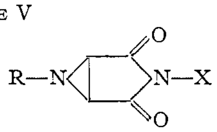
TABLE V

AZIRIDINE DERIVATIVES



Aziridine[b] derivs.		Pyrolysis temp., °C.	M.p.,[a] °C.	Yield, %	Crystn. solvent	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
X	R						Calcd.	Found	Calcd.	Found	Calcd.	Found
C_6H_5	C_6H_5	140	120	91	A	$C_{16}H_{12}N_2O_2$	72.73	72.54	4.55	4.36	10.60	10.53
C_6H_5	C_6H_4Cl-*p*	140	98	77	B	$C_{16}H_{11}N_2O_2Cl$	64.32	64.12	3.68	3.61	9.37	9.25[c]
C_6H_5	$C_6H_4NO_2$-*p*	180	240	58	C	$C_{16}H_{11}N_3O_4$	62.13	62.04	3.56	3.32	13.59	13.45
$C_6H_4CH_3$-*p*	C_6H_5	145	140	86	B	$C_{17}H_{14}N_2O_2$	73.38	73.34	5.03	4.78	10.07	9.95
$C_6H_4CH_3$-*p*	C_6H_4Cl-*p*	150	250	81	D	$C_{17}H_{13}N_2O_2Cl$	65.28	65.15	4.16	4.07	8.96	8.72[d]
$C_6H_4CH_3$-*p*	$C_6H_4NO_2$-*p*	160	146	84	B	$C_{17}H_{13}N_3O_4$	63.15	63.01	4.02	3.93	13.00	12.78
$C_6H_4OCH_3$-*p*	C_6H_5	160	178	71	A	$C_{17}H_{14}N_2O_3$	69.38	69.16	4.76	4.61	9.52	9.34
$C_6H_4OCH_3$-*p*	C_6H_4Cl-*p*	150	120	65	B	$C_{17}H_{13}N_2O_3Cl$	62.07	61.96	3.98	3.77	8.52	8.45[e]
$C_6H_4OCH_3$-*p*	$C_6H_4NO_2$-*p*	160	118	58	A	$C_{17}H_{13}N_3O_5$	60.17	60.01	3.83	3.64	12.38	12.14
$C_6H_4OC_2H_5$-*p*	C_6H_5	130	106	61	B	$C_{18}H_{16}N_2O_3$	70.13	69.85	5.19	5.06	9.08	8.84
$C_6H_4OC_2H_5$-*p*	C_6H_4Cl-*p*	140	130	64	B	$C_{18}H_{15}N_2O_3Cl$	63.06	62.85	4.38	4.31	8.17	8.03[f]
$C_6H_4OC_2H_5$-*p*	$C_6H_4NO_2$-*p*	160	180	65	A	$C_{18}H_{15}N_3O_5$	61.20	61.07	4.25	4.21	11.89	11.80
$C_6H_3(CH_3)_2$-2,4	C_6H_5	160	130	92	B	$C_{18}H_{16}N_2O_2$	73.97	73.78	5.48	5.32	9.58	9.46

[a] Melting points are uncorrected. [b] They give yellow solution with cold sulfuric acid, and are regenerated on dilution. A, benzene–petroleum ether (b.p. 80–100°) mixture; B, petroleum ether (b.p. 80–100°); C, xylene; D, ethyl alcohol. [c] Cl: Calcd.: 11.89. Found: 11.77. [d] Cl: Calcd.: 11.36. Found: 11.27. [e] Cl: Calcd.: 10.80. Found: 10.54. [f] Cl: Calcd.: 10.36. Found: 10.21.

the case of the pyrazolines. The oily product was washed several times with light petroleum and the solid, so obtained, was recrystallized.

The aziridine derivatives VI listed in Table V form yellow crystals, are easily soluble in benzene and ethyl alcohol, but sparingly soluble in petroleum ether and cold ethyl alcohol. They dissolve in hot aqueous sodium hydroxide solution (10%) and sublime readily when heated above their melting points.

Action of Sodium Azide on VIIb.—To a suspension of 0.7 g. of VIIb in 20 ml. of ethyl alcohol was added a concentrated aqueous solution of 1 g. of sodium azide The reaction mixture was heated (steam-bath) for five minutes, during which time VIIb gradually went into solution, followed by the separation of a yellow crystalline deposit on cooling. These were filtered off, washed with cold water and crystallized from dilute ethyl alcohol as yellow crystals, m.p. 100° (vigorous decomp.).

