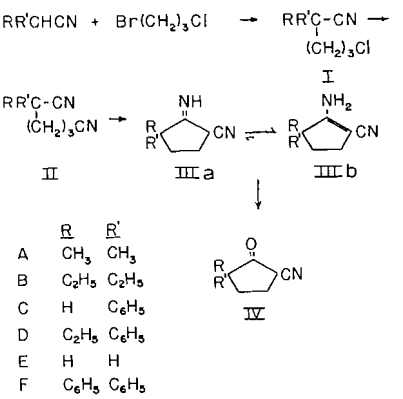
SYNTHESIS OF 2,2-DISUBSTITUTED-5-CYANOCYCLOPENTANONES[1]

STUART S. KULP,[2] VELMER B. FISH, AND NELSON R. EASTON[3]
Wm. H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania
Received April 21, 1965

ABSTRACT

The synthesis of a series of 2,2-disubstituted-5-cyanocyclopentanones by hydrolysis of the precursor 3,3-disubstituted-2-amino-1-cyanocyclopentenes (2,2-disubstituted-5-cyanocyclopentanoneimines) is described. The new compounds possess the following substituents: dimethyl, diethyl, phenyl hydrogen, and ethyl phenyl.

The difficulty in hydrolyzing 2,2-diphenyl-5-cyanocyclopentanoneimine to 2,2-diphenyl-5-cyanocyclopentanone (1) led us to the preparation of other compounds of this series and a study of the hydrolyses of these materials. The synthetic approach is outlined in Scheme 1. The new compounds reported here involve the preparation of IV A–D.



SCHEME 1.

The intermediate chloro compounds (I) were obtained by alkylation of the appropriately substituted acetonitrile with 1-bromo-3-chloropropane at −70°. When the dihalide was added at 0°, both halogens were replaced and dicondensation to a substituted pimelonitrile occurred. This is in contrast to the alkylation of diphenylacetonitrile which gave IF in quantitative yield at 0° (1). The dicondensation product from dimethylacetonitrile was 2,2,6,6-tetramethylpimelonitrile which was characterized and hydrolyzed to its corresponding diamide and diacid.

The dinitriles (II) were prepared by treating the chloro nitriles (I) with potassium cyanide. The dinitriles were characterized by hydrolyzing IIA to the amide acid, IIB to its amide acid and diacid, and IIC to its diamide.

Cyclization of the dinitriles (II) was best accomplished with sodium hydride in dioxane. The alicyclics obtained (III A–D) are best represented as enamines (III*b*) rather than iminonitriles (III*a*) as previously found for IIIE (2). These compounds are listed in Table I.

[1]*From the Ph.D. dissertation of S. S. K., Lehigh University, 1957.*
[2]*To whom inquiries should be addressed. Present address: Moravian College, Bethlehem, Pennsylvania.*
[3]*Present address: Eli Lilly and Company, Indianapolis, Indiana.*

TABLE I

Substituted 2-amino-1-cyanocyclopentenes (III*b*)

Compd.	Yield (%)	Melting point (°C)	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
IIIA	90	110–111*	$C_8H_{12}N_2$	70.54	70.75	8.88	8.76	20.60	20.80
IIIB	70	104–106†	$C_{10}H_{16}N_2$	73.10	73.30	9.83	9.92	17.07	17.12
IIIC	98	109–110.5‡	$C_{12}H_{12}N_2$	78.22	78.40	6.57	6.50	15.23	15.15
IIID	85	120–121.5*	$C_{14}H_{16}N_2$	79.20	79.30	7.60	7.81	13.20	12.97

*Recrystallized from methanol.
†Recrystallized from ether.
‡Recrystallized from ethyl acetate.

TABLE II

Substituted 2-cyanocyclopentanones (IV)

Compd.	Boiling point (mm)	Yield (%)	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
IVA	114–117 (2)	70	$C_8H_{11}NO$*	70.04	69.75	8.08	7.97	10.21	10.00
IVB	160–163 (20)	66	$C_{10}H_{15}NO$	72.69	72.42	9.15	9.15	8.47	8.41
IVC	174–175 (2)	90	$C_{12}H_{11}NO$†	77.81	77.90	5.99	6.02	7.56	7.70
IVD	144–145 (0.15)	82	$C_{14}H_{15}NO$	78.84	78.61	7.09	7.28	6.56	6.58

*The 2,4-dinitrophenylhydrazone melted at 149°. Anal. Calcd. for $C_{14}H_{18}N_5O_4$: C, 52.99; H, 4.77; N, 22.07. Found: C, 53.08; H, 4.90; N, 21.95.
†The 2,4-dinitrophenylhydrazone melted at 204°. Anal. Calcd. for $C_{18}H_{18}N_5O_4$: C, 59.17; H, 4.14; N, 19.17. Found: C, 59.35; H, 4.20; N,19.25.

