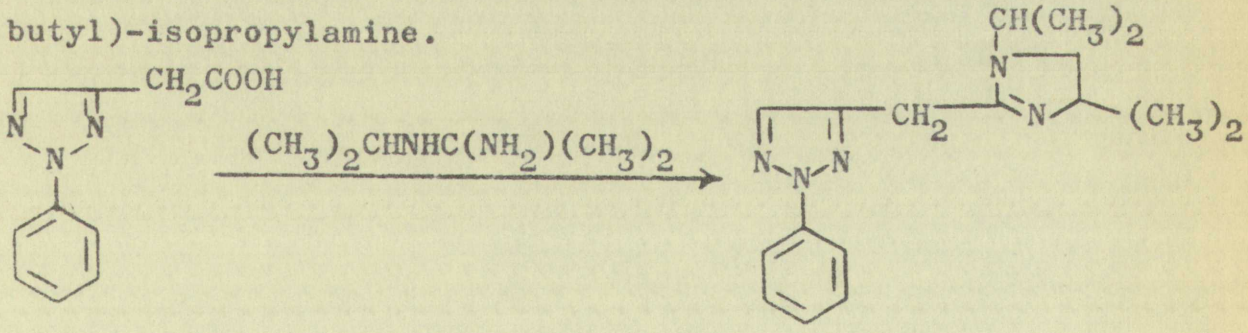
Methyl-γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyrate (XLVI) was prepared from the acid (XLV) by refluxing with methyl alcohol saturated with dry hydrogen chloride. The ester (XLVI) was converted to γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyramide (XLVII) by shaking with concentrated ammonium hydroxide.

The infra-red absorption spectra of the above series of compounds were determined. The absorption band for the


XXXVIII
LiAlH4
(CH2)3OH
XLII
HBr
(CH2)3Br
XLIII
NaCN
Acetone
(CH2)3CN
XLIV
H2SO4
(CH2)3COOH
XLV
CH3OH
HCl
(CH2)3COOCH3
XLVI
NH4OH
(CH2)3CONH2
XLVII

hydroxyl group in XLII is located at 2.9 μ (Fig. 13). Figure 14 depicts the absorption spectrum of the bromide (XLIII). The characteristic band for the nitrile (XLIV) appears at 4.4 μ (Fig. 15). The characteristic absorption bands for the acid (XLV) (Fig. 16), the ester (XLVI) (Fig. 17) and the amide (XLVII) (Fig. 18) appear in the wave length regions normally associated with the groups present in the respective molecules.

Attempts were made to prepare the imidazoline derivatives of the three acids (XXXIV, XXXVII and XLV) by allowing them to react with N-(2-aminoisobutyl)-isopropylamine (b.p. 50° at 20 mm.) and N-(2-aminoisobutyl)-aniline (b.p. 163° at 20 mm.). These experiments were performed as described by Riebsomer[48]. The only imidazoline isolated was 1-isopropyl-2-(2'-phenyl-1',2',3',2'H-triazol-4'-ylmethyl)-4,4-dimethyl-2-imidazoline (XLVIII), obtained from the reaction of the acid (XXXIV) with N-(2-aminoisobutyl)-isopropylamine.

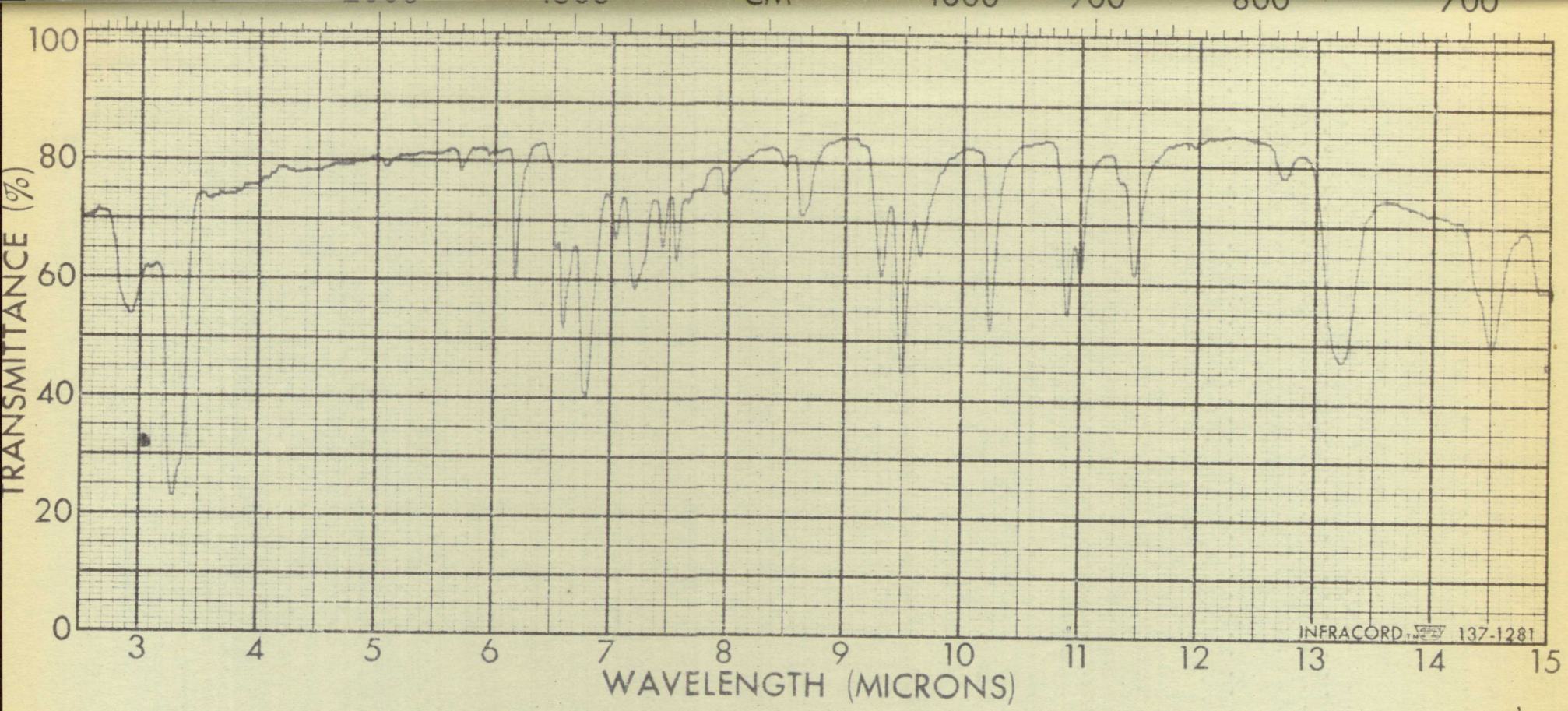


XXXIV XLVIII

(48) J. L. Riebsomer, J. Am. Chem. Soc., 70, 1629 (1948).