Anal. Calcd. for $C_{10}H_5N_7O_2$: C, 47.05; H, 1.96; N, 38.43. Found: C, 46.94; H, 1.76; N, 38.23.

2,3-Diazido-(N-phenyl)-maleimide (XI) is easily soluble in hot ethyl alcohol, but sparingly soluble in ether. It gives a red solution with cold sulfuric acid accompanied with vigorous decomposition.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Bicyclic Carboxylic Acid Derivatives from *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran

BY ARTHUR C. COPE AND BURTON C. ANDERSON

RECEIVED JULY 11, 1955

Bicyclic carboxylic esters (III, VIII and IX) were the only products isolated from the reaction of *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) with diethyl malonate and ethyl cyanoacetate. The esters were saponified to carboxylic acids V, X and XI. Decarboxylation of the dialkyl malonic acid V formed two isomeric carboxylic acids VI and VII, while the dialkylcyanoacetic acids X and XI on heating alone or in quinoline yielded the isomeric nitriles XIII and XIV. The decarboxylation reaction in quinoline is interpreted as proceeding through a common intermediate such as XV since both X and XI formed the two nitriles in essentially the same proportions.

cis-2,5-Bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) has been shown to form derivatives of 8-oxa-3-azabicyclo[3.2.1]octane in reactions in which it dialkylates the nitrogen atom of ammonia,[1,2] primary amines[3] and secondary amines.[4] In an attempt to determine whether or not the ditosylate I would form bicyclic derivatives of active methylene compounds, its reactions with diethyl malonate and ethyl cyanoacetate have been studied. In a somewhat analogous case the cyclic dicarboxylic ester, diethyl dibenzo[a,c][1,3]cycloheptadiene-6,6-dicarboxylate, was the only product isolated when 2,2′-bis-(bromomethyl)-biphenyl was allowed to react with diethyl malonate.[5]

Experimental conditions similar to those known to favor dialkylation of diethyl malonate by trimethylene bromide[6] were used in the first experiments of this series. The reaction of the ditosylate I with diethyl malonate and two molar equivalents of sodium ethoxide in ethanol heated under reflux

---

[1] F. H. Newth and L. F. Wiggins, *J. Chem. Soc.*, 155 (1948).

[2] D. J. C. Wood and L. F. Wiggins, *Nature*, **164**, 402 (1949).

[3] A. C. Cope and W. N. Baxter, THIS JOURNAL, **77**, 393 (1955).

[4] A. C. Cope and B. C. Anderson, *ibid.*, **77**, 995 (1955).

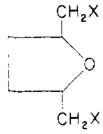
[5] J. Kenner, *J. Chem. Soc.*, **103**, 615 (1913).

[6] J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949); J. Cason and H. Rappoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, p. 299ff.

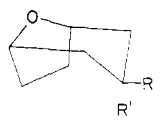
was not complete after twenty-one hours. All fractions of the product isolated after this period were treated with aqueous ammonium hydroxide to remove diethyl malonate and monoalkylmalonic esters as amides. Fractional distillation afforded 25% of *cis*-2,5-bis-(ethoxymethyl)-tetrahydrofuran (II) and 29% of diethyl 3,6-epoxycycloheptane-1,1-dicarboxylate (III). The diether II, formed by reaction of the ditosylate I with sodium ethoxide, was identical with an authentic sample prepared by the method of Newth and Wiggins.[1] The dicarboxylic ester III was identified by saponification as described below.

Since the formation of II represents a serious side-reaction in ethanol, tetrahydrofuran was investigated as a solvent. The sodium enolate of diethyl malonate was prepared as a fine suspension in dry tetrahydrofuran from the ester and sodium hydride. The ditosylate I was added and the mixture was heated under reflux. Reaction did not occur under these conditions; consequently, the mixture was heated in a stainless steel autoclave for 16 hours at 110°. From this reaction mixture 66% of the dicarboxylic ester III was isolated. In this and other cases products less volatile than III which might have included tetraethyl 3,6-epoxyoctane-1,1,8,8-tetracarboxylate (IV) amounted to less than 6% of the theoretical amount calculated as IV and could not be purified or converted to pure acids by saponification.

Saponification of the dicarboxylic ester III afforded 3,6-epoxycycloheptane-1,1-dicarboxylic acid (V) as well as each of the isomeric 3,6-epoxycycloheptanecarboxylic acids (VI and VII) (shown in the formulas with the six-membered heterocyclic ring in the chair form). The available evidence does not permit assignment of specific stereochemical configurations to the acids VI and VII, m.p. 102.2–103.2° and 133.5–135.0°. The structure of III was further confirmed by conversion to a crystalline barbituric acid.



