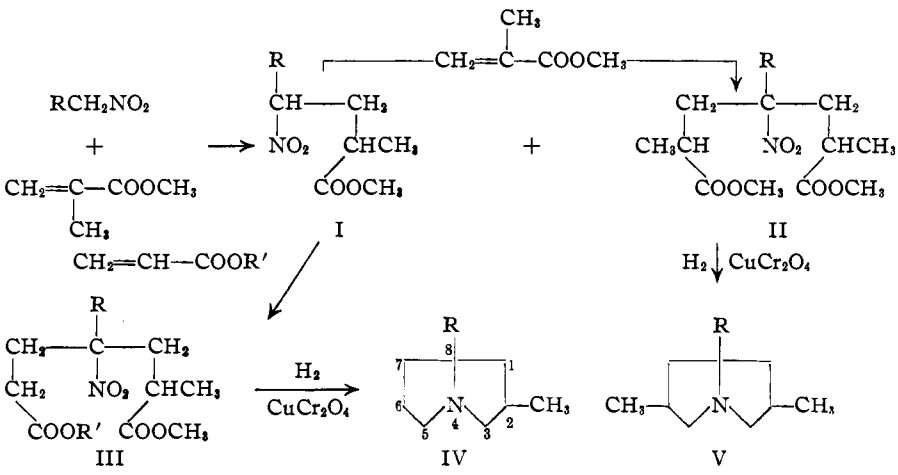
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines. IV. Condensation of Nitroparaffins with Methyl Methacrylate and Subsequent Formation of 2-, 6- and 8-Alkyl-Substituted Pyrrolizidines

BY NELSON J. LEONARD AND GRADUS L. SHOEMAKER

Convenient and efficient methods of synthesis for pyrrolizidine,[1] 8-alkylpyrrolizidines,[1,2] and 1-alkylpyrrolizidines[3] have been described in earlier papers. The present investigation is concerned with the condensation of nitroparaffins with methyl methacrylate and the subsequent formation of 2-alkyl-, 2,6-dialkyl-, 2,8-dialkyl-, and 2,6,8-trialkylpyrrolizidines (IV, V). The compound 2-methylpyrrolizidine (IV, R = H) had been prepared previously by Men'shikov[4] and by Clemo and Melrose[5] for comparison with the alkaloid degradation product, *l*-heliotridane. Neither



method furnished the compound in satisfactory yield, and there was some discrepancy in the melting points of the picrates obtained as derivatives. No other pyrrolizidines of type IV or V had been obtained prior to the present work.

The first step in the synthesis of these pyrrolizidines was the condensation of nitroparaffins with methyl methacrylate to produce the mono- and di-esters I and II. A careful study of the conditions for this reaction indicated that the base most effective for bringing about the formation of esters of type I was diethylamine. The use of diethylamine at 25° also caused the formation of some di-ester (II, R = H), but the most effective base for bringing about the formation of symmetrical γ-nitropimelic esters of type II was found to be benzyltrimethylammonium butoxide, preferably by the route of condensation of the mono-ester (I) with additional methyl methacrylate. Where secondary amines were employed to bring about the Michael condensations, no attempt was made to isolate the by-product adducts of amine and methacrylate.[6] The Michael condensation of other methylene compounds with methyl methacrylate had been previously realized.[7]

The unsymmetrical γ-nitropimelic esters of type III were best prepared by condensation of the α-methyl-γ-nitroesters (I) with acrylic ester in the presence of benzyltrimethylammonium hydroxide or butoxide. The properties of all three types of esters (I, II, III) are given in Table I. The usual method of reductive cyclization[1,2,3] was employed for the conversion of esters of type III and II to substituted pyrrolizidines of type IV and V. Hydrogenation over copper chromite in dioxane solution at high temperature and pressure gave good yields of the bicyclic bases. These are described along with their picrate and picrolonate derivatives in Table II. In each case, more than one racemic form of the product was to be expected, but one racemate evidently predominated because the solid derivatives invariably were formed in excellent yield and possessed sharp melting points. In the case of the 2-methylpyrrolizidine, the melting point of the picrate obtained (182.5–183.5°) corresponds to that observed by Men'shikov (182–184°)[4] but not to that reported by Clemo and Melrose (169–170°)[5] for the same compound.

Experimental[8]

γ-Nitroesters

The procedures which follow are typical of those which were found to be most efficient for the preparation of the γ-nitroesters given in Table I. Variations in basic reagents, time and temperature were tried systematically.