Figure 13

The Infra-red Absorption Spectrum of 1-Hydroxy-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLII).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

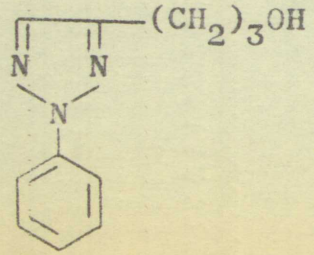
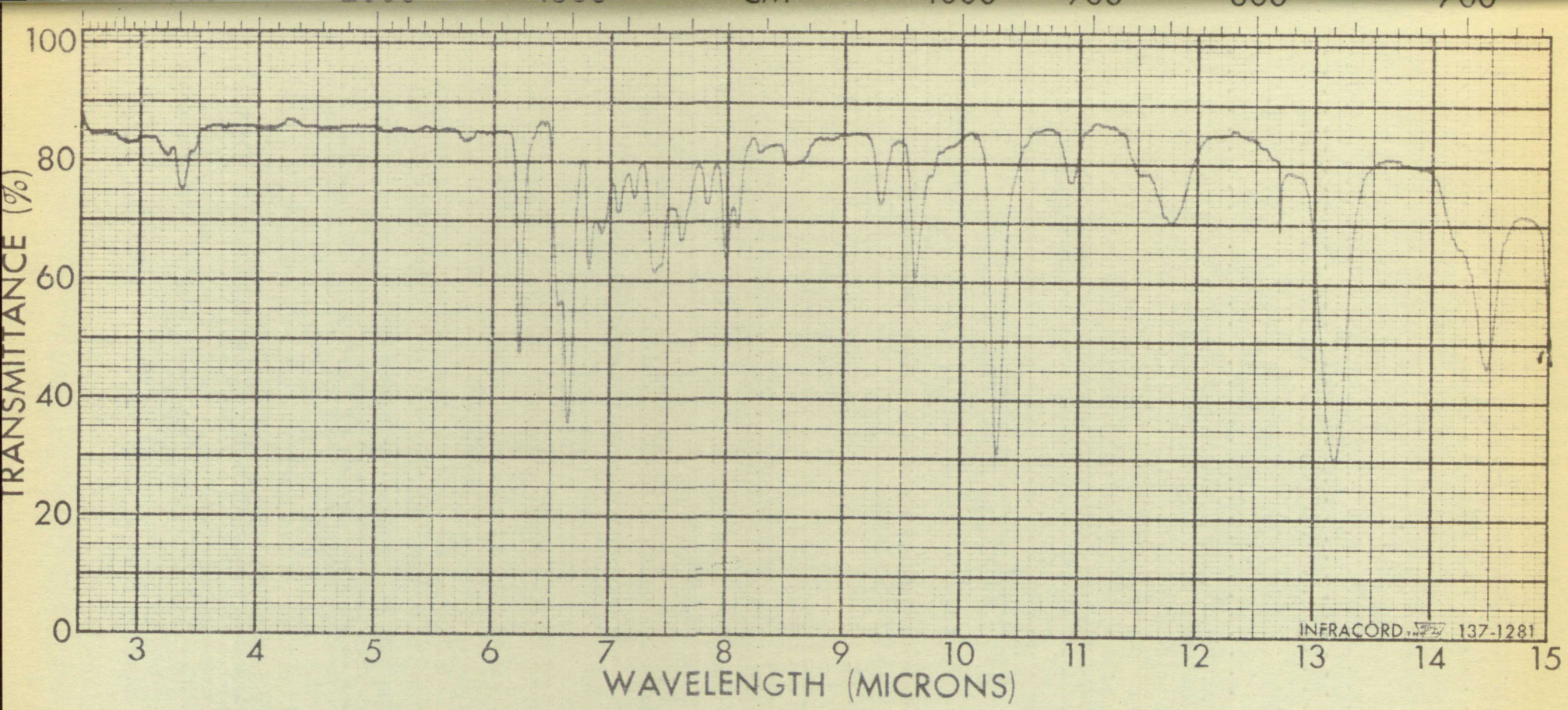

(CH2)3OH
N
N
N

Figure 14

The Infra-red Absorption Spectrum of 1-Bromo-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLIII).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

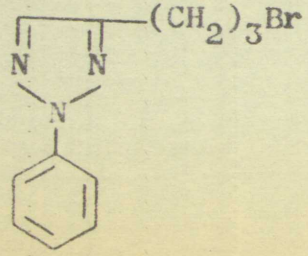
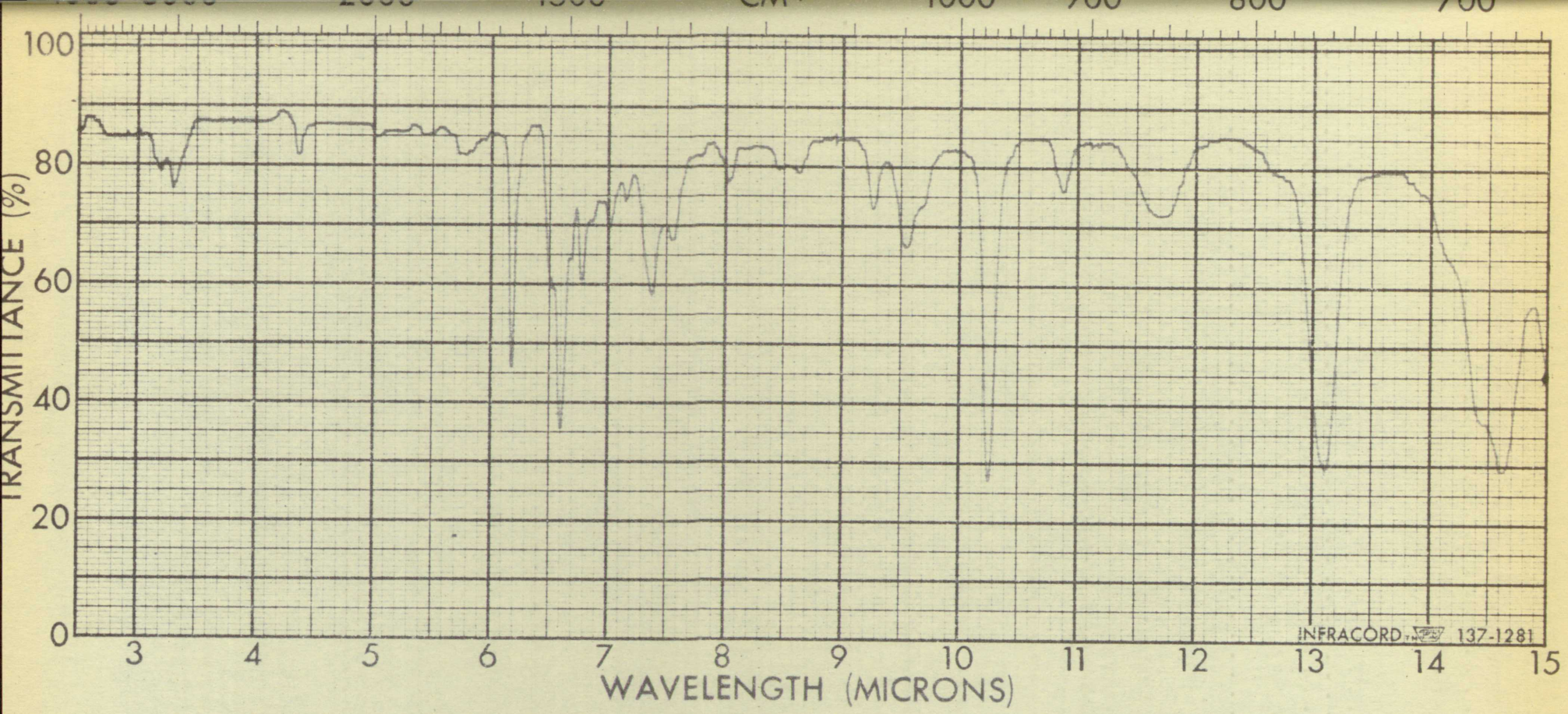