I, X = $OSO_2C_6H_4CH_3$-*p*
II, X = OC_2H_5
IV, X = $CH(CO_2C_2H_5)_2$



III, R = R' = $CO_2C_2H_5$
V, R = R' = CO_2H
VI and VII, R and R' = CO_2H and H
VIII and IX, R and R' = $CO_2C_2H_5$ and $C{\equiv}N$
X and XI, R and R' = CO_2H and $C{\equiv}N$
XIII and XIV, R and R' = H and $C{\equiv}N$

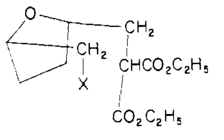
The alkylation reaction was extended to the case of ethyl cyanoacetate. It was expected that the major product of this reaction would be a mixture of the geometrically isomeric ethyl 1-cyano-3,6-epoxycycloheptanecarboxylates (VIII and IX), if the pattern of the diethyl malonate case were followed.

The reaction was performed using the conditions which gave the best yield of III from diethyl malonate and afforded 68% of a mixture of the isomeric esters VIII and IX. The distillate partially crystallized on standing, and crystalline material amounting to nearly one-half of the product was separated. This compound, purified by recrystallization, was one of the isomeric esters VIII or IX. The liquid product was refractionated and elementary analysis indicated that it was the second geometric isomer, although it contained some of the crystalline ester as an impurity, as shown below. It was not possible to isolate the product derived from the ditosylate I and two equivalents of ethyl cyanoacetate, diethyl 1,8-dicyano-3,6-epoxyoctane-1,8-dicarboxylate, from the small high-boiling residue.

The esters VIII and IX were saponified in an attempt to determine their purity. The crystalline isomer yielded 75% of 1-cyano-3,6-epoxycycloheptanecarboxylic acid (X or XI) with a narrow melting range, and after recrystallization the acid had m.p. 177.2–178.6° dec. Similar treatment of the refractionated liquid ester afforded 79% of a mixture of acids, m.p. 180–215° dec. Fractional crystallization yielded 45% of a second isomeric acid X or XI, which after recrystallization melted at 214.5–216.6° dec.

Similar evidence concerning the purity of the esters VIII and IX was obtained by conversion of the isomeric esters to crystalline hydrazides. Treatment of the ester, m.p. 63.5–65.0°, with 95% hydrazine afforded a hydrazide with a narrow melting range in high yield. Similar treatment of the liquid formed a mixture of hydrazides with a wide melting range which could be purified only by repeated recrystallization. From these facts and the results of the saponifications it is apparent that the solid ester is isomerically pure while the liquid is a mixture.

The formation of bicyclic esters (III, VIII and IX) in high yields parallels the formation of bicyclic amines from the ditosylate I and ammonia or amines. It is noteworthy that III and VIII and IX are the major products even though the sodium enolate of the active methylene compound is present in excess. The intramolecular alkylations forming these esters result in closure of six-membered rings, and are particularly favored in these cases by the steric proximity of the tosylate groups to the negative centers of the intermediate enolates (XII in the alkylation leading to III). The intermediate XII obviously is similar to the intermediate alkylation product in the reaction of the ditosylate I with amines,[4] which also leads to bicyclic derivatives.



XII, X = $OSO_2C_6H_4CH_3$-*p*

The decarboxylation of the pure acids X and XI was studied as a means of obtaining the isomeric 3,6-epoxycycloheptanecarbonitriles XIII and XIV. It was found that decarboxylation of either of the pure isomeric acids X or XI by heating above their melting points or by heating in quinoline led to mixtures of the nitriles XIII and XIV. Chromatography on alumina served to separate the isomeric nitriles, m.p. 87.0–88.0° and m.p. 102.8–103.6°. The nitrile with m.p. 87.0–88.0° showed strong absorption in the infrared at 11.43 μ, absorption which was absent from the spectrum of the higher melting isomer. Similarly the nitrile with m.p. 102.8–103.6° showed intense absorption at 11.22 μ, absorption which was absent from the spectrum of the lower melting isomer. These absorption peaks were used to estimate quantitatively[7] the composition of the mixtures formed on decarboxylation. Table I records yields of the two nitriles obtained from each of the acids by each of the decarboxylation methods as estimated by isolation and by quantitative infrared analysis.