(1) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).
(2) Leonard and Beck, *ibid.*, **70**, 2504 (1948).
(3) Leonard and Felley, *ibid.*, **71**, 1758 (1949).
(4) Men'shikov, *Ber.*, **69**, 1802 (1936).
(5) Clemo and Melrose, *J. Chem. Soc.*, 424 (1942).
(6) Weisel, Taylor, Mosher and Whitmore, THIS JOURNAL, **67**, 1071 (1945).
(7) *E. g.*, Ruzicka, *Helv. Chim. Acta*, **2**, 144 (1919); Cox, Kroeker and McElvain, THIS JOURNAL, **56**, 1173 (1934); Connor and McClellan, *J. Org. Chem.*, **3**, 570 (1939).
(8) Melting points are corrected for both emergent stem and thermometer errors. Microanalyses by Mrs. Jane Wood and Mr. Maurice Dare.

TABLE I

PROPERTIES OF γ-NITROESTERS

Nitroester	Boiling pt. °C.	Mm.	$n^{20}D$	d^{20}_4	Formula	MR_D Calcd.	MR_D Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl α-methyl-γ-nitrobutyrate	82–83	3	1.4379	1.132	$C_6H_{11}NO_4$	37.19	37.38	8.69	8.82
Methyl α-methyl-γ-nitrovalerate	88–89	2	1.4348	1.099	$C_7H_{13}NO_4$	41.81	41.60	8.00	8.33
Methyl α-methyl-γ-nitrocaproate	92–93	3	1.4358	1.072	$C_8H_{15}NO_4$	46.43	46.13	7.40	7.92
Methyl α,γ-dimethyl-γ-nitrovalerate	73–75	2	1.4380	1.077	$C_8H_{15}NO_4$	46.43	46.11	7.40	7.83
Dimethyl α,α'-dimethyl-γ-nitropimelate	134–136	3	1.4480	1.130	$C_{11}H_{19}NO_6$	61.93	61.87	5.36	5.61
Dimethyl α,α',γ-trimethyl-γ-nitropimelate	123–125	2	1.4620	1.140	$C_{12}H_{21}NO_6$	66.55	66.40	5.08	5.29
Dimethyl γ-ethyl-α,α'-dimethyl-γ-nitropimelate	142–145	2	1.4565	1.112	$C_{13}H_{23}NO_6$	71.18	70.81	4.84	5.17
Dimethyl γ-ethyl-α-methyl-γ-nitropimelate	138–140	2	1.4592	1.144	$C_{12}H_{21}NO_6$	66.55	65.84	5.09	5.40
Methyl ethyl α-methyl-γ-nitropimelate	143–145	2	1.4480	1.129	$C_{11}H_{19}NO_6$	61.93	61.94	5.36	5.61
Methyl ethyl α,γ-dimethyl-γ-nitropimelate	152–153	2	1.4534	1.123	$C_{12}H_{21}NO_6$	66.55	66.29	5.08	5.59

TABLE II

PYRROLIZIDINES

Pyrrolizidine	Formula	Yield, %	Boiling pt. °C.	Mm.	$n^{20}D$	d^{20}_4	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Methyl	$C_8H_{15}N$	61.5	58–60	20	1.4602	0.897	76.73	76.51	12.08	12.16	11.19	11.27
2,6-Dimethyl	$C_9H_{17}N$	61.0	83–85	44	1.4559	.868	77.63	77.82	12.31	12.41	10.06	10.20
2,8-Dimethyl	$C_9H_{17}N$	73.0	76–77	42	1.4542	.878	77.63	77.67	12.31	12.22	10.06	9.86
2,6,8-Trimethyl	$C_{10}H_{19}N$	71.0	86–88	40	1.4502	.867	78.36	78.54	12.49	12.65	9.14	8.87
2-Methyl-8-ethyl	$C_{10}H_{19}N$	51.6	90–93	38	1.4612	.887	78.36	78.03	12.49	12.50	9.14	9.36
2,6-Dimethyl-8-ethyl	$C_{11}H_{21}N$	80.5	106–108	43	1.4579	.877	78.97	79.26	12.65	12.81	8.37	8.06

Pyrrolizidine	Picrate M. p., °C.	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found	Picrolonate M. p., °C.	Picrolonate Nitrogen, % Calcd.	Picrolonate Nitrogen, % Found
2-Methyl	183–184[a]	15.81	15.83	153[b]	17.98	17.84
2,6-Dimethyl	124.6–125[a]	15.20	15.00	167–168[a]	17.36	17.47
2,8-Dimethyl	193–194.5[a]	15.20	15.25	155–156[b]	17.36	17.33
2,6,8-Trimethyl	165.5–167[b]	14.65	14.68	177–178[b]	16.78	17.01
2-Methyl-8-ethyl	154.5–155.5[a]	14.65	14.75	171.5–172[b]	16.78	16.58
2,6-Dimethyl-8-ethyl	136–137[b]	14.13	13.88	184–185.5[b]	16.23	16.41

[a] Recrystallized from ethanol. [b] Recrystallized from methanol.

