were 85–90%. Benzene solutions of the chloro compound (II) were dehydrohalogenated to N-vinyl-2-pyrrolidone (III) using potassium hydroxide, sodium amide or sodium methoxide. Using powdered sodium hydroxide a 76% yield of the alcohol (I) was obtained.

A less attractive method involved the conversion of the chloro compound (II) to the quaternary iodide (IV) with sodium iodide and trimethylamine in acetone. Treatment of a methanolic solution of the quaternary iodide with silver oxide and subsequent distillation afforded an 82% yield of III.

Experimental[5,6]

N-(β-Hydroxyethyl)-2-pyrrolidone (I).—A solution formed by adding 860.0 g. (10.0 moles) of butyrolactone to 750.0 g. (12.3 moles) of 2-aminoethanol was heated at a temperature of 180–190° so that over a period of 20 hours the excess 2-aminoethanol and the liberated water were distilled over. Distillation of the residue afforded 1,135 g. of I (88%), b.p. 142–143° at 2.3 mm.

Anal. Calcd. for $C_6H_{11}O_2N$: C, 55.81; H, 8.53. Found: C, 55.74; H, 8.64.

N-(β-Chloroethyl)-2-pyrrolidone (II).—To a cooled solution of 129.0 g. (1.0 mole) of I in 100 ml. of benzene was added 119.0 g. (1.0 mole) of thionyl chloride at such a rate that the temperature did not go higher than 35°. After the addition, stirring was continued for three hours at room temperature. The benzene was removed under vacuum and distillation of the residue gave 112 g. (76%) of a colorless product which slowly became yellow on standing; b.p. 118–119.5° at 7 mm.

Anal. Calcd. for $C_6H_{10}ClNO$: C, 48.64; H, 6.76; N, 9.46. Found: C, 48.68; H, 6.51; N, 9.42.

Dehydrohalogenation of the Chloro Compound (II) to N-Vinyl-2-pyrrolidone (III). A.—To a solution of 22.2 g. (0.15 mole) of II in a 100 ml. of benzene was added 9.0 g. (0.17 mole) of sodium methoxide. After stirring at room temperature for four hours, the mixture was filtered and the benzene was removed under vacuum. Distillation of the residue yielded 8.1 g. (48%) of III, b.p. 64–66° at 2.0 mm., m.p. 17°.

Anal. Calcd. for C_6H_9NO: C, 64.86; H, 8.11; N, 12.61. Found: C, 64.93; H, 7.88; N, 12.44.

B.—A mixture of 14.8 g. (0.1 mole) of II, 100 ml. of benzene and 3.9 g. (0.1 mole) of sodium amide was refluxed for five hours. After filtering and removing the benzene under vacuum, 6.1 g. (55%) of III was isolated by distillation.

C.—A mixture of 14.8 g. (0.1 mole) of II, 125 ml. of benzene and 6.7 g. (assay 85% KOH, corresponding to 0.1 mole) of potassium hydroxide was refluxed for 22 hours, while the liberated water was collected in a Dean and Stark receiver. The reaction mixture was filtered and concentrated. Distillation afforded 6.2 g. (56%) of III.

Polymerization to polyvinylpyrrolidone was effected by keeping a solution containing 1.0 ml. of III, 1.0 ml. of water, 0.01 ml. of Superoxol and 0.01 ml. of concentrated aqueous ammonium hydroxide at 70°. In a short time the temperature rose spontaneously and the solution became extremely viscous.

It was observed that distillation of II was accompanied by some decomposition losses. In order to obtain better over-all yields a benzene solution of I was treated with thionyl chloride as described above. At the end of the stirring an excess of solid sodium bicarbonate was added, the reaction mixture was filtered, and the conversion to III effected by the treatment with the theoretical amount of potassium hydroxide as described above under method C. In this manner 21.8 g. (49% over-all yield) of III was isolated from 51.6 g. (0.4 mole) of I.