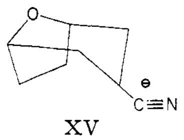
TABLE I

DECARBOXYLATION OF CYANOACETIC ACIDS X AND XI

Acid X or XI m.p. (dec.), °C.	Decarboxylation method	Isolated by chromatography % of nitrile M.p., 103–104°	Isolated by chromatography % of nitrile M.p., 87–88°	Indicated by infrared % of nitrile (normalized) M.p., 103–104°	Indicated by infrared % of nitrile (normalized) M.p., 87–88°	Unnormalized total yield, %
177.2–178.6	Heat in quinoline	69	10	90	10	101
177.2–178.6	Heat above m.p.	8.8	60	30	70	110
214.5–216.6	Heat in quinoline	53	9.2	86	14	104
214.5–216.6	Heat above m.p.	23	31	56	44	107

Both nitriles were shown to be stable on heating in quinoline at the temperature used for decarboxylation of the acids or on heating alone at the temperature used for the thermal decarboxylation. Also, both nitriles could be recovered after heating with an equal weight of adipic acid with or without added quinoline under the conditions described above without significant change. The four control experiments in which the nitriles were heated with adipic acid were performed to simulate the conditions of the actual decarboxylations of X and XI, since the unreacted carboxylic acids X and XI might conceivably catalyze interconversion of XIII and XIV. Infrared spectra of both nitriles recovered after such treatment showed that no isomerization of either nitrile had occurred.

From these results it is clear that the decarboxylation reaction does not occur with retention of the configuration of the carbon atom to which the nitrile group is attached. It can be seen that the compositions of the nitrile mixtures obtained by decarboxylating both acids in quinoline are essentially identical. A possible explanation of this result involves the intervention of a common intermediate such as XV derived from both acids. It is not surprising that different amounts of the nitriles XIII and XIV should be formed from such an intermediate, since the rates of addition of a proton to the front and back sides of XV to form the stereoisomers need not be the same, if addition from one side is favored sterically.



XV

Experimental[8]

Reaction of *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate with Diethyl Malonate.—A solution of 16.7 g. of diethyl malonate in 400 ml. of freshly-distilled, dry tetrahydrofuran was placed in a dry 1.5-l. stainless steel autoclave and 2.4 g. of sodium hydride was added in portions. When the evolution of hydrogen had ceased (about 1 hour), 20.0 g. of *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate was added and the autoclave was sealed and heated at 110 ± 5° for 17.5 hours. The autoclave was cooled and opened and the contents were washed into a flask with dry ether. The solvents were distilled and the residue was poured into iced, dilute hydrochloric acid solution. Filtration of this mixture yielded 4.0 g. (20%) of the unreacted ditosylate I (recrystallized from ethanol). The filtrate was extracted with three 150-ml. portions of ether, the combined extracts were dried with magnesium sulfate, and the ether was distilled. Fractionation of the residue afforded 6.61 g. (57%) of diethyl 3,6-epoxycycloheptane-1,1-dicarboxylate (III), b.p. 105–110° (0.50 mm.).

When the alkylation reaction was performed using ethanol as a solvent and conditions similar to those previously described for the preparation of diethyl cyclobutane-1,1-dicarboxylate,[6] 20.0 g. of the ditosylate I yielded, after 23 hours heating under reflux and treatment of the high-boiling products with ammonium hydroxide, 2.03 g. (25%) of *cis*-2,5-bis-(ethoxymethyl)-tetrahydrofuran, b.p. 50–52° (0.45 mm.), $n^{25}\mathrm{D}$ 1.4297, and 3.34 g. (29%) of diethyl 3,6-epoxycycloheptane-1,1-dicarboxylate, b.p. 104–104.5° (0.45 mm.), $n^{25}\mathrm{D}$ 1.4618–1.4619.

A sample of the dicarboxylic ester III purified by distillation through a 30 × 0.8-cm. semi-micro column with a spinning band had $n^{25}\mathrm{D}$ 1.4679, d^{25}_{4} 1.146.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.71; H, 7.99.

