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Original Scientific Paper

The Reformatsky Reaction with Aliphatic γ - and δ -Halonitriles. The Synthesis of Some 2-Substituted Δ^1 -Pyrrolines and Δ^1 -Piperideines*

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Starting from aliphatic γ - or δ -halonitriles and α -bromoesters, ω -halo- β -ketoesters, 2-substituted Δ^1 -pyrrolines or 2-substituted Δ^1 -piperideines, were obtained. Some of the chemical and spectroscopic properties of the prepared compounds are described.

The reaction of α -bromoesters containing a tertiary (III), a secondary (IV) or a primary (V) bromine atom with aliphatic γ or δ -halonitriles (I and II) in the presence of zinc was investigated. Different products were obtained depending on reaction conditions. If the reaction was carried out in ether, tetrahydrofuran or benzene, the main product was the corresponding ω -halo- β -ketoester (VI, VII VIII and IX), but if anisole was employed as solvent, 2-substituted Δ^1 -pyrroline (XI) or 2-substituted Δ^1 -piperideines (XIII and XIV) were obtained. In both cases the reaction probably occurred as in the Grignard reaction with the same halonitriles.¹⁻⁶ Consequently, the preparation of these compounds was performed according to the reactions Scheme.

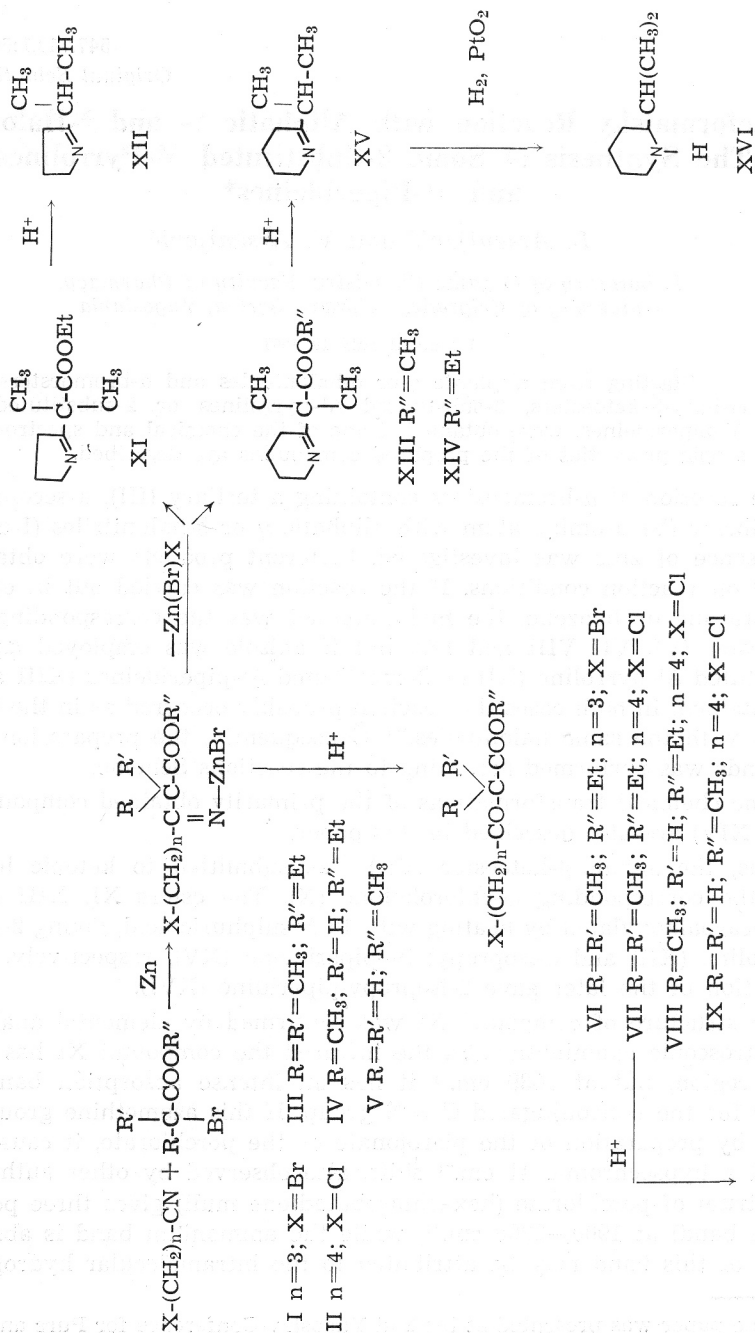
Some chemical transformations of the primarily obtained compounds (VII, XI and XIV) are also described in this paper.

