[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reductive Cyclization. A General Method for the Synthesis of 1-Azabicyclo Compounds[1,2]

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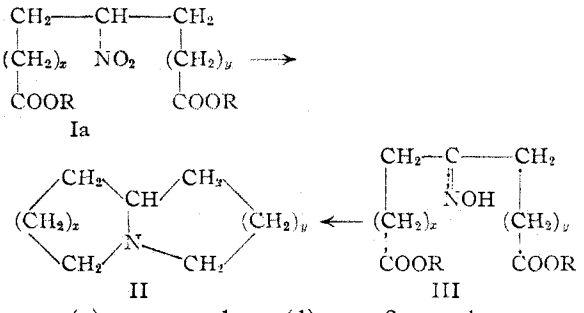
The reductive cyclization of nitro diesters over copper chromite catalyst at high temperature and high hydrogen pressure has been employed for the synthesis of certain 1-azabicyclo compounds.[4] Since only γ-nitropimelic esters (Ia) have thus far been readily obtainable, the method in general has been limited to the synthesis of pyrrolizidine (IIa) and substituted pyrrolizidines.



Ia

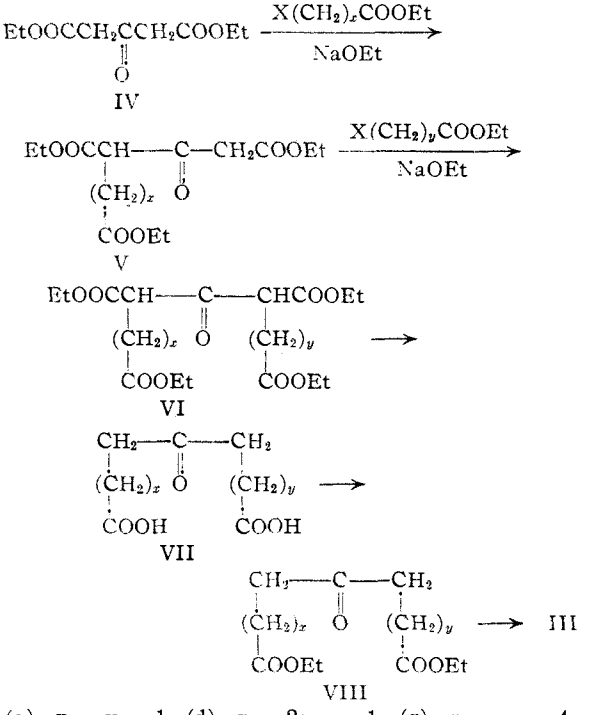
II

III

(a) x = y = 1 (d) x = 2; y = 1
(b) x = y = 2 (e) x = 1; y = 3
(c) x = y = 3 (f) x = 2; y = 3

The reductive cyclization of oximino diesters (III) has now been found to occur in the same manner, with the oximino nitrogen as the incipient bridge-head of the final 1-azabicyclo compounds (II). Because of the greater flexibility in the preparation of the precursor oximino diesters (III), this approach permits the convenient synthesis of bicyclic systems, not only of the pyrrolizidine type, but of those containing other than five-membered rings. By this method pyrrolizidine (IIa), octahydropyrrocoline (IId), quinolizidine (IIb), 1-azabicyclo[5.3.0]decane (IIe), 1-azabicyclo[5.4.0]hendecane (IIf) and 1-azabicyclo[5.5.0]dodecane (IIc) have been synthesized in yields in the range 50–60%. The relative ease of preparation of the precursors and the good yields obtained in the synthesis of the bicyclic amines IIc and IIe, containing seven-membered rings, indicate that our reductive cyclization method is superior to procedures previously reported for the synthesis of these two compounds.[5,6]

The facile formation of the 1-azabicyclo compounds containing seven-membered rings prompted an investigation of the possible synthesis of bicyclic amines containing larger rings by this reductive cyclization process. However, attempts to prepare 1-azabicyclo[6.6.0]tetradecane, 1-azabicyclo[7.7.0]-hexadecane and 1-azabicyclo-[12.12.0]hexacosane by the reduction of the appropriate oximino diesters resulted only in the formation of uncyclized material. In the case of the catalytic hydrogenation of diethyl 13-oximinopentacosanedioate, for example, the major product was 13-aminopentacosane-1,25-diol, formed by a normal reduction unaccompanied by cyclization.