Hydrolyses of the enamines (III) proceeded readily to the α-cyanocyclopentanones (IV A–D) which is in marked contrast to the findings with the diphenyl analog (IVF) (1). The keto nitriles IV A–D are listed in Table II. Only the dimethyl (IVA) and the monophenyl (IVC) ketones formed 2,4-dinitrophenylhydrazones under the usual conditions.

Additional evidence for the anomalous behaviour of the *gem*-diphenyl enamine (IIIF), previously ascribed to steric hindrance, was sought. The infrared and ultraviolet spectra of compounds III A–F are listed in Table III and show no significant deviation from those reported for the parent compound (IIIE) (2). Likewise, the infrared spectra of IV A–F

TABLE III

Infrared and ultraviolet spectra of substituted 2-amino-1-cyanocyclopentenes (III*b*)

Compd.	Infrared (μ) NH	NH	CN	NH	C=C	Ultraviolet (mμ) Max.	a_M
IIIA	2.88	2.98	4.58	6.10	6.26	263	12 500
IIIB	2.85	2.93	4.57	6.09	6.25	263	13 700
IIIC	2.87	2.94	4.57	6.09	6.25	263	14 080
IIID	2.86	2.94	4.57	6.08	6.24	264	13 050
IIIE	2.85*	2.93*	4.56*	6.07*	6.22*	265	13 200*
IIIF†	2.87	2.94	4.56	6.07	6.25	269	13 650

*See ref. 2 for reported values of 2.85, 2.92, 4.57, 6.08, 6.23 μ and 263 mμ (13 000).
†Preparation reported in ref. 1.

are similar and are listed in Table IV. The β-keto nitriles (IV) have absorption maxima around 235 mμ in acid or neutral ethanolic solutions except IVD and IVF. The latter compounds exhibit no absorption maxima in the ultraviolet other than carbonyl absorption at ca. 297 mμ in acid or neutral medium. Most of the keto nitriles have absorption at

TABLE IV

Infrared and ultraviolet spectra of substituted α-cyanocyclopentanones (IV)

	Infrared (μ)			Ultraviolet (mμ)			
				Acid and neutral		Basic	
Compd.	OH	CN	C=O	Max.	a_M	Max.	a_M
IVA	2.86	4.45	5.79	235	1 630	264	10 500
IVB	2.87	4.45	5.70	235	2 640	264	11 100
IVC	2.85	4.45	5.66	238	5 940	264	13 000
IVD	2.87	4.45	5.70	297*	144	270	11 400
IVE	2.89	4.47†	5.75†	235	2 400	262	16 840
IVF‡	2.87	4.44	5.68	296*	246	278	13 750

*No absorption peak in the 235 mμ region.
†See ref. 2 for values of 4.44 and 5.70 μ.
‡Preparation reported in ref. 4.

about 264 mμ in basic ethanolic solution; however, IVD and IVF have peaks at 270 and 278 mμ under these conditions. Thus, the bathochromic shift of about 29 mμ in changing from neutral to basic solution is comparable to shifts of 36 and 31 mμ as noted for other β-keto nitriles (3).

The enolization of the β-keto nitriles will be reported later.

EXPERIMENTAL

All melting points were determined in an oil bath and are uncorrected. Ultraviolet spectra were determined with a Warren Spectracord in 95% alcohol. Infrared spectra were determined on a Perkin–Elmer model 21 instrument in $CHCl_3$ solution.

5-Chloro-2,2-dimethylpentanenitrile (IA)

An ether solution of 1 mole of the lithium salt of dimethylacetonitrile was prepared from lithium diethylamide as described previously (5). After cooling to −70°, 1 mole of 1-bromo-3-chloropropane was added dropwise over 1 h at a rate to maintain the reaction temperature below −60°. The mixture warmed to room temperature overnight as the acetone – dry ice bath evaporated. After refluxing for 1 h, cooling, and decomposition in the usual manner, the solvent was removed. The remaining liquid was heated to 70° at 20 mm and the crude residue, 136 g (93%), was satisfactory for further synthesis. The following analogs were prepared: IB-diethyl, 70%, b.p. 123° at 10 mm; IC-phenyl, 81%; ID-ethyl-phenyl, 68%, 145–147° at 2 mm.

Addition of the 1-bromo-3-chloropropane to the reaction mixture at 0° gave a quantitative amount of dicondensation product, 2,2,6,6-tetramethylpimelonitrile, m.p. 118–119° from methanol.

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18. Found: C, 74.20; H, 10.02.

2,2,6,6-Tetramethylpimelamide

Hydrolysis of the pimelonitrile with 80% sulfuric acid on a steam bath for 3 h gave a white solid, m.p. 193–194°.