The preferred procedures which gave maximum yields are described in detail.

Type I.—A solution of 50 g. (0.5 mole) of methyl methacrylate, 134 g. (1.50 mole) of 1-nitropropane, and 14 g. (0.2 mole) of diethylamine was allowed to stand at 25° for fifteen days. The unchanged materials were removed by distillation at reduced pressure (30 mm.). Fractional distillation of the residual oil gave **methyl α-methyl-γ-nitrocaproate**, b. p. 90–93° (4 mm.); yield 42.5 g. (45%). When the reaction mixture was allowed to stand for twenty-five or forty days, there was no substantial increase in the yield obtained. This was true also for the nitromethane and nitroethane adducts. **Methyl α-methyl-γ-nitrobutyrate** was obtained in 21% yield and **methyl α-methyl-γ-nitrovalerate**, in 39% yield under the same reaction conditions. Many other basic catalysts were tried, but only when benzyltrimethylammonium hydroxide was employed (seventy hours at 78°) did the yields approach those realized with diethylamine. In the addition of 2-nitropropane to methyl methacrylate, benzyltrimethylammonium hydroxide (33% yield) was more effective than diethylamine (23% yield) in the producing **methyl α,γ-dimethyl-γ-nitrovalerate.**

Type II.—To a stirred solution of 80 g. (0.5 mole) of methyl α-methyl-γ-nitrobutyrate and 10 g. of benzyltrimethylammonium butoxide (25% solution in butanol, Rohm and Haas Co.) was added 150 g. (1.5 moles) of methyl methacrylate. The temperature was raised to 75–80° and stirring was continued for seventy-two hours. The product was acidified with 1 *N* hydrochloric acid and was dissolved in an equal volume of ethylene dichloride. The ethylene dichloride layer was washed with three successive 100-ml. portions of water, and the solvent and unreacted material were removed at reduced pressure (50 mm.). The residual oil was fractionated *in vacuo* to give 79.3 g. (61%) of **dimethyl α,α'-dimethyl-γ-nitropimelate**, b. p. 134–136° (3 mm.). **Dimethyl α,α',γ-trimethyl-γ-nitropimelate** was obtained from methyl α-methyl-γ-nitrovalerate and methyl methacrylate in 62% yield under the same conditions. **Dimethyl γ-ethyl-α,α'-dimethyl-γ-nitropimelate** was obtained in 88% yield under similar conditions from methyl α-methyl-γ-nitrocaproate and excess methyl methacrylate in the presence of benzyltrimethylammonium butoxide.

Type III.—To a stirred solution of 21 g. (0.11 mole) of methyl α-methyl-γ-nitrocaproate, 6 ml. of benzyltrimethylammonium hydroxide (40% in water, Rohm and Haas Co.), and 20 ml. of dioxane was added dropwise 28 g. (0.33 mole) of methyl acrylate. After the initial exothermic reaction subsided heat was applied to keep the reaction mixture at 75° for thirty-six hours. The mixture was then made faintly acid with 1 *N* hydrochloric acid and was added to an equal volume of ethylene dichloride. After thorough washing with water, the ethylene dichloride layer was separated and the solvent was removed at reduced pressure (50 mm.). Fractionation of the residue gave 22.6 g. (74.5%) of an oil, b. p. 157–161° (3 mm.), identified as **dimethyl γ-ethyl-α-methyl-γ-nitropimelate. Methyl ethyl α-methyl-γ-nitropimelate** was obtained in 55% yield by the reaction of methyl α-methyl-γ-nitrobutyrate with ethyl acrylate in the presence of "Triton B" at 36° for twenty-four hours. **Methyl ethyl α,γ-dimethyl-γ-nitropimelate** was obtained in 69% yield by the reaction of methyl α-methyl-γ-nitrovalerate with ethyl acrylate in the presence of benzyltrimethylammonium butoxide at 60° for twelve hours.

Pyrrolizidines

The general procedure for the reductive cyclization of γ-nitropimelic esters to pyrrolizidines is illustrated below in the specific directions for the preparation of 2,6,8-trimethylpyrrolizidine.