Thus, the ω -halo- β -ketoester (VII) was submitted to ketonic hydrolysis giving the corresponding ω -chloroketone (X). The esters XI, XIII and XIV were decarbalkoxylated by heating with 10 *N* sulphuric acid, giving 2-isopropyl Δ^1 -pyrroline (XII) and 2-isopropyl Δ^1 -piperideine (XV), respectively. The hydrogenation of the later gave 2-isopropylpiperidine (XVI).

The structure of compound XI was confirmed by elemental analysis and by spectroscopic examination. In the infrared the compound XI has no band in NH region, but at 1639 cm^{-1} it has an intense absorption band characteristic for the nonconjugated C = N group. If this azomethine group is protonated by preparation of the picrolonate or the perchlorate, it causes in the infrared a hypsochromic 41 cm^{-1} shift, also observed by other authors.⁷ The IR spectrum of perchlorate (hexachlorobutadiene mull) gives three peaks (immonium band) at 1900—2200 cm^{-1} , while the ammonium band is absent. The absence of this band may be attributed to the intramolecular hydrogen bond

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SCHEME



between the carbonyl of ester and the hydrogen of C = NH group.* The presence of this intramolecular hydrogen bond is confirmed by the fact that in the spectrum of perchlorate of XI the carbonyl of ester gives absorption at 1680 cm^{-1} , while this group in unprotonised compound XI absorbs at the normal position (1735 cm^{-1}). In the IR spectrum of picrolonate of XI both the ammonium and the immonium bands are very weak (KBr pellets and hexachlorobutadiene mull), which has been observed in some Δ^1 -pyrrolines.⁹

In the NMR spectrum of XI, the vinyl proton was absent; the spectrum shows a triplet centered at $\tau = 6.3$ ($\text{H}\alpha'$), a triplet centered at $\tau = 7.61$ ($\text{H}\beta$) and a multiplet centered at $\tau = 8.18$ ($\text{H}\beta'$) which is consistent with the presence of a Δ^1 -pyrroline ring.

That the pyrroline ring was not changed during the decarbalkoxylation of XI in strong acidic medium, can be shown by the following**:

a) The IR spectrum of XII has no band in the NH region, either, while at 1648 cm^{-1} it gives absorption for the C = N group. The spectrum of its hydrochloride (hexachlorobutadiene mull) shows a strong ammonium band at 2550 cm^{-1} , three peaks (immonium band) at 1900—2200 cm^{-1} and a strong band at 1683 cm^{-1} (protonated azomethine group). In contrast to this, in the spectrum of its picrate these bands are very weak.⁹

The NMR spectrum of XII shows a triplet centered at $\tau = 6.36$ ($\text{H}\alpha'$), a multiplet centered at $\tau = 7.66$ ($\text{H}\beta$ and H tert.) and a multiplet centered at $\tau = 8.21$ ($\text{H}\beta'$) while the vinyl proton is absent.

b) Compound XII prepared directly, *i. e.* by reaction between γ -bromobutyronitrile and isopropylmagnesium bromide in boiling xylene, was identical (IR spectra and mixed m. p. of picrates) with the compound obtained by decarbalkoxylation of XI. The Grignard synthesis was carried out as it was described for preparation of 2-ethyl Δ^1 -pyrroline.⁴

The structure of the compound XIV was proved by its IR spectrum as well as by its conversion into known substances XV and XVI.

Our conclusion about the Δ^1 -position of the double bond in the pyrroline and piperidine ring in our compounds is in agreement with the results obtained by other authors¹¹ using different methods.