IV

V

VI

VII

VIII

(a) x = y = 1 (d) x = 2; y = 1 (g) x = y = 4
(b) x = y = 2 (e) x = 1; y = 3 (h) x = y = 5
(c) x = y = 3 (f) x = 2; y = 3 (i) x = y = 10

The keto diacids (VII) required in this investigation were prepared by the dialkylation of diethyl acetonedicarboxylate (IV) with ω-halogen esters, followed by hydrolysis and decarboxylation of the resulting tetracarboxylic esters (VI). This procedure was first utilized by von Pechmann and Sidgwick[7] for the synthesis of δ-ketoazelaic acid (VIIb), and was later applied to the synthesis of γ-ketopimelic acid (VIIa),[8] 6-keto-

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(2) This investigation was supported in part by a grant from the Research Board of the University of Illinois.

(3) Eli Lilly and Company Fellow, 1949–1950.

(4) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947); Leonard and Beck, *ibid.*, **70**, 2504 (1948); Leonard and Felley, *ibid.*, **71**, 1758 (1949); Leonard and Shoemaker, *ibid.*, **71**, 1760 (1949); Leonard and Shoemaker, *ibid.*, **71**, 1762 (1949); Leonard and Felley, *ibid.*, **72**, 2537 (1950).

(5) Prelog and Shönbaum, *Ann.*, **545**, 231 (1940).

(6) Prelog and Seiwerth, *Ber.*, **72**, 1638 (1939).

(7) von Pechmann and Sidgwick, *ibid.*, **37**, 3817 (1904).

(8) Robinson and Zaki, *J. Chem. Soc.*, 2411 (1927).

TABLE I

KETO DIESTERS[a]

Diethyl keto diesters	Yield, %	B. p., °C.	Mm.	M. p., °C.	d^{20}_4	$n^{20}D$	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	MR_D Calcd.	Found
γ-Ketosuberate (VIIId)	79	117–118	0.20	...	1.0779	1.4434	59.00	58.54	8.25	8.19	60.95	60.13
γ-Ketoazelate (VIIIe)	72	128–130	.15	...	1.0538	1.4453	60.44	60.52	8.59	8.68	65.57	65.43
δ-Ketoazelate (VIIIb)	75	123–127	.15	...	....	1.4504[b]	60.44	60.41	8.59	8.53	...	...
δ-Ketosebacate (VIIIf)	72	129	.15	...	1.0335	1.4460	61.74	61.82	8.88	8.88	70.19	70.27
6-Ketohendecanedioate (VIIIc)	67	143–145	.20	...	1.0262	1.4488	62.91	63.01	9.15	9.29	74.81	74.82
7-Ketotridecanedioate (VIIIg)	73	159–163	.15	34–35	....	....	64.94	64.84	9.62	9.72	...	...
8-Ketopentadecanedioate (VIIIh)	79	.....	..	32	....	....	66.63	66.59	10.00	10.11	...	...
13-Ketopentacosanedioate (VIIIi)	84	.....	..	78–79	....	....	72.14	72.30	11.28	11.33	...	...

[a] Diethyl γ-ketopimelate (VIIIa) was prepared from furylacrylic acid by the method of Marckwald, *Ber.*, **20**, 2811 (1887); $n^{21.5}D$ 1.4415. [b] $n^{21}D$.

hendecanedioic acid (VIIc)[9] and 7-ketotridecanedioic acid (VIIg).[9] We have repeated these syntheses and have extended the method to include the preparation of 8-ketopentadecanedioic acid (VIIh), 13-ketopentacosanedioic acid (VIIi), γ-ketosuberic acid (VIId), γ-ketoazelaic acid (VIIe) and δ-ketosebacic acid (VIIf). Where x and y were equal it was unnecessary to isolate the intermediate monoalkylation product (Va, b, c, g, h, i) or the corresponding dialkylation product (VI). In the preparation of the unsymmetrical keto diacids (VIId, e, f), however, where two different ω-halogen esters were employed, it was necessary to separate the monoalkylation product from the accompanying symmetrical dialkylate and the unchanged diethyl acetonedicarboxylate before reaction with the second ω-halogen ester.

Esterification of the keto diacids (VII) was effected in 70–80% yield by distillation of the ternary azeotrope from a mixture of the acid, benzene, ethanol and a catalytic amount of concentrated sulfuric acid. The keto diesters (VIII) thus formed (see Table I) were converted to the corresponding oximino diesters (III) in the usual manner, and in all but two cases (see Table II) the oximino diesters were not isolated in a pure form but were employed directly in the final step of reductive cyclization.