2,6,8-Trimethylpyrrolizidine.—A solution of 21.4 g. (0.067 mole) of dimethyl α,α',γ-trimethyl-γ-nitropimelate in 110 ml. of purified dioxane was reduced with hydrogen in the presence of 10 g. of copper chromite catalyst at 260° and 300–350 atmospheres. Rocking was continuous from the time that heat was applied. At 130°, rapid exothermic reduction of the nitro group occurred and the theoretical amount of hydrogen was absorbed after three hours at 255–260°. The catalyst was removed by filtration and the filtrate was fractionated at reduced pressure. The colorless, basic fraction boiling at 86–88° (40 mm.) was collected and purified by redistillation; yield 8.5 g. (71%).

Summary

The conditions for bringing about the condensation of nitroparaffins with methyl methacrylate have been explored.

A number of 2-alkyl-, 2,6-dialkyl-, 2,8-dialkyl- and 2,6,8-trialkylpyrrolizidines have been synthesized in good yield by the method comprising Michael condensations and reductive cyclization.

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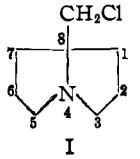
The Synthesis of Pyrrolizidines. V. 8-Hydroxymethylpyrrolizidine and 8-Chloromethylpyrrolizidine[1]

BY NELSON J. LEONARD AND GRADUS L. SHOEMAKER[2]

The availability of 8-chloromethylpyrrolizidine (I) through a convenient method of synthesis offers an excellent opportunity for testing the typical β-chloroamine rearrangement in the bicyclic series. The rearrangement of β-chloroamines through an ethyleneimonium ion intermediate has been observed in the acyclic series (2-dialkylamino-1-chloropropane → 1-dialkylamino-2-chloropropane)[3] and in the monocyclic series (2-chloromethyl-1-ethylpyrrolidine → 3-chloro-1-ethylpiperidine).[4] It would be expected that 8-chloromethylpyrrolizidine could not undergo rearrangement under analogous conditions because of the constraint which the ring structure places on the formation of the necessary rearrangement intermediates. Compound I has now been synthesized and has been found to be stable.



I

The general method for the synthesis of pyrrolizidines[5,6] has been applied successfully to the preparation of 8-hydroxymethylpyrrolizidine (IV), and this compound has been converted, through its hydrochloride, to the hydrochloride of 8-chloromethylpyrrolizidine. The first step in the synthesis of IV was the Michael condensation of ethyl nitroacetate with ethyl acrylate in the presence of benzyltrimethylammonium hydroxide to give diethyl α-nitroglutarate (II) and diethyl γ-carbethoxy-γ-nitropimelate (III). The diester II could be converted to the triester III by further condensation with ethyl acrylate. 8-Hydroxymethylpyrrolizidine (IV), a position isomer of the *Senecio* alkaloid product, isoretronecanol,[7] was obtained by catalytic hydrogenation of III over copper chromite at high temperature and pressure.[6] 8-Hydroxymethylpyrrolizidine hydrochloride (V) was converted to 8-chloromethylpyrrolizidine hydrochloride (VI) by means of thionyl chloride. The ring structure of these compounds was established by catalytic hydrogenation of VI to give VII, which was identical with an authentic sample of 8-methylpyrrolizidine.[5]

If compound I could undergo rearrangement in a manner analogous to the acyclic and monocyclic β-chloroamines,[3,4] the product would be 5-chloro-1-azabicyclo[3.3.1]nonane(X). However, no rearranged product was obtained following the methods which have been employed for bringing about such rearrangements: (a) heating the β-chloroamine hydrochloride above its melting point, and (b) freeing the β-chloroamine from its salt through the action of alkali. The resistance of compound I to rearrangement is not due to di-α-substitution in the β-chloroamine since Kerwin, Ullyot, Fuson and Zirkle found that a compound with two alkyl groups on the α-carbon undergoes rearrangement (XI → XII).[3] The reason why compound I remains unchanged appears rather to be due to the fact that the necessary ethyleneimonium ion (VIII) or carbonium ion (IX) intermediate cannot be formed. Even if the ethyleneimonium ion (VIII) could be formed by methylenic linkage between positions 4 and 8 of the inflexible pyrrolizidine nucleus, the subsequent formation of the coplanar carbonium ion (IX) would be impossible

(1) For paper IV in this series, see Leonard and Shoemaker, THIS JOURNAL, **71**, 1760 (1949).

(2) Present address: Department of Chemistry, Rutgers University, New Brunswick, New Jersey.

(3) Kerwin, Ullyot, Fuson and Zirkle, THIS JOURNAL, **69**, 2961 (1947).

(4) Fuson and Zirkle, *ibid.*, **70**, 2760 (1948).

(5) Leonard, Hruda and Long, *ibid.*, **69**, 690 (1947).

(6) Leonard and Beck, *ibid.*, **70**, 2504 (1948).

(7) Adams and Hamlin, *ibid.*, **64**, 2597 (1942).