EXPERIMENTAL

Melting points were determined on a Kofler heating microscope. The IR spectra were recorded on a Perkin-Elmer spectrophotometer model 237. The NMR spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as internal standard. Carbon tetrachloride was used as solvent.

Ethyl 6-bromo-2,2-dimethyl-3-oxohexanoate (VI)

A mixture of halonitrile I (14.8 g., 0.1 mole), zinc wool (7.8 g., 0.12 at.), α -bromoester III (23.4 g., 0.12 mole), a few mg. of mercuric chloride and 70 ml. of dry ether was stirred and heated. After a while the reaction started and if it became too vigorous the flask had to be cooled in cold water. When the reaction rate decreased, the mixture was refluxed and stirred for 3 hours; a white precipitate was formed and most of the zinc was dissolved. The reaction mixture was then cooled and decomposed

* In a similar example,⁸ the absence of the ammonium band is attributed to the strong intramolecular hydrogen bonding.

** Resistance of the 2-substituted Δ^1 -pyrroline ring to acids was earlier observed.¹⁰

by stirring with 10% ice-cooled sulphuric acid (300 ml.) for 30 minutes. The aqueous layer was separated and extracted with ether. The combined ethereal layers were shaken with sodium bicarbonate solution, and water and dried with $MgSO_4$. The solvent was removed and the residue distilled *in vacuo*, b.p. 148°/14 mm. Yield 9.2 g. (35%). IR spectrum (liquid film): 1718 s (ketone CO), 1745 s (ester CO) cm^{-1} .

Anal. $C_{10}H_{17}BrO_3$ (265.23) calc'd.: C 45.34; H 6.45%
found: C 45.53; H 6.50%

Ethyl 7-chloro-2,2-dimethyl-3-oxoheptanoate (VII)

Prepared as before from halonitrile II (23.4 g., 0.2 mole), zinc (15.6 g., 0.24 at.) and α -bromoester III (47 g., 0.24 mole) in 200 ml. of dry benzene. The haloketoester VII has, b.p. 150°/9 mm. Yield 23 g. (48%). IR spectrum (liquid film): 1710 s (ketone CO), 1745 s (ester CO) cm^{-1} .

Anal. $C_{11}H_{19}ClO_3$ (234.65) calc'd.: C 56.40; H 8.12%
found: C 56.41; H 8.37%

Ethyl 7-chloro-2-methyl-3-oxoheptanoate (VIII)

Prepared as before from halonitrile II (11.7 g., 0.1 mole), zinc (13 g., 0.2 at.) and α -bromoester IV (36.2 g., 0.2 mole) in 100 ml. of dry benzene. Haloketoester VIII has b.p. 150—151°/12 mm. Yield 8.5 g. (38%). IR spectrum (liquid film): 1714 s (ketone CO), 1740 s (ester CO) cm^{-1} .

Anal. $C_{10}H_{17}ClO_3$ (220.68) calc'd.: C 54.39; H 7.76%
found: C 54.42; H 7.72%

Methyl 7-chloro-3-oxoheptanoate (IX)

Halonitrile II (11.7 g., 0.1 mole), zinc (13 g., 0.2 at.), mercuric chloride (0.1 g.) and 50 ml. of dry tetrahydrofuran were placed in a flask and the mixture was heated to boiling where upon a solution of α -bromoester V (30.6 g., 0.2 mole) in 50 ml. of tetrahydrofuran was added dropwise,¹² over a period of 40—50 minutes. The boiling was continued for 2 hours. The solvent was removed by distillation, at atmospheric pressure and finally *in vacuo*. Then 100 ml. of benzene was added and the solution was treated in the same way as VI. Haloketoester IX has b.p. 154°/17 mm. Yield 6.2 g. (40%). IR spectrum (liquid film): 1720 s (ketone CO), 1750 s (ester CO) cm^{-1} .

Anal. $C_8H_{13}ClO_3$ (192.63) calc'd.: C 50.00; H 6.61%
found: C 50.38; H 6.61%

7-Chloro-2-methyl-3-heptanone (X)

Haloketoester VII (4 g.), *p*-toluenesulphonic acid (2 g.) and 80% acetic acid (12 ml.) were heated under reflux for 3 hours. The reaction mixture was cooled, neutralized with potassium carbonate solution and extracted with ether. The organic layer was washed with water and dried with $MgSO_4$. The ether was removed and the residue was distilled, b.p. 109°/15 mm. Yield 2 g. (70%).