A sample of the ether II was purified by shaking with sodium hydroxide and distillation through the spinning-band column, b.p. 99° (13 mm.), $n^{25}\mathrm{D}$ 1.4308. It was identical according to a comparison of the infrared spectrum with an authentic sample of *cis*-2,5-bis-(ethoxymethyl)-tetrahydrofuran, b.p. 98.5° (13 mm.), $n^{25}\mathrm{D}$ 1.4313, prepared by the method of Newth and Wiggins.[1]

Saponification of Diethyl 3,6-Epoxycycloheptane-1,1-dicarboxylate.—A mixture of 2.0 g. of sodium hydroxide, 50 ml. of water and 6.0 g. of diethyl 3,6-epoxycycloheptane-1,1-dicarboxylate was heated under reflux for 16 hours. The homogeneous reaction mixture was cooled to 0°, acidified to the congo red end-point with iced, 6 *N* hydrochloric acid and extracted continuously for 24 hours with methylene chloride. The methylene chloride extract was distilled to a volume of about 20 ml., and 10 ml. of ligroin was added. The solid precipitate was collected on a filter, and ligroin (10 ml.) was added to the filtrate. Cooling of this solution afforded a second batch of crystals. The total yield was 1.90 g.

The less soluble portion (1.20 g.) was boiled with carbon tetrachloride and filtered while hot. The filtrate on cooling yielded one of the isomeric 3,6-epoxycycloheptanecarboxylic acids (VI or VII) which had m.p. 133.5–135° after four recrystallizations from carbon tetrachloride.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; neut. equiv., 156. Found: C, 61.36; H, 7.60; neut. equiv., 156.

The residue, insoluble in carbon tetrachloride, was 3,6-epoxycycloheptane-1,1-dicarboxylic acid (V), which after three recrystallizations from ethyl acetate had m.p. 161.4–162.6° dec.

---

[7] G. R. Harrison, R. C. Lord and J. R. Loofbourow, "Practical Spectroscopy," Prentice-Hall, Inc., New York, N. Y., 1948, pp. 497 ff.

[8] Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Infrared spectra were determined with a Baird double beam recording spectrometer, model B, with a sodium chloride prism.

Anal. Calcd. for $C_9H_{12}O_5$: C, 53.99; H, 6.04; neut. equiv., 100. Found: C, 54.08; H, 6.17; neut. equiv., 101.

The crystals more soluble in ligroin were recrystallized three times from this solvent; this procedure yielded a second isomeric 3,6-epoxycycloheptanecarboxylic acid (VI or VII), m.p. 102.2–103.2°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; neut. equiv., 156. Found: C, 61.64; H, 7.87; neut. equiv., 155.

Ethyl 1-Cyano-3,6-epoxycycloheptanecarboxylate (VIII and IX).—In a clean, dry 1.5-l. stainless steel autoclave were placed 600 ml. of dry tetrahydrofuran and 51.5 g. of ethyl cyanoacetate. The autoclave was closed immediately with a rubber stopper fitted with a drying tube and 11.0 g. of sodium hydride was added in portions. After 1 hour, 100 g. of *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate was added in one portion and the autoclave was sealed and heated at 110 ± 5° for 19.5 hours. The bomb was cooled and opened, the reaction mixture was filtered to remove sodium tosylate, and most of the solvent was removed by distillation. The residue was diluted with about 500 ml. of ether; 3.75 g. of the ditosylate I was removed by filtration. The ether solution was washed with cold dilute hydrochloric acid and water and dried with magnesium sulfate. Fractionation of the high-boiling residue through a semi-micro column afforded 32.5 g. (68%) of a mixture of the esters VIII and IX, b.p. 92.5–95° (0.2 mm.), which partially crystallized on standing.

An additional 2.0 g. of the ditosylate I was recovered by crystallization of the distillation residue, making the yield of the mixture of esters VIII and IX 72.5%, taking account of the 5.75 g. of I which was recovered.

Attempted short path distillation of the high-boiling residue from the mother liquors afforded less than 0.5 g. of a liquid which was not examined further.

The portion of the product that crystallized was separated by filtration. A sample that was recrystallized from ligroin three times had m.p. 63.5–65°.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.00; H, 7.24; N, 6.94.

The liquid residue was redistilled carefully through the semi-micro column with a spinning band. A fraction, which did not crystallize on seeding, had b.p. 89° (0.75 mm.), $n^{25}D$ 1.4700.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.28; H, 7.37; N, 6.62.

A quantitative separation of 44.3 g. of crude product prepared as described above was performed as follows: the product was cooled to 0° and the crystals that separated were collected on a filter quickly with suction. The filtrate amounted to 18.2 g. The crystals, after recrystallization from ligroin, weighed 18.4 g. and the remainder of the material was in the ligroin mother liquors.