Anal. Calcd. for $C_{11}H_{22}O_2N_2$: N, 13.05. Found: N, 12.97.

2,2,6,6-Tetramethylpimelic Acid

The above pimelamide gave the diacid by the butyl nitrite procedure (6). The m.p. was 168–169.5° from methanol.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.15; H, 9.32. Found: C, 61.25; H, 9.10.

Attempts to prepare this diacid by basic hydrolysis of either the precursor dinitrile or diamide were unsatisfactory

2,2-Dimethyladiponitrile (IIA)

A mixture of 55 g (1.41 mole) of sodium cyanide in 125 ml of dimethylformamide and 1 ml of water was stirred under reflux. To this was added 125 g (0.86 mole) of crude 5-chloro-2,2-dimethylpentanenitrile over 0.4 h. After refluxing for 2 h the mixture was cooled slightly and 25 ml of water was added. The mixture was refluxed 0.5 h, cooled, poured into a large volume of water, and allowed to stand overnight. The layers were separated, the aqueous layer was extracted with ether, and the combined organic layers were washed with ice-cold 50% sulfuric acid. The ether layer was dried over magnesium sulfate and filtered, and the solvent was distilled and gave a clear distillate, b.p. 145–151° at 14 mm with only a slight forerun and about 8 g of

residue. The product weighed 93 g (80%). The following analogs were prepared: IIB-diethyl, b.p. 144–146° at 5 mm, 76%; IIC-phenyl, b.p. 170° at 0.5 mm, 60%; IID-ethyl-phenyl, b.p. 180–200° at 3 mm, 52%, after standing several days this oil solidified, m.p. 45.5–47°.

5-Carbamoyl-5,5-dimethylpentanoic Acid

Hydrolysis of IIA with 80% sulfuric acid on a steam bath for 3 h gave a white solid, m.p. 159–161°. Recrystallization from ethyl acetate with a little methanol gave m.p. 160.5–161°.

Anal. Calcd. for $C_8H_{15}O_3N$: N, 8.10. Found: N, 8.19.

5-Carbamoyl-5,5-diethylpentanoic Acid

A mixture of 300 g of IIB and 1 500 ml of 80% sulfuric acid was heated at 110° for 16 h. Sufficient water was cautiously added to decrease the sulfuric acid concentration to about 50%. This mixture was heated at 110° for 24 h, poured on crushed ice, and allowed to stand for 3 days. The solid was collected and dissolved in sodium hydroxide; acidification gave a dark brown solid. Recrystallization from methanol with charcoal did not improve the quality of the product. The solid was distilled, b.p. 190–200° at 0.1 mm. This distillate after two recrystallizations from methanol melted at 152–153.5°.

Anal. Calcd. for $C_{10}H_{19}O_3N$: N, 6.97. Found: N, 6.97.

2,2-Diethyladipic Acid

Obtained from the above amide-acid by the butyl nitrite procedure (6). The crude product, m.p. 99–102°, after three recrystallizations from methanol–water had constant m.p. 102.5–103.5° (reported (7) 90–92°).

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.96. Found: C, 59.40; 59.50; H, 8.83, 8.95.

The infrared spectrum ($CHCl_3$ solution) was in agreement with this structure.

2-Phenyladipamide

A small sample of IIC was treated with 30% hydrogen peroxide and sodium hydroxide (8) and melted at 171–171.5°.

Anal. Calcd. for $C_{12}H_{16}O_2N_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.50; H, 7.63; N, 12.72.

3,3-Dimethyl-2-amino-1-cyanocyclopentene (IIIA)

A suspension of 12 g (0.55 mole) of active sodium hydride (added as 50% dispersion in oil) and 250 ml of dry dioxane was vigorously stirred under reflux in a large 3-neck flask equipped as usual. To this was added 66 g (0.48 mole) of 2,2-dimethyladiponitrile very carefully over 1.5 h. The mixture was refluxed an additional 3 h and then cooled in ice. Water was added cautiously, acetic acid was added to acidify, and the mixture was allowed to stand in ice overnight. The crude brown solid, 60 g (90%), had m.p. 106–108°. Recrystallization raised the melting point to the value reported in Table I. Compounds III B–D were similarly prepared.

5-Cyano-2,2-diethylcyclopentanone (IVB)

A mixture of 30 g (0.18 mole) of IIIB, 15 ml of concentrated HCl (0.18 mole), 85 ml of 8 *N* sulfuric acid, and 100 ml of toluene was heated under reflux for 1 h. The toluene layer was separated, washed with water, and extracted with 10% sodium hydroxide. The aqueous basic solution was cooled and acidified, and the acid solution was extracted with ether. The ether solution was dried (magnesium sulfate), filtered, concentrated, and distilled to give the product reported in Table II. Compounds IVA, IVC, and IVD were similarly prepared.

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