Anal. $C_8H_{15}ClO$ (162.66) calc'd.: C 59.04; H 9.32%
found: C 59.30; H 9.54%

2,4-Dinitrophenylhydrazone: m.p. 87° (ethanol).

Anal. $C_{14}H_{19}ClN_4O_4$ (342.77) calc'd.: N 16.34%
found: N 16.37%

Ethyl 2-methyl-2(Δ^1 -pyrrolinyl-2)-propionate (XI)

Halonitrile I (7.4 g., 0.05 mole), zinc (3.9 g., 0.06 at.), mercuric chloride (0.1 g.) α -bromoester III (12 g., 0.06 mole) and dry anisole (25 ml.) were heated carefully to initiate the reaction. When the reaction rate decreased, the mixture was refluxed for further 30 minutes. After cooling, 80 ml. of ice-cooled 10% sulphuric acid was

added and the mixture was stirred 15 minutes. The aqueous layer was washed twice with ether, cooled to 0°, made strong alkaline with potassium hydroxide (pellets) and the base was extracted with ether. The combined ethereal extract was shaken with saturated sodium chloride solution and dried with potassium hydroxide. Ether was removed and the residue distilled *in vacuo*, b. p. 108—110°/16 mm. Yield 4.8 g. (55%).

Anal. C₁₀H₁₇NO₂ (183.24) calc'd.: C 65.54; H 9.35; N 7.64%
found: C 65.48; H 9.49; N 7.71%

Picrolonate: m. p. 189—190° (from ethanol). IR spectrum (KBr Pellet.): 1680 m (C = NH), cm⁻¹.

Anal. C₂₀H₂₅N₅O₇ (447.44) calc'd.: N 15.65%
found: N 15.79%

2-Isopropyl-Δ¹-pyrroline (XII)

Ester XI (10 g.) and 10 N sulphuric acid (50 ml.) were refluxed* for 30 minutes. To the ice-cooled solution potassium hydroxide (pellets) was added (pH about 12) and extracted with ether. The ethereal extract was washed with saturated sodium chloride solution and dried with potassium hydroxide. Ether was removed and the amine distilled, b. p. 138°/740 mm. Yield 5 g. (82%).

Picrate: m. p. 114° (from ethanol).

Anal. C₁₃H₁₆N₄O₇ (340.29) calc'd.: C 45.88; H 4.74; N 16.47%
found: C 45.57; H 4.70; N 16.50%

Preparation of XII by the Grignard Reaction

To a Grignard reagent [from magnesium turnings (2.9 g.) isopropyl bromide (14.3 g.) in dry ether (50 ml.) by refluxing during one hour] a solution of halonitrile I (5. g.) in dry ether (15 ml.) was added with stirring and ice-cooling for 15 minutes. The reaction mixture was then refluxed for 30 minutes, ether removed by distillation and replaced by dry xylene (30 ml.). After boiling for 30 minutes and cooling to 0°, the mixture was treated with saturated ammonium chloride solution. The organic layer, was separated and extracted with diluted hydrochloric acid. The acidic aqueous layer was washed with ether, made strong alkaline by adding potassium hydroxide (pellets) and extracted three times with ether. The combined ethereal layers were washed with saturated sodium chloride solution and dried with potassium hydroxide. Ether was removed, the residue distilled and transformed into picrate, m. p. 114°. Yield: 1.1 g.

Methyl 2-methyl-2(Δ¹-piperideinyl-2)-propionate (XIII)

Prepared as compound XI, from halonitrile II (19.9 g., 0.17 mole), zinc (13 g., 0.2 at.) and methyl α-bromoisobutyrate (36.2 g., 0.2 mole) in 80 ml. of dry anisole. The crude product (15 g.) was isolated by continuous extraction of alkaline aqueous layer and distilled through a short fractionating column under reduced pressure. The fraction boiling at 107°/11 mm. was collected. Yield 6—7 g. (33—38 %). This compound has a tendency to polymerize on standing.