Experimental[10]

ω-Halogen Nitriles and Esters

γ-Iodobutyronitrile.—The treatment of γ-chlorobutyronitrile[11] with a solution of sodium iodide in acetone gave a 92% yield of γ-iodobutyronitrile, b. p. 109–111° (15 mm.).[12]

Ethyl δ-Iodovalerate.—The action of bromine on the silver salt of the half-ester of adipic acid, according to the procedure described by the Hunsdieckers,[13] yielded **ethyl δ-bromovalerate**, b. p. 106–108° (15 mm.); $n^{20}D$ 1.4582; d^{20}_4 1.3043; MR_D calcd., 43.95; found, 43.76. A halogen-interchange with sodium iodide in acetone gave an 85% yield of **ethyl δ-iodovalerate**, b. p. 122–125° (17 mm.[14]; $n^{20}D$ 1.4970; d^{20}_4 1.5294.

Anal. Calcd. for $C_7H_{13}IO_2$: C, 32.83; H, 5.16; MR_D, 48.99. Found: C, 33.24; H, 5.15; MR_D, 49.00.

Ethyl ε-Iodocaproate.—The degradation of the silver salt of the half-ester of pimelic acid with bromine yielded **ethyl ε-bromocaproate**, b. p. 122–125° (17 mm.); $n^{20}D$ 1.4590; d^{20}_4 1.2544.

Anal. Calcd. for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78; Br, 35.82; MR_D, 48.57. Found: C, 43.75; H, 6.97; Br, 35.53; MR_D, 48.62.

Treatment of ethyl ε-bromocaproate with sodium iodide in acetone gave a 92% yield of **ethyl ε-iodocaproate**, b. p. 135–137° (16 mm.); $n^{20}D$ 1.4941; d^{20}_4 1.4731.

Anal. Calcd. for $C_8H_{15}IO_2$: C, 35.57; H, 5.60; MR_D, 53.61. Found: C, 35.62; H, 5.70; MR_D, 53.39.

Ethyl 11-Iodohendecanoate.—The esterification of 11-bromohendecanoic acid[15] yielded **ethyl 11-bromohendecanoate**, b. p. 120–124° (0.3 mm.)[16]; $n^{20}D$ 1.4627; d^{20}_4 1.1263. The corresponding iodo ester was obtained in 80% yield by treatment of ethyl 11-bromohendecanoate with sodium iodide in acetone; b. p. 135–141° (0.5 mm.)[12]; $n^{20}D$ 1.4861; d^{20}_4 1.2790.

Symmetrical Keto Diacids

The general procedure for the synthesis of symmetrical keto diacids is illustrated below by the specific directions for the preparation of 13-ketopentacosanedioic acid (VIIi).

13-Ketopentacosanedioic Acid.—To a solution of sodium ethoxide (prepared from 4.6 g. of sodium and 100 ml. of absolute ethanol) was added 40.4 g. (0.2 mole) of diethyl acetonedicarboxylate. The stirred solution was heated to the reflux temperature, and 68.0 g. (0.2 mole) of ethyl 11-iodohendecanoate was added slowly. Stirring and heating were continued for two hours. After another solution of sodium ethoxide (0.2 mole) had been added, 0.2 mole of ethyl 11-iodohendecanoate was dropped in slowly. The mixture was heated and stirred for two hours after addition was complete. Most of the ethanol was removed by distillation, water was added, and the oil which separated was collected in ether. The ethereal solution was washed with water, and the ether was evaporated. The oil which remained was hydrolyzed by boiling for eighteen hours with a mixture of 200 ml. of concentrated hydrochloric acid and 100 ml. of glacial acetic acid. The hydrolysis mixture was evaporated to dryness, and the solid residue was recrystallized from acetone.

(9) English, THIS JOURNAL, **63**, 941 (1941).

(10) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel and Mr. Maurice Dare.

(11) "Organic Syntheses," Coll. Vol. I, 156 (1941).

(12) Case, THIS JOURNAL, **55**, 2927 (1933).

(13) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

(14) Carter, THIS JOURNAL, **50**, 1968 (1928).

(15) Ashton and Smith, *J. Chem. Soc.*, 435 (1934).

(16) Ashton and Smith, *ibid.*, 1308 (1934).

After three recrystallizations from acetone, 35.5g. (42%) of 13-ketopentacosanedioic acid was obtained as colorless, waxy plates, m. p. 98–99°.