(CH2)3Br
N
N
N

Figure 15

The Infra-red Absorption Spectrum of γ-2-Phenyl-1,2,3,2H-triazol-4-yl-n-butyronitrile (XLIV).


100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD 137-1281

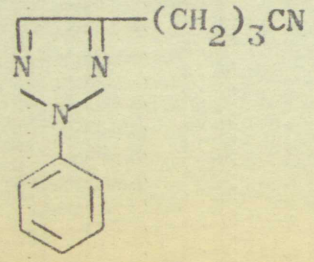
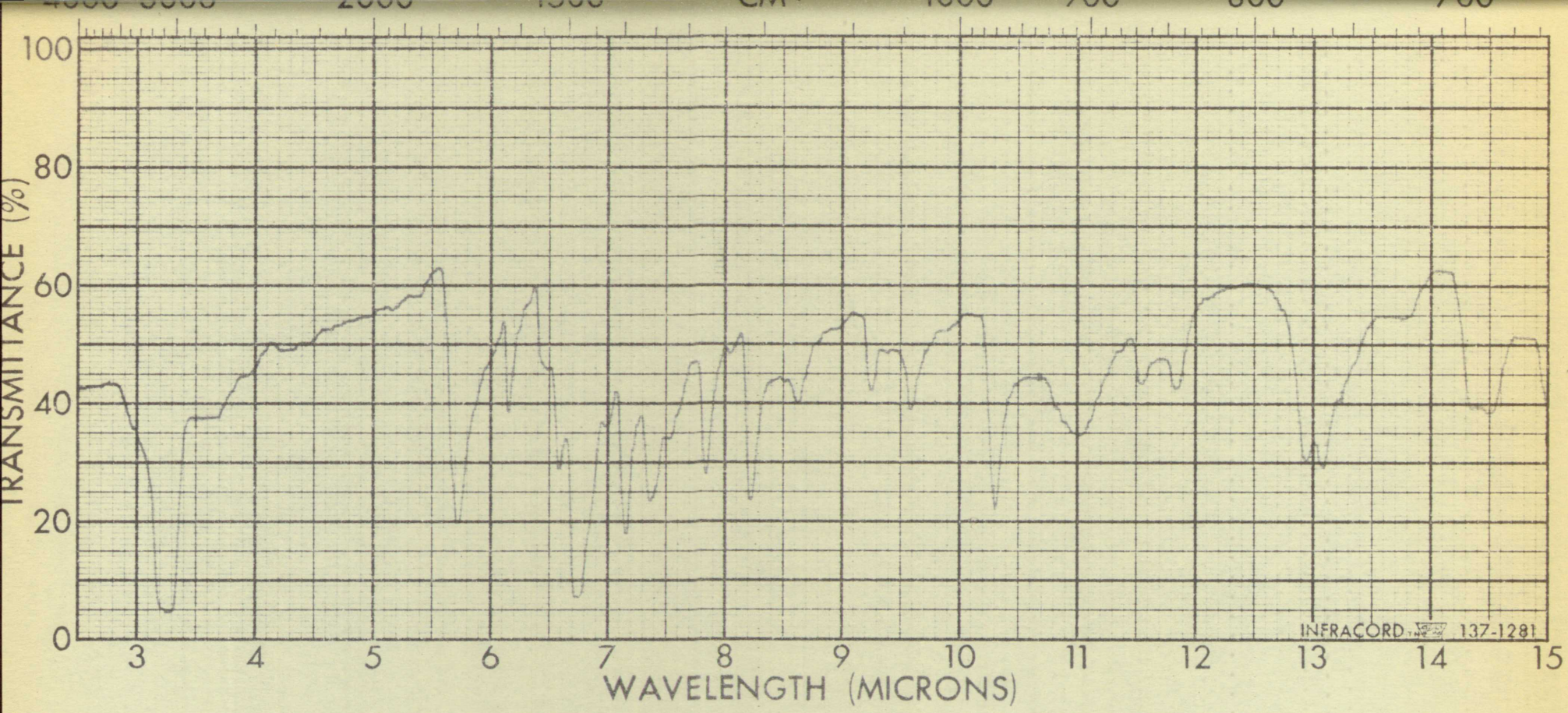

(CH2)3CN
N
N
N

Figure 16

The Infra-red Absorption Spectrum of γ-2-Phenyl-1,2,3,2H-triazol-4-ylbutyric Acid (XLV).


TRANSMITTANCE (%)
100
80
60
40
20
0
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1281