Saponification of Ethyl 1-Cyano-3,6-epoxycycloheptanecarboxylate (VIII or IX, m.p. 63.5–65.0°).—A mixture of 8.40 g. of recrystallized ethyl 1-cyano-3,6-epoxycycloheptanecarboxylate, m.p. 63.5–65.0°, and 160 ml. of 0.254 *N* sodium hydroxide solution was heated under reflux for 18 hours. The cooled solution was extracted with ether and concentrated to a volume of 30 ml. under reduced pressure. The solution was frozen and made strongly acidic with cold concentrated hydrochloric acid. The product which precipitated was collected on a filter and dried to constant weight under reduced pressure in a drying pistol containing phosphorus pentoxide. The yield was 5.47 g. (75%) of 1-cyano-3,6-epoxycycloheptanecarboxylic acid (X or XI). A sample recrystallized four times from a mixture of ethyl acetate and cyclohexane had m.p. 177.2–178.6° dec.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.74; H, 6.24; N, 7.78.

Saponification of Ethyl 1-Cyano-3,6-epoxycycloheptanecarboxylate (Liquid Containing Some of the Crystalline Isomer).—Saponification of 18.2 g. of ethyl 1-cyano-3,6-epoxycycloheptanecarboxylate, prepared by refractionation of the filtrate from the separation of the isomers, as described above, yielded 12.5 g. (79.3%) of a mixture of acids, m.p. 180–215° dec. Purification of the main component was effected by dissolving 11.3 g. of this mixture in 400 ml. of ethyl acetate, filtering, adding 200 ml. of cyclohexane and boiling until crystallization had just begun. This solution was cooled to 0° and 6.3 g. (45%) of 1-cyano-3,6-epoxycycloheptanecarboxylic acid (X or XI) with m.p. 212–215° dec. was separated by filtration. A sample purified by four recrystallizations from ethyl acetate had m.p. 214.5–216.6° dec.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.86; H, 6.29; N, 7.72.

Hydrazide from the Crystalline Isomer of Ethyl 1-Cyano-3,6-epoxycycloheptanecarboxylate.—A mixture of 2.65 g. of ethyl 1-cyano-3,6-epoxycycloheptanecarboxylate, m.p. 63.5–65.0°, and 0.5 ml. of 95% hydrazine was heated in an oil-bath at 130° until the mixture was viscous (approximately 0.5 hour). The product, which crystallized on cooling, was washed with cold ether and dried over phosphorus pentoxide at 1 mm. and room temperature. The yield was 1.70 g. (69%) of 1-cyano-3,6-epoxycycloheptanecarboxhydrazide. A sample recrystallized three times from ethyl acetate had m.p. 283–285° dec.

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.37; H, 6.82; N, 21.59.

Hydrazide from the Liquid Isomer of Ethyl 1-Cyano-3,6-epoxycycloheptanecarboxylate.—Treatment of 1.35 g. of redistilled ethyl 1-cyano-3,6-epoxycycloheptanecarboxylate as described above yielded 0.62 g. (50%) of 1-cyano-3,6-epoxycycloheptanecarboxhydrazide with a wide melting range. After five recrystallizations from ethyl acetate–methanol a pure isomer was isolated with m.p. 249.7–251.5°.

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.21; H, 7.00; N, 21.52.

3,6-Epoxyspiro-(barbituric Acid-5,1′-cycloheptane).—Into a 100-ml. flask was distilled 50 ml. of absolute ethanol and 0.55 g. of sodium metal was added. To the solution of sodium ethoxide 0.78 g. of urea and 2.10 g. of diethyl 3,6-epoxycycloheptane-1,1-dicarboxylate was added, and the solution was heated under reflux for 16 hours, at which time a white precipitate had formed. The ethanol was removed under reduced pressure, and the solid was collected on a filter and added slowly to iced 20% hydrochloric acid. The precipitate amounted to 1.22 g. (66.5%) of 3,6-epoxyspiro-(barbituric acid-5,1′-cycloheptane), m.p. 284.5–286.5°. After three recrystallizations from ethanol–water the compound melted at 285.7–286.8°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.71; H, 5.35; N, 12.34.