Anal. Calcd. for $C_{25}H_{46}O_5$: C, 70.38; H, 10.87. Found: C, 71.03; H, 11.12.

Other keto diacids prepared by this method were **δ-ketoazelaic acid** (VIIb), m. p. 108–109°[7,17]; **6-ketohendecanedioic acid** (VIIc), m. p. 110–111°[9,18]; **7-ketotridecanedioic acid** (VIIg), m. p. 115–116°[9]; and **8-ketopentadecanedioic acid** (VIIh), m. p. 113–114°.[19]

Unsymmetrical Keto Diacids

Diethyl β-Keto-γ-carbethoxyadipate (V, x = 1).—To a solution of sodium ethoxide (from 13.8 g. of sodium in 400 ml. of absolute ethanol) was added 121.2 g. (0.6 mole) of diethyl acetonedicarboxylate. The resulting solution was heated to reflux temperature, and 100.4 g. (0.6 mole) of ethyl bromoacetate was added slowly with stirring. Heating and stirring were continued until the solution became neutral (two hours). Most of the ethanol was removed by distillation, water was added and the oil which separated was collected in ether. The ethereal solution was washed with water and dried. The ether was removed and the residual oil was distilled through a short-path apparatus. The first fraction consisted of 34.85 g. of recovered diethyl acetonedicarboxylate, b. p. 100–116° (0.5 mm.). **Diethyl β-keto-γ-carbethoxyadipate** boiled at 123–124° (0.2 mm.); $n^{20}D$ 1.4465; d^{20}_4 1.1403; yield, 70.4 g. (40.6%).

Anal. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99; MRD, 67.22. Found: C, 54.24; H, 7.18; MRD, 67.48.

A higher boiling fraction, **diethyl γ-keto-β,δ-dicarbethoxypimelate** (VIa) was collected at 154–157° (0.2 mm.); $n^{20}D$ 1.4523; d^{20}_4 1.1506; yield, 18.1 g. (8.1%).

Anal. Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00; MRD, 87.35. Found: C, 54.07; H, 7.37; MRD, 87.83.

Hydrolysis of 15.0 g. of the tetracarboxylic ester with a mixture of concentrated hydrochloric acid and glacial acetic acid, followed by evaporation to dryness and recrystallization of the residue from water, yielded 4.8 g. (69%) of **γ-ketopimelic acid** (VIIa) as glistening white plates, m. p. 140–141°.[8]

Diethyl β-Keto-γ-carbethoxypimelate (V, x = 2).—The monoalkylation of diethyl acetonedicarboxylate (121.2 g., 0.6 mole) with ethyl β-bromopropionate (108.5 g., 0.6 mole) in the presence of sodium ethoxide was carried out as described above. On distillation, 22.5 g. of diethyl acetonedicarboxylate, b. p. 93–108° (0.3 mm.), was recovered. **Diethyl β-keto-γ-carbethoxypimelate** boiled at 142–145° (0.1 mm.) with decomposition; $n^{20}D$ 1.4500; d^{20}_4 1.1194; yield, 41.3 g. (22.8%).

Anal. Calcd. for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33; MRD, 71.84. Found: C, 56.37; H, 7.56; MRD, 72.57.

The higher boiling fraction, **diethyl δ-keto-γ,ε-dicarbethoxyazelate** (VIb) (25.5 g., 10.6%) distilled at 174–175° (0.25 mm.) with extensive decomposition; $n^{20}D$ 1.4592; d^{20}_4 1.1426.

Anal. Calcd. for $C_{19}H_{30}O_9$: C, 56.70; H, 7.51; MRD, 96.59. Found: C, 56.77; H, 7.24; MRD, 96.57.

Hydrolysis of 8.04 g. (0.02 mole) of the tetracarboxylic ester with a mixture of 25 ml. of concentrated hydrochloric acid and 10 ml. of glacial acetic acid, followed by evaporation to dryness and recrystallization of the residue from water, yielded 2.8 g. (69%) of **δ-ketoazelaic acid** (VIIb) as white plates, m. p. 108–109°. The semicarbazone, obtained as colorless crystals from water, melted at 177–178°.[7]

γ-Ketosuberic Acid (VIId).—To a solution of sodium ethoxide (prepared from 2.99 g. of sodium and 100 ml. of absolute ethanol) was added 39.3 g. (0.13 mole) of diethyl β-keto-γ-carbethoxypimelate. The solution was heated to the reflux temperature and stirred, and 21.7 g. (0.13 mole) of ethyl bromoacetate was added slowly. Stirring and heating were continued until the solution became neutral (two hours). Most of the ethanol was removed by distillation, water was added and the oil which separated was collected in ether. The ethereal solution was washed with water, and the ether was removed under diminished pressure. The residual oil was heated for twelve hours under reflux with a mixture of 100 ml. of concentrated hydrochloric acid and 50 ml. of glacial acetic acid. The solution then was evaporated to dryness under diminished pressure, and the solid residue was triturated with cold ether. The ether-insoluble portion was recrystallized twice from water, yielding 14.5 g. (59.5%) of glistening white needles, m. p. 130–132°.