Regeneration of I.—To 14.8 g. (0.1 mole) of N-(β-chloroethyl)-2-pyrrolidone (II) was added a suspension of 4.0 g. (0.1 mole) of finely powdered sodium hydroxide in 100 ml. of benzene and the reaction mixture refluxed for 12 hours. After filtering and removing the benzene, 9.8 g. (76% yield) of I was isolated by distillation.

Formation of the Quaternary, IV.—A solution containing 7.4 g. (0.05 mole) of II and 7.5 g. (0.05 mole) of sodium iodide in 120 ml. of acetone was refluxed for four hours. The resulting reddish solution was filtered and added to 120 ml. of acetone in a 500-ml. centrifuge bottle. To the resulting solution gaseous trimethylamine was introduced for 15 minutes and the bottle stoppered. Within ten hours separation of the quaternary appeared complete. The crystalline precipitate was collected by filtration; yield 7.9 g. (53%). An analytical sample of IV, white plates, m.p. 224–225°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_9H_{19}ION_2$: C, 36.24; H, 6.37; N, 9.39; I, 42.61. Found: C, 36.30; H, 6.42; N, 9.16; I, 42.94.

On standing for several days the quaternary became discolored.

Attempts were made after refluxing II with sodium iodide to isolate the corresponding iodo compound. After removal of the sodium chloride by filtration and the acetone by vacuum evaporation, careful distillation gave a yellow viscous oil, b.p. 125–127.5° at 0.5 mm., corresponding to a 74% conversion to the iodo compound. This freshly distilled product analyzed only closely for N-(β-iodoethyl)-2-pyrrolidone and on standing it assumed a deep red color. If the temperature of the bath on distillation was allowed to rise much over 150° considerable decomposition occurred as evidenced by the deepening color of the distillate. The analytical results reported are those obtained from a freshly redistilled sample.

Anal. Calcd. for $C_6H_{10}INO$: C, 30.13; H, 4.18; N, 5.86; I, 53.1. Found: C, 32.54; H, 4.43; N, 8.34; I, 50.89.

Decomposition of the Quaternary IV.—To a solution of 10.2 g. (0.034 mole) of IV dissolved in 100 ml. of absolute methanol was added 7.0 g. of silver oxide and the resulting mixture allowed to stand overnight in the dark. Filtration and evaporation in the cold gave an amber-colored residue. Distillation yielded 3.1 g. (81%) of III.

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(5) The melting points and boiling points are uncorrected.

(6) All microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Illinois.

Hexahydroindolo[2,3-a]quinolizine[1]

BY WARREN A. RECKHOW AND D. S. TARBELL

RECEIVED MAY 9, 1952

In a program carried out in these laboratories to investigate the relationship between curariform activity and chemical structure, a number of β- and γ-carbolinium salts were synthesized and found to exhibit weak curare activity.[2] It was felt that compounds approaching the structure believed at that time[3] to be present in the calabash curare alkaloids should be synthesized, and some compounds[4] prepared on this basis showed marked curare activity.

A continuation of this approach has led us to prepare the tetracyclic compound hexahydroindolo-[2,3-a]-quinolizine (II).

This compound was readily obtained by application of the Fischer indole synthesis to 1-ketoquinolizidine.[5] The synthesis of the latter by simplified

(1) Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

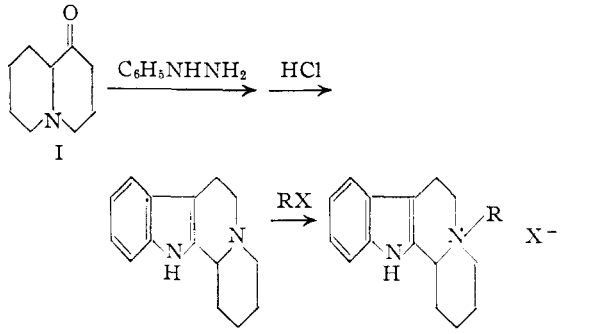
(2) V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2132 (1950).

(3) P. Karrer and H. Schmid, *Helv. Chim. Acta*, **29**, 1853 (1946). More recent work [H. Schmidt, A. Ebnöther and P. Karrer, *ibid.*, **33**, 1486 (1950)] indicates that the earlier ideas on the structure of the calabash curare alkaloids may require considerable modification.