Decarboxylation of 1-Cyano-3,6-epoxycycloheptanecarboxylic Acid, m.p. 177.2–178.6° dec. in Quinoline.—A solution of 4.00 g. of 1-cyano-3,6-epoxycycloheptanecarboxylic acid, m.p. 174–177° dec., in 50 ml. of quinoline was heated at 160° until the evolution of gas had ceased (approximately 15 minutes) and then at 200° for 10 minutes. The reaction mixture was cooled, poured into excess dilute, iced sulfuric acid, and the product was extracted with ether. The ether solution was dried and evaporated, and the product obtained was chromatographed on 100 g. of alumina (Brockmann grade I).

Fractions 2–37 were eluted with petroleum ether and amounted to 2.035 g.; fractions 38–43 were eluted with 1% ether–99% petroleum ether (0.049 g.); fractions 44–50 were eluted with 10% ether–90% petroleum ether (0.110 g.); fractions 51–57 were eluted with ether (0.309 g.); and fractions 58–61 were eluted with 30% methanol–70% ether (0.005 g.).

Fractions 2–43 amounted to 2.08 g. (69%) of 3,6-epoxycycloheptanecarbonitrile (XIII or XIV) which after three crystallizations from ligroin had m.p. 102.8–103.6°.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.18; H, 8.32; N, 10.35.

Fractions 44–50 could not be crystallized and were discarded. Fractions 51–57 yielded 0.31 g. (10%) of the second isomeric 3,6-epoxycycloheptanecarbonitrile (XIII or XIV), which after four crystallizations from hexane and sublimation under reduced pressure had m.p. 87.0–88.0°.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.21; N, 10.46.

Fractions 58–61 were discarded.

The infrared spectra of these two compounds differed markedly in the region 11–12 μ but were similar in many respects.

Thermal Decarboxylation of 1-Cyano-3,6-epoxycycloheptanecarboxylic Acid, m.p. 177.2–178.6° dec.—Three grams of 1-cyano-3,6-epoxycycloheptanecarboxylic acid, m.p. 174–177° dec., was heated in an oil-bath at 220° for 20 minutes at which time the evolution of gas had ceased. The product was taken up in ether, washed with sodium bicarbonate solution and dried with magnesium sulfate. The ether was distilled and the liquid residue was chromatographed on 100 g. of activity I alumina as described above. There was obtained 0.199 g. (8.8%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 102.8–103.6°, and 1.37 g. (60%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 87–88°.

Decarboxylation of 1-Cyano-3,6-epoxycycloheptanecarboxylic Acid, m.p. 214.5–216.6° dec., in Quinoline.—Treatment of 2.50 g. of 1-cyano-3,6-epoxycycloheptanecarboxylic acid, m.p. 214–217° dec., as described above for the isomeric acid X or XI with m.p. 177.2–178.6° dec. afforded 0.963 g. (53%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 102.8–103.6°, and 0.168 g. (9.2%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 87–88°.

Thermal Decarboxylation of 1-Cyano-3,6-epoxycycloheptanecarboxylic Acid, m.p. 214.5–216.6° dec.—1-Cyano-3,6-epoxycycloheptanecarboxylic acid, m.p. 214–217° dec., 2.00 g., was heated at 240° until the evolution of gas had ceased (approximately 20 minutes). The product was isolated in the manner described above and afforded 0.353 g. (23%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 102.6–103.8°, and 0.467 g. (31%) of 3,6-epoxycycloheptanecarbonitrile, m.p. 87–88°.

Quantitative Infrared Analysis of the Nitrile Mixtures.—Mixtures of the nitriles XIII and XIV obtained by heating the acids X or XI either alone or in quinoline were purified as described above, but subjected to infrared analysis rather than chromatography on alumina. The spectra were determined at concentrations of 100 mg./ml. in carbon tetrachloride solution. The same sample and blank cells were used for each determination and the 0 and 100% transmission lines were determined for each of the pure nitriles. The compositions of the mixtures were estimated from these curves in the usual manner, using the percentage transmission at 11.22 μ of the nitrile with m.p. 102.8–103.6° and the percentage transmission at 11.43 μ of the nitrile with m.p. 87.0–88.0° in the calculations. The normalized results and the unnormalized total yields are recorded in Table I.

Thermal Stability of 3,6-Epoxycycloheptanecarbonitrile (XIII and XIV).—A sample of the pure isomeric nitrile with m.p. 87–88° was heated in an oil-bath at 235 ± 5° for 30 minutes. The sample was cooled and its infrared spectrum determined at a concentration of 100 mg./ml. in carbon tetrachloride. The spectrum was identical with that of the starting material. A sample of the nitrile with m.p. 102.8–103.6° also showed no change when treated as described above. Heating both of the nitriles in this manner with an equal weight of adipic acid resulted in no change in the spectrum of the nitrile with m.p. 87.0–88.0°, and while the spectrum of the product recovered from the nitrile with m.p. 102.8–103.6° was changed, it did not show absorption peaks characteristic of the lower-melting isomer.