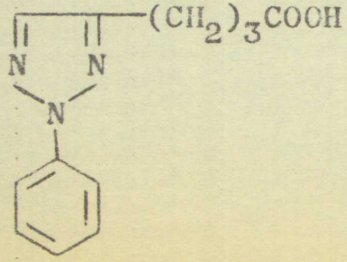
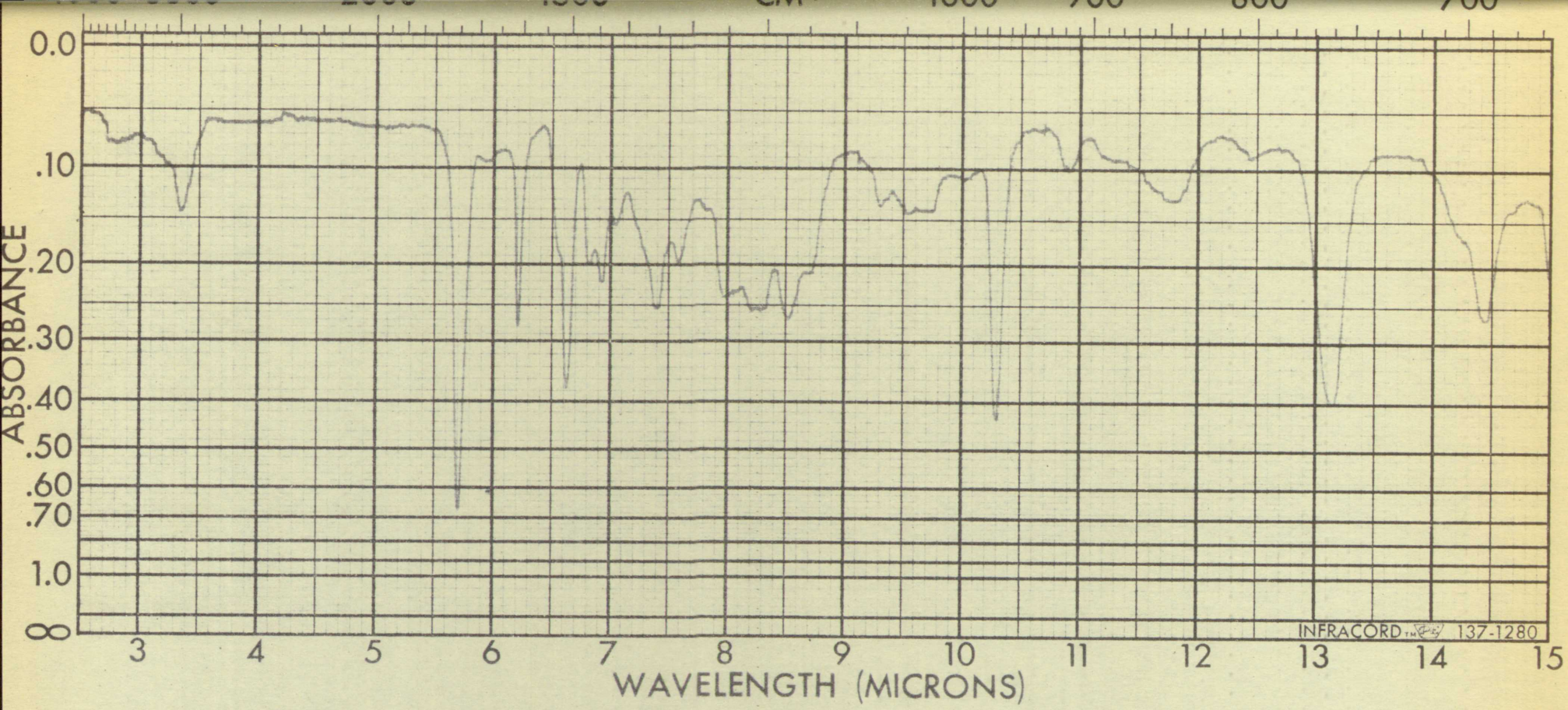

(CH2)3COOH
N
N
N

Figure 17

The Infra-red Absorption Spectrum of Methyl-γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyrate (XLVI).


0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1280

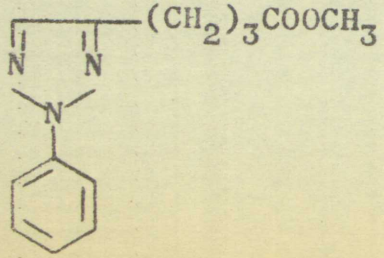
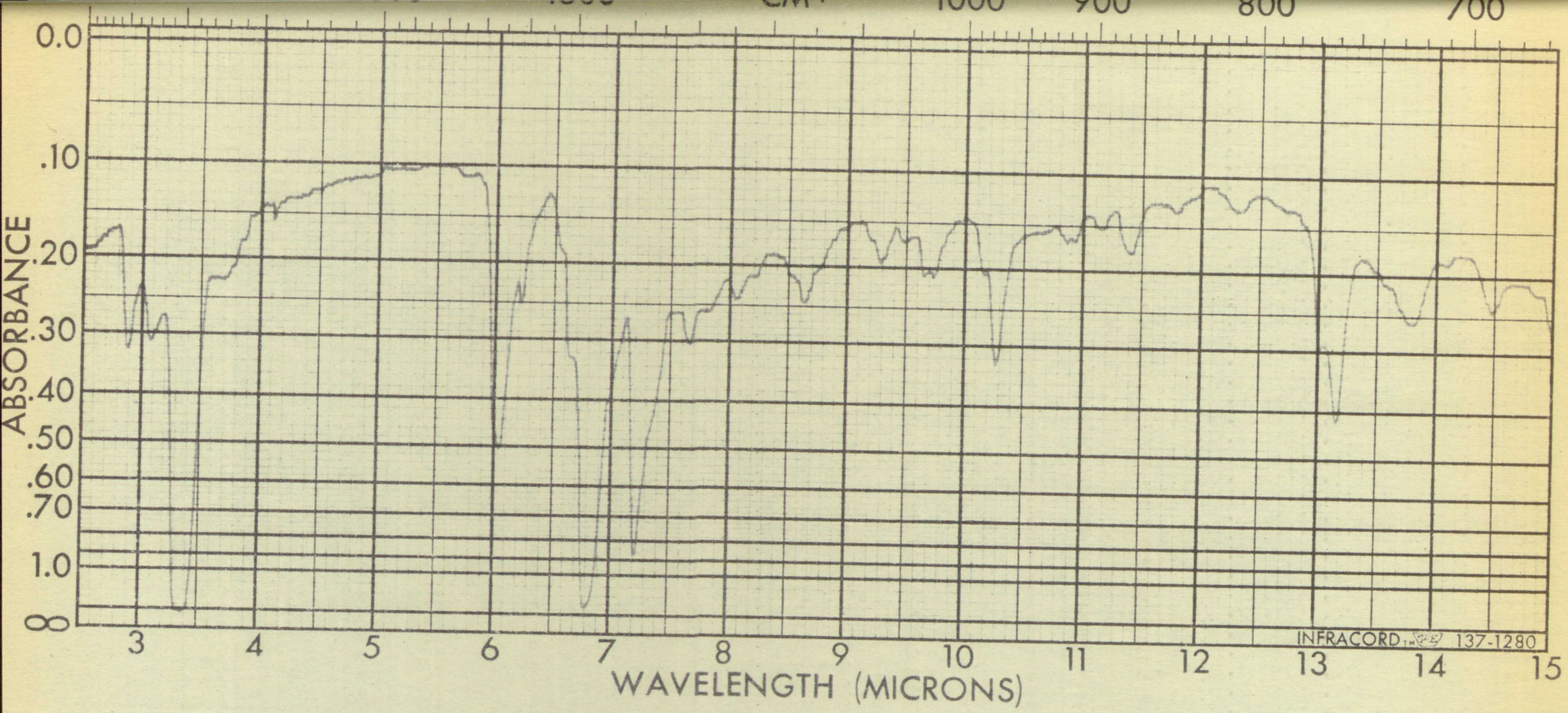
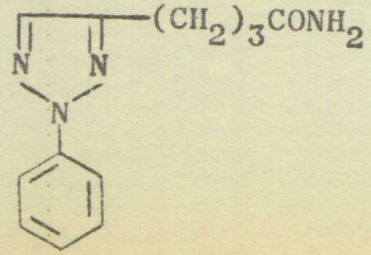

(CH2)3COOCH3
N
N
N

Figure 18

The Infra-red Absorption Spectrum of γ-2-Phenyl-1,2,3,2H-triazol-4-ylbutyramide (XLVII).