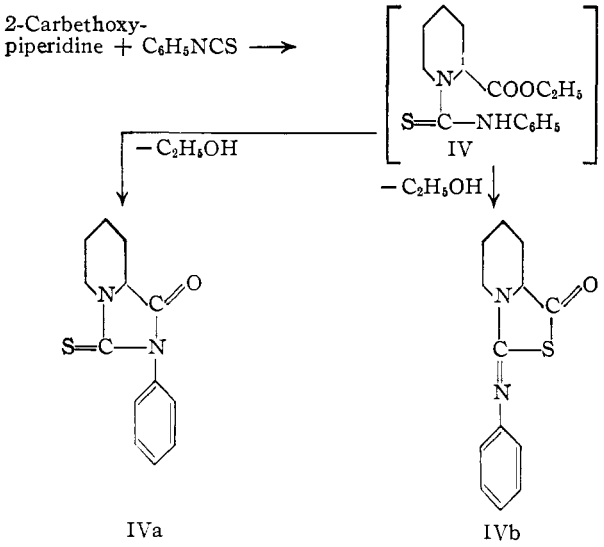
(4) L. E. Craig and D. S. Tarbell, THIS JOURNAL, **71**, 462 (1949).

(5) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 437 (1931). An analogous synthesis of a benzo derivative of II was reported by G. R. Clemo and G. A. Swan, *ibid.*, 617 (1946).

procedures is described in the experimental part; a marked improvement was realized by using ethyl γ-bromobutyrate, which is readily prepared from the commercially available butyrolactone,[6] for the alkylation of 2-carbethoxypiperidine.



An attempt to prepare a solid derivative of 2-carbethoxypiperidine with phenyl isothiocyanate led to a product which had lost the elements of ethanol. Of the two possible structures (IVa and IVb), the latter is preferred because it is more highly conjugated and the compound is white, whereas most 2-thiohydantoins (IVa) are yellow.[7] The ultraviolet absorption spectrum showed peaks at λ 232 mμ and λ 271 mμ, which might be expected for the azomethine and thioester linkages of IVb, but no absorption band in the region of 400 mμ for the thiocarbonyl group of structure IVa.



The quaternary salts IIIa and IIIb were prepared for pharmacological tests. In mice neither salt (IIIa nor IIIb) caused paralysis below the lethal dose. Moderate curariform activity was noted in cats at dosages of 7 mg./kg. and 10 mg./kg., respectively.[8]

(6) We are indebted to the Cliffs Dow Chemical Company for a sample of butyrolactone.

(7) T. B. Johnson and B. H. Nicolet, THIS JOURNAL, **33**, 1973 (1911); H. L. Wheeler and C. A. Brautlecht, *Am. Chem. J.*, **45**, 446 (1911).

(8) Private communication from I. H. Slater, M.D., The University of Rochester School of Medicine and Dentistry.

Experimental[9]

2-Carboxypiperidine.—Picolinic acid[10] was dissolved in 50 ml. of water, and 50 ml. of concentrated hydrochloric acid was added. The reduction was carried out at 50° under three atmospheres pressure of hydrogen in the presence of 0.5 g. of Adams catalyst. Evaporation to dryness of the filtered reaction mixture gave the crude hydrochloride in quantitative yield as white crystals, m.p. 245–250°. A small portion was recrystallized from ethanol–benzene, m.p. 258–261°.[11]

2-Carbethoxypiperidine.—A solution of 700 ml. of absolute ethanol, 100 ml. of benzene, 20 ml. of concentrated sulfuric acid and 66.4 g. (0.4 mole) of the crude hydrochloride salt of 2-carboxypiperidine was heated at reflux for 90 hours. During this time, 10-ml. portions of the ternary azeotropic mixture were distilled out several times. The solvent was removed, the residual acid mixture cooled, and made alkaline by adding excess potassium carbonate solution, care being taken to keep the solution below 5° to prevent formation of the diketopiperazine. The mixture was extracted with benzene and ether, dried and concentrated, and the residue was distilled under reduced pressure. This gave 37.5 g. (60%) of clear colorless oil, b.p. 83–85° (7 mm.), reported[5] b.p. 92° (12 mm.). The hydrochloride was obtained from alcohol–ether as fine white needles, m.p. 202–203°. *Anal.*[12] Calcd. for $C_8H_{16}ClNO_2$: C, 49.75; H, 8.26. Found: C, 50.01; H, 8.41.