Anal. C₁₀H₁₇NO₂ (183.24) calc'd.: C 65.54; H 9.35; N 7.64%
found: C 65.35; H 9.32; N 7.82%

Ethyl 2-methyl-2(Δ¹-piperideinyl-2)-propionate (XIV)

Prepared as before from halonitrile II (19.9 g., 0.17 mole), zinc (13 g., 0.2 at.) and ethyl α-bromoisobutyrate (39 g., 0.2 mole) in anisole (80 ml.). The crude product (15.5 g.) was fractionated, b. p. 132°/23 mm. IR spectrum (liquid film): 1728 s (ester CO), 1661 s (C = N) cm⁻¹.

* We have recently employed this method of decarbalkoxylation in the isoquinoline series.¹⁶

Anal. C₁₁H₁₉NO₂ (197.27) calc'd.: C 66.97; H 9.71; N 7.10%
found: C 66.61; H 9.55; N 6.86%

Picrolonate: m. p. 180⁰ (from ethanol). IR spectrum (KBr Pellet.): 1695 s (C = NH)⁺, 1930 vw (immonium band) cm.⁻¹

Anal. C₂₁H₂₅N₅O₇ (459.45) calc'd.: C 54.89; H 5.48; N 15.24%
found: C 54.47; H 5.73; N 15.17%

2-Isopropyl-Δ¹-piperideine (XV)

Ester XIV (2 g.) and 10 N sulphuric acid (10 ml.) were refluxed for 30 minutes. To the ice-cooled solution potassium hydroxide was added to make the solution strongly alkaline and the amine was isolated by continuous extraction with ether. The ethereal extract was washed with saturated sodium chloride solution and dried with »Drierite«. Ether was removed and the residue (1.2 g., 88%) was distilled in a micro-apparatus. Picrate: m. p. 120—121⁰ (from ethanol). Lit.^{13,14} m. p. 118—119⁰. IR spectrum of picrate (KBr pellet): 1690 m (C = NH)⁺ cm.⁻¹.

2-Isopropylpiperidine (XVI)

A solution of compound XV (1.1 g.) in glacial acetic acid (10 ml.) containing platinum oxide (0.2 g.) was hydrogenated at atmospheric pressure of hydrogen. The uptake of 1 mole equivalent of hydrogen required 40—45 minutes. The catalyst was removed by suction and the solvent was distilled at atmospheric pressure over a Vigreux column. The residue was treated with a solution of picric acid in ether. The picrate has m. p. 137—138⁰ (from ethanol). Lit.^{13,15} m. p. 137—138⁰. Hydrochloride: m. p. 215⁰ (from ethanol-acetone). Lit.^{13,14} m. p. 210—216⁰.

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IZVOD

Reakcija Reformatskog na alifatične γ - i δ -halogen-nitrile. Dobijanje 2-supstituisanih Δ^1 -pirolina i Δ^1 -piperideina*L. Arsenijević i V. Arsenijević*

Proučavana je reakcija α -brom-estara i cinka sa γ i δ -halogen-nitrilima sa ciljem da se sintetiziraju *N*-heterociklična jedinjenja. Ako se reakcija izvodi u niskoključajućim rastvaračima npr. u etru, tetrahidrofuranu ili benzolu, dobijaju se ω -halogen- β -keto-estri, dok u anizolu nastaje 2-karbetoksi-alkil- Δ^1 -pirolin, odnosno 2-karbetoksi-alkil- Δ^1 -piperidein. Ova poslednja jedinjenja lako gube karbetoksi-grupu zagrevanjem sa 10 *N* sumpornom kiselinom uz nastajanje 2-alkil- Δ^1 -pirolina, odnosno 2-alkil- Δ^1 -piperideina.

Δ^1 -Položaj dvogube veze u pirolinskom i piperideinskom prstenu potvrđen je odsustvom vibracije NH-grupe u IR spektrima a struktura 2-supstituisanih Δ^1 -pirolina potvrđena je i pomoću NMR spektara.

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