CM⁻¹
1000
900
800
700
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1280

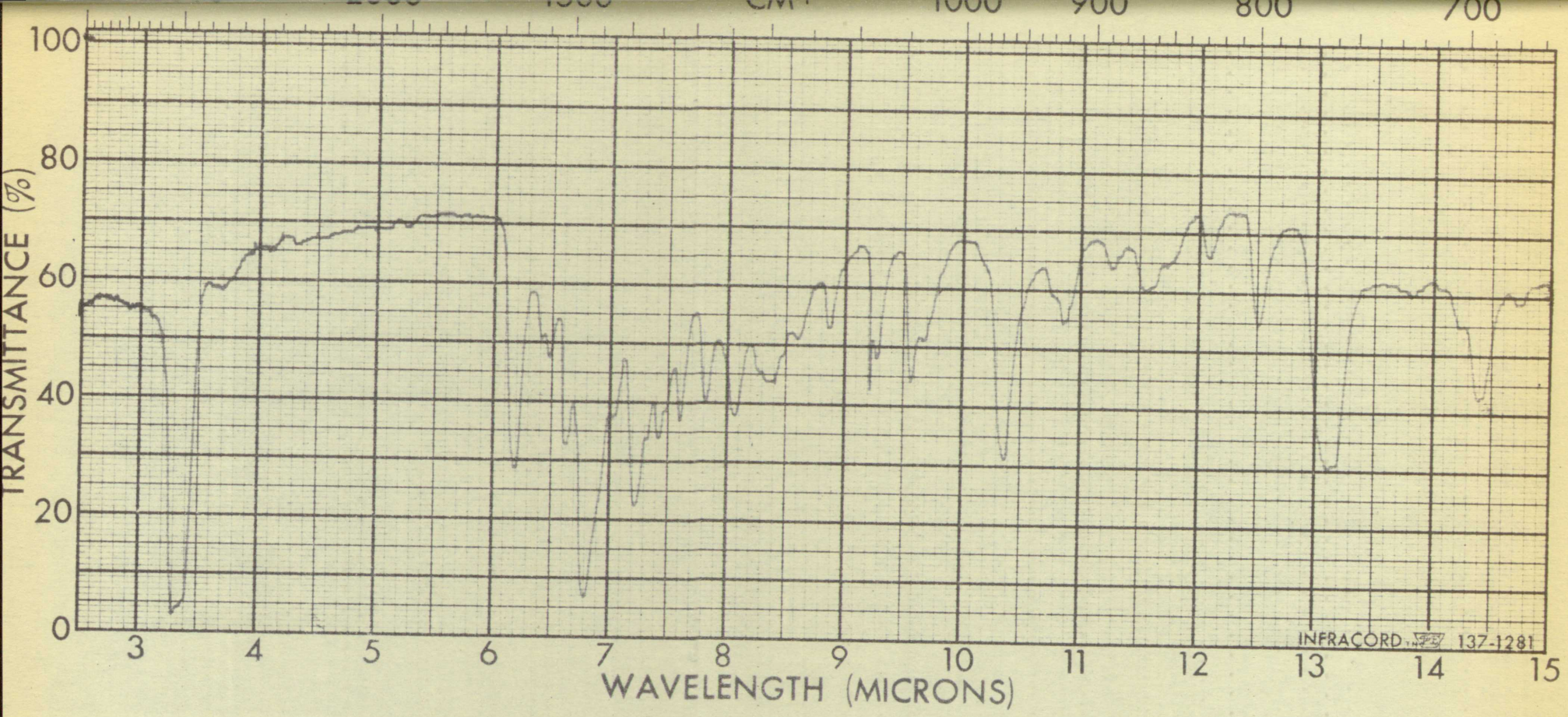

(CH2)3CONH2
N
N
N

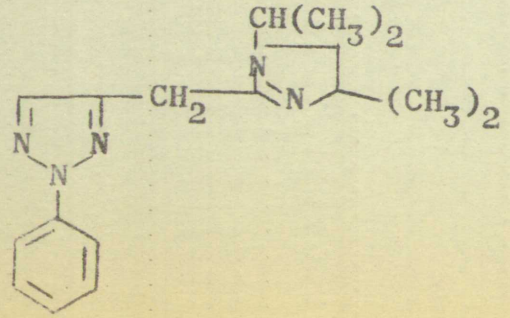
The imidazoline (XLVIII) was isolated as a crystalline solid in low yield. The remainder of the reaction products were liquid mixtures which could not be separated into pure components, perhaps due mainly to the small amounts of starting materials available. Infra-red studies of the mixtures indicated the presence of considerable quantities of the intermediate amides, showing that ring closure was not complete. These experiments should be repeated when reasonable amounts of the acids (XXXIV, XXXVII and XLV) are available.

The infra-red absorption spectrum of the imidazoline (XLVIII) (Fig. 19) shows that no amide is present as an impurity in the compound since the bands at 2.9-3.1 μ and at 5.9-6.1 μ are missing.

Figure 19

The Infra-red Absorption Spectrum of 1-Isopropyl-2-(2'-phenyl-1',2',3',2'H-triazol-4'-ylmethyl)-4,4-dimethyl-2-imidazoline (XLVIII).


CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
INFRACORD
137-1281


CH(CH3)2
CH2
N
N
(CH3)2
N
N
N

EXPERIMENTAL*

The starting materials used in this work were 2-phenyl-1,2,3,2H-triazol-4-ylcarboxylic acid (III) and 2-phenyl-1,2,3,2H-triazol-4-ylcarboxaldehyde (VIII). The latter was prepared from D-glucose phenylosazone (VI) according to the method of Hann and Hudson[7] described by Riebsomer and Sumrell[46]. The former was synthesized by the procedure of Riebsomer and Sumrell[46].