Equal amounts of 2-carbethoxypiperidine and phenyl isothiocyanate in alcoholic solution were warmed on a steam-bath for a few minutes. The fine white crystals which formed were collected and recrystallized from ethanol, m.p. 159–159.5°. *Anal.* Calcd. for $C_{15}H_{20}N_2O_2S$ (IV): C, 61.61; H, 6.89. Calcd. for $C_{13}H_{14}N_2OS$ (IVa or IVb): C, 63.39; H, 5.73. Found: C, 63.12, 62.96; H, 5.35, 5.60.

Ethyl γ-Bromobutyrate.[13]—Dry hydrogen bromide was bubbled into 500 ml. of absolute ethanol until 81 g. (1.0 mole) had been absorbed. To this was added 43 g. (0.5 mole) of γ-butyrolactone, and the solution was refluxed on the steam-bath for 4 hours. Excess ethanol was removed, and the residue was distilled under reduced pressure. The product (55 g., 58%) was a clear colorless oil, b.p. 76–78° (7 mm.), $n^{25}D$ 1.4538; the reported values[14] are b.p. 104–105° (28 mm.), $n^{25}D$ 1.4539.

2-Carbethoxy-N-(γ-carbethoxypropyl)-piperidine.—A mixture of 2-carbethoxypiperidine (31.4 g., 0.2 mole), ethyl γ-bromobutyrate (39 g., 0.2 mole), and anhydrous potassium carbonate (27.6 g., 0.2 mole) was stirred and heated on a steam-bath for 45 minutes. The mixture was cooled, water was added, and it was extracted with two 100-ml. portions of benzene. The benzene extracts were combined, washed with water, and concentrated. The product was distilled under reduced pressure as a clear colorless oil, b.p. 159–162° (8–9 mm.). This was redistilled giving 31 g. (57%) of colorless oil, b.p. 162° (8 mm.), $n^{20}D$ 1.4604; the reported[5] b.p. is 169° (14 mm.).

The methiodide was obtained as a white crystalline solid from absolute ethanol, m.p. 147–148°. *Anal.* Calcd. for $C_{15}H_{28}INO_4$: C, 43.59; H, 6.83. Found: C, 43.80; H, 6.77.

1-Ketoquinolizidine (I).—This compound was obtained through a Dieckmann condensation of the above diester as described,[5] except that sodium ethoxide was used as the basic condensing agent, and the reaction was carried out in an atmosphere of nitrogen. The product (72% yield) was obtained as a nearly colorless oil, b.p. 104° (12 mm.), $n^{20}D$ 1.4935; reported[5] b.p. 107° (14 mm.).

The semicarbazone and methiodide derivatives corresponded closely in the melting points with those reported.[5]

(9) All melting points are uncorrected. Analyses by Mrs. G. L. Sauvage and Micro-tech Laboratories.

(10) G. Black, E. Depp and B. B. Corson, *J. Org. Chem.*, **14**, 14 (1949).

(11) This is the m.p. reported by C. M. Stevens and P. B. Ellman, *J. Biol. Chem.*, **182**, 75 (1950), who obtained the product in 55% yield by essentially the above procedure.

(12) The analytical sample was prepared by Dr. W. E. Langeland during another investigation (Ph.D. Thesis, Univ. of Rochester, 1950).

(13) The preparation of methyl γ-bromobutyrate from butyrolactone by a two stage process was described recently by J. F. Tinker, *J. Org. Chem.*, **16**, 1417 (1951).

(14) E. A. Prill and S. M. McElvain, THIS JOURNAL, **55**, 1233 (1933).