Stability of 3,6-Epoxycycloheptanecarbonitriles (XIII and XIV) in Quinoline at 200°.—A sample, 0.109 g., of 3,6-epoxycycloheptanecarbonitrile, m.p. 102.5–103.5°, was dissolved in 1.0 ml. of quinoline and heated in an oil-bath at 200° for 1 hour. The solution was cooled and poured into excess, iced, dilute sulfuric acid and the acidic solution was extracted with four 25-ml. portions of ether. The ether extracts were dried with potassium carbonate and the ether was distilled. The infrared spectrum of the product obtained, 0.105 g., was identical with the spectrum of the original nitrile.

Similar treatment of 0.100 g. of 3,6-epoxycycloheptanecarbonitrile, m.p. 87–88°, afforded 0.100 g. of recovered material which was identical, according to the infrared spectrum, with the starting material. Similar treatment of both nitriles mixed with an equal weight of adipic acid resulted in no change in the spectrum of either isomer.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

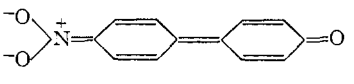
Conjugation in the Naphthalene System. I. Acidity of Nitronaphthols

BY KURT C. SCHREIBER AND SR. MARY CLAIRE KENNEDY, S.S.J.

RECEIVED JULY 28, 1955

The dissociation constants of 4-, 5- and 6-nitro-1-naphthol, 3-phenanthrol and 9-nitro-3-phenanthrol have been measured in 48% aqueous ethanol. The data are interpreted as indicating a lack of significant contribution by resonance structures involving conjugation between the two rings making up the naphthalene system to the electronic structures of the ground states of the conjugate base of these compounds.

In a recent paper[1] it was shown that a nitro group in the 4′-position of a biphenyl system enhances the acidity of 4-hydroxybiphenyl only inductively and that, therefore, resonance structure I contributes little toward the stabilization of the anion.



I

These results have focused attention upon the naphthalene system where a similar situation is present when the two functional groups are attached in the 1,5-positions, respectively.

Methods and Results

Materials.—**4-Nitro-1-naphthol** was prepared according to the method of Hodgson and Kilner,[2] but in the separation of the 2-isomer the method of Fourneau[3] proved more useful.

5-Nitro-1-naphthol.—5-Nitro-1-naphthylamine was diazotized by the inverse addition method of Hodgson and Walker[4] and converted to the naphthol by the procedure of Kaufler and Bauer.[5]

6-Nitro-1-naphthol.—This compound was prepared according to the procedure of Hodgson and Turner[6] except for the reductive decomposition of the 6-nitro-2-diazo-1-naphthol, which was carried out with alkaline sodium hydrosulfite in ethanol.

3-Phenanthrol and 9-nitro-3-phenanthrol were prepared by the methods of Fieser[7] and Burger,[8] respectively.

Dissociation Constants.—The data required for the calculation of the apparent pK_a using the Henderson–Hasselbalch equation were obtained (a) potentiometrically and (b) spectrophotometrically. Potentiometric titrations of the compounds in 48% ethanol with 48% aq. ethanolic sodium hydroxide solutions (0.03 to 0.06 *N*) were made with the aid of a Beckman Model G *p*H meter using glass and calomel electrodes. The pK_a's were determined from the half neutralization point on the titration curve. No sodium ion corrections for the glass electrode at high *p*H's were made, since it was found that using Nomograph 22N of Beckman Bulle-

---

(1) V. P. Kreiter, Wm. A. Bonner and R. H. Eastman, THIS JOURNAL, **76**, 5770 (1954).

(2) H. H. Hodgson and E. Kilner, *J. Chem. Soc.*, **125**, 807 (1924).

(3) E. Fourneau and Balaceano, *Bull. soc. chim. France*, **37**, 1602 (1925).

(4) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

(5) F. Kaufler and E. Bauer, *Ber.*, **40**, 3269 (1907).

(6) H. H. Hodgson and H. S. Turner, *J. Chem. Soc.*, 8 (1944).

(7) L. Fieser, THIS JOURNAL, **51**, 2460 (1929).

(8) A. Burger and E. Mosettig, *ibid.*, **56**, 1745 (1934).