2-Phenyl-1,2,3,2H-triazol-4-ylcarbinol (XXIII). A three liter three necked flask equipped with ground glass joints, fitted with a reflux condenser, a dropping funnel and a rubber sealed stirrer was flame dried and swept with nitrogen. To the flask was added 19 g. (0.5 mole) of lithium aluminum hydride and 800 ml. of anhydrous ether. To the lithium aluminum hydride was added dropwise with stirring 40.6 g. (0.2 mole) of the methyl ester of III dissolved in 400 ml. of anhydrous ether. The addition was made at such a rate as to maintain a gentle reflux. After the addition was complete, the stirred reaction mixture was allowed to reflux for an additional thirty minutes. The mixture was cooled and water was added with

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*All melting points are uncorrected.

caution to destroy the excess lithium aluminum hydride. The contents of the flask were poured into 400 ml. of ice-water and 200 ml. of 10% sulfuric acid was then added to the mixture. The organic layer was removed and the aqueous layer was extracted with ether. The combined organic portions were washed well with water and dried over anhydrous sodium sulfate. After the evaporation of the ether on the steam bath, a white solid residue of 2-phenyl-1,2,3,2H-triazol-4-ylcarbinol (XXIV) remained, weighing 29.5 g. (84% yield). After two crystallizations from benzene, colorless needles were obtained, m.p. 70.5-72°.

Anal. Calculated for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.48; H, 5.28; N, 23.70.

This compound was reported previously[46], m.p. 64-65°. It was prepared from VIII *via* the Cannizzaro reaction and was not completely analyzed. It is probable that the original material was impure.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl Bromide (XXXI). To 250 ml. of 48% aqueous hydrobromic acid was added 28 g. (0.16 mole) of XXIII and the mixture was refluxed for one hour. The reaction mixture was cooled in an ice bath and the product crystallized. The solid was filtered with suction, washed well with water and air-dried. The light yellow 2-phenyl-1,2,3,2H-triazol-4-ylmethyl bromide (XXXI)

weighed 30.8 g. (81% yield). After three crystallizations from cyclohexane, colorless crystals were obtained, m.p. 45-46°.

Anal. Calculated for $C_9H_8N_3Br$: C, 45.40; H, 3.39; N, 17.65. Found: C, 45.60; H, 3.69; N, 17.33.

This compound was reported previously[24] as melting at 37-38°. However, it was prepared by a different method and was not analyzed completely. It may be assumed that the original material was impure.

2-Phenyl-1,2,3,2H-triazol-4-ylacetamide (XXXII). Into a 50 ml. three necked flask fitted with ground glass joints, equipped with a condenser, a dropping funnel and a rubber sealed stirrer was placed a solution of 0.7 g. (0.014 mole) of sodium cyanide in 10 ml. of water. A solution of 2.4 g. (0.010 mole) of the bromide (XXXI) in 10 ml. of ethyl alcohol was added to the stirred mixture over a period of one-half to three-quarters hour. After the addition was complete, the mixture was warmed on the steam bath for four hours. The reaction mixture was cooled and filtered to remove the sodium bromide formed. The ethyl alcohol was removed by distillation under reduced pressure. The residue was taken up in hot benzene and the water removed by azeotropic distillation. After treatment with Norit, the 2-phenyl-1,2,3,2H-triazol-4-ylacetamide (XXXII) crystallized

as pale tan plates, m.p. 149°. The yield was 0.33 g. (16.5%).

Anal. Calculated for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.72. Found: C, 59.76; H, 5.08; N, 27.68.

2-Phenyl-1,2,3,2H-triazol-4-ylacetonitrile (XXXIII). A solution of 6.5 g. (0.13 mole) of sodium cyanide in 60 ml. of water was placed in a 250 ml. three necked flask, equipped with ground glass joints and fitted with a condenser, a dropping funnel and a rubber sealed stirrer. A solution of 21.5 g. (0.09 mole) of XXXI in 70 ml. of acetone was added to the stirred contents of the flask over a period of one-half to three-quarters hour. During the addition, the mixture was gently refluxed. After completion of the addition, refluxing was continued for an additional four hours. Benzene was added to the cooled reaction mixture and the organic layer was washed thoroughly with water. The excess water was removed by azeotropic distillation. The 2-phenyl-1,2,3,2H-triazol-4-ylacetonitrile (XXXIII) crystallized from the benzene solution and weighed 7 g. (42% yield). One further crystallization from benzene gave fine colorless needles, m.p. 65-67°.

Anal. Calculated for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.51; H, 4.49; N, 30.21.

This compound was reported previously[24], m.p. 53-54°. A different procedure was used in its preparation and its analysis was incomplete. The original material was probably impure.

2-Phenyl-1,2,3,2H-triazol-4-ylacetic Acid (XXXIV). Six and nine-tenths grams (0.04 mole) of the nitrile (XXXIII) was refluxed with stirring for four hours with 25 ml. of concentrated sulfuric acid diluted to twice its volume with water. After the reaction mixture had cooled somewhat, it was poured onto cracked ice. The resultant precipitate was filtered, washed with water and air-dried. The 2-phenyl-1,2,3,2H-triazol-4-ylacetic acid (XXXIV) weighed 6.2 g. (76.5% yield). Two crystallizations from ethyl acetate afforded colorless rods, m.p. 110-111°.

Anal. Calculated for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68; neutral equivalent, 203. Found: C, 59.34; H, 4.67; N, 20.28; neutral equivalent, 205.

The acetic acid derivative (XXXV) was prepared previously[24] by the alkaline hydrolysis of XXXIV, m.p. 108-109°.

Methyl-2-phenyl-1,2,3,2H-triazol-4-ylacetate (XXXV). Absolute methyl alcohol (25 ml.) was saturated with dry hydrogen chloride in the cold and in it was dissolved 0.2 g. (0.001 mole) of the acid (XXXIV). The solution was refluxed

overnight on the steam bath, after which the solvent was removed by distillation under reduced pressure. The residue of methyl-2-phenyl-1,2,3,2H-triazol-4-ylacetate (XXXV) was taken up in ether and washed well with 5% sodium carbonate solution, followed by water. Colorless plates, m.p. 44-45°, remained after the evaporation of the dried ether solution on the steam bath. No further purification was necessary. The yield was 0.19 g. (92%).

Anal. Calculated for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 61.16; H, 5.02; N, 19.52.

1-Isopropyl-2-(2'-phenyl-1',2',3',2'H-triazol-4'-ylmethyl)-4,4-dimethyl-2-imidazoline (XLVIII). The apparatus for this preparation consisted of a 3-foot vacuum-jacketed Vigreaux type column which was equipped with a decanter still-head filled with benzene, and arranged to drain off the water layer and return the benzene to the column. A mixture of 1.5 g. (0.007 mole) of XXXIV and 1.0 g. (0.007 mole) of N-(2-aminoisobutyl)-isopropylamine dissolved in a few ml. of anhydrous benzene was heated to 210-230° for about five hours. During this time approximately 0.25 g. of water was removed. The reaction mixture was cooled and taken up in ether. The ether solution was washed thoroughly with cold 5% sodium hydroxide solution, followed by water and dried over potassium hydroxide pellets. A light brown oil remained after evaporation of the ether on the steam

bath which solidified on cooling to give 0.7 g. (32.5% yield) of 1-isopropyl-2-(2'-phenyl-1',2',3',2'H-triazol-4'-ylmethyl)-4,4-dimethyl-2-imidazoline (XLVIII). Three crystallizations from ligroin (b.p. 30-60°) and treatment with Norit afforded pale yellow crystals, m.p. 83-85°.