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.18; H, 6.31.

In a similar manner, the alkylation of 48.3 g. (0.16 mole) of diethyl β-keto-γ-carbethoxypimelate with 23.7 g. (0.16 mole) of γ-bromobutyronitrile, followed by hydrolysis and decarboxylation of the product, yielded 19.0 g. (55%) of **δ-ketosebacic acid** (VIIf), m. p. 115–116°.[20,21] **γ-Ketoazelaic acid** (VIIe), m. p. 109–110°[22,23] was prepared in 30% yield by the alkylation of diethyl β-keto-γ-carbethoxyadipate with γ-iodobutyronitrile, using the same procedure.

Keto Diesters

The general procedure for the esterification of the keto diacids is illustrated in the specific case below.

Diethyl 13-Ketopentacosanedioate (VIIIi).—A few drops of concentrated sulfuric acid was added to a solution of 29.8 g. (0.07 mole) of 13-ketopentacosanedioic acid in 100 ml. of absolute ethanol and 50 ml. of dry benzene. The solution was distilled until the temperature reached 78°; the distillate was dried over anhydrous potassium carbonate and returned to the distillation flask. Distillation was resumed until the temperature reached 80°, and the remainder of the benzene and ethanol was removed under diminished pressure. The solid residue was recrystallized from petroleum ether (b. p. 92–104°). Diethyl 13-ketopentacosanedioate (28.5 g., 84.3%) was obtained as white, glistening plates, m. p. 78–79°. Recrystallization from ethanol failed to raise the melting point (for analysis, see Table I).

Oximino Diesters

The general procedure for the preparation of the oximino diesters from the corresponding keto diesters is illustrated in the specific case below.

Diethyl 13-Oximinopentacosanedioate.—A few drops of glacial acetic acid was added to a solution of 24.2 g. (0.05 mole) of diethyl 13-ketopentacosanedioate, 9.8 g. (0.1 mole) of potassium acetate and 6.95 g. (0.1 mole) of hydroxylamine hydrochloride in 100 ml. of 50% ethanol. The solution was heated under reflux for three hours, cooled and filtered. The solid was recrystallized from acetone and then from petroleum ether (b. p. 92–104°). The oxime (20.6 g., 82.6%) formed white needles from petroleum ether, m. p. 32–33° (for analysis, see Table II).

1-Azabicyclo Compounds

The general method for the reductive cyclization of oximino diesters to 1-azabicyclo compounds is illustrated below in the directions for the preparation of 1-azabicyclo[5.4.0]hendecane from diethyl δ-oximinosebacate.

1-Azabicyclo[5.4.0]hendecane (IIf).—A solution of 12.0 g. (0.042 mole) of diethyl δ-oximinosebacate in 100 ml. of purified dioxane was reduced with hydrogen in the presence of 10 g. of copper chromite catalyst at 265° and 350 atmospheres. At 120°, rapid reduction of the oximino group occurred, and the theoretical amount of hydro-

(17) Šorm, *Coll. Czech. Chem. Commun.*, **12**, 150 (1947).
(18) Sauer, THIS JOURNAL, **69**, 2444 (1947).
(19) Kenner and Morton, *Ber.*, **72**, 452 (1939).
(20) Hückel and Brinkelmann, *Ann.*, **441**, 21 (1925).
(21) Hückel and Schluter, *Ber.*, **67**, 2108 (1934).
(22) Mannich, *ibid.*, **74**, 557 (1941).
(23) Šorm and Dolejs, *Coll. Czech. Chem. Commun.*, **14**, 108 (1949).