Anal. Calculated for $C_{17}H_{23}N_5$: C, 68.65; H, 7.80; N, 23.55; neutral equivalent, 297. Found: C, 68.62; H, 8.04; N, 23.96; neutral equivalent, 285.

β-2-Phenyl-1,2,3,2H-triazol-4-ylacrylic Acid (XXXVI). A mixture of 15 g. (0.09 mole) of the aldehyde (VIII) and 9.5 g. (0.09 mole) of malonic acid was dissolved in 150 ml. of pyridine containing a trace of piperidine. The solution was warmed on the steam bath until the evolution of carbon dioxide had ceased. The mixture was cooled and poured into water containing enough concentrated hydrochloric acid to take up the pyridine and leave a slight excess acidity. The precipitate which formed was filtered with suction, washed with water and air-dried, affording 15 g. (79% yield) of β-2-phenyl-1,2,3,2H-triazol-4-ylacrylic acid (XXXVII). The material was crystallized from benzene, giving colorless crystals, m.p. 178-179°.

Anal. Calculated for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53; neutral equivalent, 215. Found: C, 61.40; H, 4.42; N, 19.57; neutral equivalent, 215.

The acid (XXXVI) was previously reported[46], prepared *via* the Perkin reaction with VIII, m.p. 179-181°, and was not completely analyzed.

β-2-Phenyl-1,2,3,2H-triazol-4-ylpropionic Acid (XXXVII). At atmospheric pressure, 13 g. (0.06 mole) of the unsaturated acid (XXXVI), dissolved in 500 ml. of ethyl alcohol, was reduced in the presence of 0.1 g. of Adams catalyst. After thirteen hours at room temperature, when 96% of the theoretical amount of hydrogen had been taken up, the solution was filtered. Removal of the ethyl alcohol yielded *β*-2-phenyl-1,2,3,2H-triazol-4-ylpropionic acid (XXXVII) as a nearly colorless oil which solidified when cooled. Crystallization of this material from ethyl acetate afforded colorless needles, m.p. 75-75.5°.

Anal. Calculated for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35; neutral equivalent, 217. Found: C, 60.96; H, 5.22; N, 19.40; neutral equivalent, 219.

Methyl-*β*-2-phenyl-1,2,3,2H-triazol-4-ylpropionate (XXXVIII). Into 50 ml. of absolute methyl alcohol, which had been saturated in the cold with dry hydrogen chloride, was placed 2.5 g. (0.01 mole) of the acid (XXXVII) and the mixture was refluxed overnight. After removal of the solvent under reduced pressure, the residue was taken up in ether and washed several times with 5% sodium carbonate solution,

followed by water and dried over anhydrous magnesium sulfate. Removal of the ether by distillation on the steam bath left 2.1 g. (91% yield) of methyl-β-2-phenyl-1,2,3,2H-triazol-4-ylpropionate (XXXVIII) as a colorless oil which crystallized when cooled in an ice bath, m.p. 32.5-33.5°.

Anal. Calculated for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.54; H, 5.87; N, 18.52.

β-2-Phenyl-1,2,3,2H-triazol-4-ylpropionamide (XXXIX). A mixture of 0.3 g. (0.001 mole) of XXXVIII and 5 ml. of concentrated ammonium hydroxide solution was placed in a test tube and shaken vigorously for thirty minutes. The resultant solution was left standing overnight, during which time the product crystallized. The crystals were filtered with suction, washed with water and air-dried, affording 0.16 g. (73% yield) of -2-phenyl-1,2,3,2H-triazol-4-ylpropionamide (XXXIX). Crystallization of the material from benzene gave colorless crystals, m.p. 137-138°.

Anal. Calculated for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.40; H, 5.77; N, 26.14.

The Stobbe Condensation with 2-Phenyl-1,2,3,2H-triazol-4-ylcarboxaldehyde (VIII). A 50 ml. three necked flask equipped with ground glass joints, fitted with a reflux condenser, a dropping funnel and a rubber sealed stirrer was flame dried and swept with nitrogen. In the

flask was prepared a solution of 0.86 g. (0.022 g.-atom) of potassium in 20 ml. of t-butyl alcohol. A mixture of 3.46 g. (0.020 mole) of the aldehyde (VIII) and 5.22 g. (0.030 mole) of diethyl succinate was added dropwise to the boiling solution over a period of fifteen minutes. After refluxing for an additional three-quarters hour, the reaction mixture was cooled and hydrolyzed with 4 ml. of concentrated hydrochloric acid in 16 ml. of water. Ether and benzene were added and the organic layer was washed with water and extracted with dilute ammonium hydroxide solution. Acidification of the alkaline extracts yielded a light brown oil which was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether on the steam bath provided a residue of 3.9 g. (65% yield) of β-carbethoxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic acid (XL) as a light yellow solid. Three crystallizations from ethyl acetate afforded almost colorless plates, m.p. 178-179°.

Anal. Calculated for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95; neutral equivalent, 301. Found: C, 59.67; H, 5.17; N, 13.86, neutral equivalent, 297.

Attempts to Hydrolyze and Decarboxylate the Half-ester (XLI). In one experiment, 0.8 g. (0.003 mole) of XL was refluxed for four and one-half hours with a mixture of 10 ml. of glacial acetic acid, 5 ml. of concentrated

hydrochloric acid and 7.5 ml. of water. After cooling, the reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water and extracted with 10% sodium carbonate solution. Acidification of the carbonate extracts yielded a solid material which, after two crystallizations from ethyl acetate, was shown by its neutral equivalent to be β-carboxy-γ-(2-phenyl-1,2,3,2H-triazol-4-yl)-vinylacetic acid (XLI), m.p. 223° with decomposition, as pale yellow crystals.

Anal. Calculated for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38; neutral equivalent, 137. Found: C, 57.35; H, 4.42; N, 15.40; neutral equivalent, 141.

In another experiment, the half-ester (XL) was refluxed for five hours with a solution in which 48% hydrobromic acid was substituted for the concentrated hydrochloric acid in the above experiment. The reaction product proved to be identical with the diacid (XLI).