TABLE II

DERIVATIVES OF KETO DIACIDS AND DIESTERS

Semicarbazones of:	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Diethyl δ-ketoazelate	82–83	53.30	53.22	7.99	8.00	13.32	13.28
Diethyl γ-ketosuberate	102–103	51.81	51.87	7.69	7.78	13.95	14.09
6-Ketohendecanedioic acid	194–195	50.16	49.87	7.37	7.59	14.63	14.28
Diethyl 13-ketopentacosanedioate	66–67	66.74	66.68	10.65	10.73	7.78	7.56
Oximes of:							
Diethyl γ-ketopimelate	36–38[24]						
Diethyl 13-ketopentacosanedioate	32–33	69.97	69.97	11.15	10.93	2.81	3.09

gen was absorbed after 2.5 hours at 260–265°. The catalyst was removed by filtration and the filtrate was fractionated at reduced pressure. 1-Azabicyclo[5.4.0]-hendecane boiled at 90° (16 mm.); $n^{20}D$ 1.4872; yield, 3.4 g. (53%).

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.37; H, 12.50; N, 9.14. Found: C, 78.10; H, 12.36; N, 9.32.

1-Azabicyclo[5.4.0]hendecane Picrate.—Prepared in ether and recrystallized from ethanol, the picrate formed yellow plates, m. p. 161–162°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.01; H, 5.80; N, 14.64.

1-Azabicyclo[5.4.0]hendecane Picrolonate.—Prepared in and recrystallized from ethanol, the picrolonate formed yellow plates which decomposed at 213°.

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78. Found: C, 57.62; H, 6.86; N, 16.97.

Pyrrolizidine (IIa), b. p. 140–143° (748 mm.); $n^{20}D$ 1.4561; picrate, m. p. 256–258° (dec.); **quinolizidine** (IIb), b. p. 165–169° (748 mm.): $n^{20}D$ 1.4794; picrate, m. p. 197–199°; and **octahydropyrrocoline** (IId), b. p. 66–67° (18 mm.); $n^{20}D$ 1.4711; picrate, m. p. 233–234°, were prepared by similar reductions of the appropriate oximino diesters in 50–60% yield. The picrates did not depress the melting points of authentic samples. Reduction of diethyl δ-oximinoazelate gave a 58% yield of **1-azabicyclo[5.3.0]decane** (IIe),[6] b. p. 71–73.5° (14 mm.); $n^{20}D$ 1.4822; picrate, m. p. 214–215°; picrolonate, m. p. 191–192°; methiodide, m. p. 279–280°. Reduction of diethyl 6-oximinohendecanedioate gave a 52% yield of **1-azabicyclo[5.5.0]dodecane** (IIc), b. p. 111–112° (18 mm.); $n^{20}D$ 1.4930; picrate, m. p. 139–140°; picrolonate, m. p. 186–187°; methiodide, m. p. 243–244° (reported,[5] b. p. 107–108° (16 mm.); picrate, m. p. 136°; picrolonate, m. p. 181°; methiodide, m. p. 233°).

The catalytic hydrogenation of diethyl 13-oximinopentacosanedioate yielded a basic fraction from which was isolated a white, waxy solid, m. p. 99–100° after recrystallization from ethanol. The analysis indicates that this product is probably 13-aminopentacosane-1,25-diol, which could result from normal reduction unaccompanied by cyclization.

Anal. Calcd. for $C_{25}H_{53}NO_2$: C, 75.12; H, 13.37; N, 3.55. Found: C, 75.10; H, 13.55; N, 3.73.

The reduction of crude 8-oximinopentadecanedioate yielded a neutral nitrogen-free solid, m. p. 81–82° after recrystallization from petroleum ether (b. p. 92–104°). The analysis of the product is consistent with its formulation as pentadecane-1,8,15-triol, which could result from the normal reduction of any diethyl 8-ketopentadecanedioate present in the crude oxime. No basic material was isolated from the reduction.

Anal. Calcd. for $C_{15}H_{32}O_3$: C, 69.02; H, 12.39. Found: C, 68.86; H, 12.35.

No pure chemical individual was isolated from the reduction of diethyl 7-oximinotridecanedioate.

Summary

A general method has been devised for the synthesis of 1-azabicyclo compounds by the reductive cyclization of oximino diesters. The oximino- and keto-diester intermediates are readily available from diethyl acetonedicarboxylate through dialkylation with ω-halogen esters. The reductive cyclization process is especially useful for the preparation of 1-azabicyclo compounds containing seven-membered rings, such a 1-azabicyclo[5.3.0]decane, 1-azabicyclo[5.4.0]hendecane and 1-azabicyclo[5.5.0]dodecane.

(24) Volhard, *Ann.*, **253**, 212 (1889).

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