1-Hydroxy-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLII). To a mixture of 2.5 g. (0.07 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether was added dropwise as before 10 g. (0.04 mole) of the ester (XXXVIII) dissolved in 100 ml. of anhydrous ether. After refluxing the mixture for thirty minutes and cooling water was added cautiously to destroy the excess lithium aluminum

hydride. The reaction mixture was poured into water and 10% sulfuric acid was added. The aqueous layer was extracted with ether and the combined ether extracts were added to the organic layer. After washing with water and drying over anhydrous sodium sulfate, evaporation of the ether on the steam bath yielded 8.4 g. (96% yield) of 1-hydroxy-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLII) as an almost colorless oil. The oil solidified on standing and two crystallizations from benzene-ligroin resulted in colorless plates, m.p. 45.5-47°.

Anal. Calculated for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.15; H, 6.69; N, 20.67.

1-Bromo-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLIII). A solution of 7.5 g. (0.03 mole) of the alcohol (XLII) in 75 ml. of 48% hydrobromic acid was refluxed for two hours. The cooled reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with water, 20% sulfuric acid, 5% sodium carbonate solution and again with water, in that order. The organic layer was dried over Drierite, after which the ether was evaporated on the steam bath. The oily residue of 1-bromo-3-(2'-phenyl-1',2',3',2'H-triazol-4'-yl)-propane (XLIII) weighed 9.4 g. (95% yield), b.p. 195-200° at 0.25 mm. No satisfactory analysis of this material was obtained and it was used in the next step in the impure state.

γ-2-Phenyl-1,2,3,2H-triazol-4-yl-n-butyronitrile (XLIV). A solution of 4.9 g. (0.1 mole) of sodium cyanide in 50 ml. of water was introduced into a 250 ml. three necked flask equipped with ground glass joints and fitted with a condenser, a dropping funnel and a rubber sealed stirrer. To the solution was added dropwise with stirring 9 g. (0.03 mole) of XLIII dissolved in 50 ml. of acetone. The mixture was refluxed for four hours and cooled. Benzene was added and the organic layer was washed with water. The benzene solution was dried by azeotropic distillation and the benzene was removed on the steam bath, leaving 7.1 g. (98% yield) of γ-2-phenyl-1,2,3,2H-triazol-4-yl-n-butyronitrile (XLIV) as a pale yellow oil, b.p. about 205° at 0.5 mm. An acceptable analysis of this compound was not obtained and the crude material was used in the next step.

γ-2-Phenyl-1,2,3,2H-triazol-4-ylbutyric Acid (XLV). A mixture of 6.7 g. (0.03 mole) of the nitrile (XLIV) and 15 ml. of concentrated sulfuric acid diluted to twice its volume with water was refluxed for one hour. The reaction mixture was cooled and poured onto cracked ice. The resultant precipitate was filtered with suction, washed with water and air-dried. The light tan γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyric acid (XLV) weighed 6.3 g. (85% yield). Crystallization from benzene-ligroin gave pale tan prisms, m.p. 72-73.5°.

Anal. Calculated for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17; neutral equivalent, 231. Found: C, 62.43; H, 5.84; N, 18.31; neutral equivalent, 234.

Methyl-γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyrate (XLVI). Six tenths gram (0.002 mole) of the acid (XLV) was dissolved in 25 ml. of absolute methyl alcohol which had been saturated with dry hydrogen chloride in the cold and the solution was refluxed overnight. After removal of the solvent under reduced pressure, the residue was dissolved in ether and washed thoroughly with 5% sodium carbonate solution, followed by water. The ether solution was dried over anhydrous sodium sulfate and the ether was evaporated on the steam bath, leaving an analytical sample of methyl-γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyrate (XLVI) as an almost colorless oil. The sample weighed 0.4 g. (80% yield), too small an amount for the determination of the boiling point.

Anal. Calculated for $C_{13}H_{15}N_3O_2$: C, 63.65; H, 6.16; N, 17.13. Found: C, 63.98; H, 6.52; N, 17.32.

γ-2-Phenyl-1,2,3,2H-triazol-4-ylbutyramide (XLVII). Into a test tube was placed 0.1 g. (0.0004 mole) of XLVI and 5 ml. of concentrated ammonium hydroxide. The contents of the test tube were shaken periodically for several days, after which time crystals formed. The crystals were filtered

with suction, washed with water and air-dried, yielding 0.075 g. (83% yield) of γ-2-phenyl-1,2,3,2H-triazol-4-yl-butyramide (XLVII). Crystallization from benzene afforded fine colorless needles, m.p. 105-106°.

Anal. Calculated for $C_{12}H_{14}N_4O$: C, 62.59, H, 6.13; N, 24.33. Found: C, 62.21; H, 5.89; N, 23.79.

SUMMARY

The side chain of 2-phenyl-1,2,3,2H-triazol-4-yl-carboxaldehyde (VIII) and of 2-phenyl-1,2,3,2H-triazol-4-ylcarboxylic acid (III) was extended by one, two and three carbons to effect the synthesis of 2-phenyl-1,2,3,2H-triazol-4-ylacetic acid (XXXIV), β-2-phenyl-1,2,3,2H-triazol-4-ylpropionic acid (XXXVII) and γ-2-phenyl-1,2,3,2H-triazol-4-ylbutyric acid (XLV) respectively.

Attempts to synthesize XXXIV by the Arndt-Eistert reaction failed. The material was successfully obtained in 22% over-all yield from III *via* reduction of the methyl ester of III to the alcohol (XXIII), conversion of XXIII to the bromide (XXXI) with hydrobromic acid, reaction of XXXI with sodium cyanide in acetone to give the nitrile (XXXIII), followed by acid hydrolysis of XXXIII to the acid (XXXIV).

The aldehyde (VIII) was allowed to react with malonic acid under conditions of the Knoevenagel reaction to give the unsaturated acid (XXXVI) which was reduced in the presence of Adams catalyst to the propionic acid (XXXVII) in 76% over-all yield from VIII.

The synthesis of XLV using the Stobbe condensation with VIII was unsuccessful. Attempts to decarboxylate the

initial condensation product (XL) failed. Only the diacid (XLI) was isolated.

The acid (XLV) was prepared from XXXVII by the identical procedure used to prepare XXXIV. Thus the methyl ester (XXXVIII) of XXXVII was reduced with lithium aluminum hydride and the resulting alcohol (XLII) was converted with hydrobromic acid to XLIII. The bromide (XLIII) was converted with sodium cyanide in acetone to the nitrile (XLIV) which was hydrolized with sulfuric acid to the butyric acid (XLV) in 76% yield from XXXVIII.

The amides of the three acids were prepared for identification purposes.

Attempts to form the imidazoline derivatives by reaction of the acids with diamines failed, except in the case of the reaction of the acid (XXXIV) with N-(2-aminoisobutyl)-isopropylamine which gave 1-isopropyl-2-(2'-phenyl-1',2',3',2'H-triazol-4'-ylmethyl)-4,4-dimethyl-2-imidazoline (XLVIII) in low yield.

The infra-red absorption spectra of the three acids and all the intermediates were determined, as well as the infra-red absorption spectrum of the imidazoline derivative.

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