Hexahydroindolo-(2,3-a)-quinolizine (II).—1-Ketoquinolizidine (3.06 g., 0.02 mole) and phenylhydrazine (2.4 g., 0.022 mole) were heated together on a steam-bath for 30 minutes. The liberated water was removed under reduced pressure, and the residual material was taken up in 85 ml. of absolute ethanol. The solution was saturated with dry hydrogen chloride, and then refluxed for 3.5 hours. The solution was resaturated with hydrogen chloride after it had stood overnight, and it was then refluxed for an additional hour. The alcohol was removed *in vacuo*, the residue was made basic with potassium carbonate solution, and was extracted with ether and benzene. The organic extracts were combined, washed with water and evaporated in air. Hexane was added and the solid collected on a filter. The product was dried, purified by sublimation at 150° (0.01 mm.), and was obtained as a pale yellow solid (2.1 g., 46%), m.p. 144–149°. The analytical sample was recrystallized twice from hexane, m.p. 148–151°. *Anal.* Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02. Found: C, 79.54; H, 8.39.

The picrate was obtained from ethanol, m.p. 228–230°. *Anal.* Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65. Found: C, 55.30; H, 4.63.

The Methiodide (IIIa).—The indolo-(2,3-a)-quinolizidine (0.567 g., 0.0025 mole) and an excess of methyl iodide were added to 25 ml. of ethyl acetate. The mixture was allowed to stand at room temperature for an hour, and the light tan precipitate was collected. The crude product (m.p. 150–160°) was taken up in 20 ml. of methanol, treated with decolorizing charcoal, concentrated to a few ml., and the product precipitated by adding ether. After three such treatments, 0.570 g. (62%) of nearly colorless amorphous material was obtained, m.p. 160–162°. *Anal.* Calcd for $C_{16}H_{21}IN_2 \cdot {}^1/_2H_2O$: C, 50.94; H, 5.84. Found: C, 50.60; H, 5.77.

The Benzyl Quaternary Salt (IIIb).—Sixty-six mg. of the indoloquinolizidine (II) was dissolved in 20 ml. of absolute ethanol. To this was added 2 ml. of benzyl chloride, and the solution was refluxed for 30 minutes. The solution was then concentrated to 10 ml., ether was added, and the solution was placed in the refrigerator for three days. The solid was collected and sublimed to give 64 mg. (60%) of pale yellow solid sintering about 190° and resolidifying to give tiny white prisms, m.p. 265° (dec.). It was recrystallized from alcohol-ether and showed the same melting point behavior. *Anal.* Calcd. for $C_{22}H_{23}ClN_2 \cdot H_2O$: C, 67.87; H, 7.50. Found: C, 67.86; H, 7.36.

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Dimethyleneketene: An Attempted Synthesis

BY HARRY M. WALBORSKY

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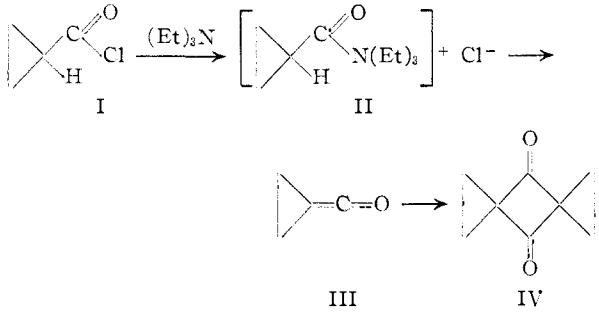
An elegant procedure for the preparation of ketoketene dimers is the reaction of an acid chloride with a tertiary amine yielding a ketoketene, which dimerizes to a 1,3-cyclobutanedione derivative. This method has been used successfully for the preparation of dimers from cyclohexanecarbonyl chloride,[1] cyclopentanecarbonyl chloride[2] and cyclobutanecarbonyl chloride.[3] In spite of the apparent generality of this method, attempts to prepare dimethyleneketene and subsequent dimer from cyclopropanecarbonyl chloride were abortive. An earlier attempt[4] to prepare this ketene by the mixed anhydride method also was futile.

When the acid chloride was added to triethylamine an immediate reaction occurs. The solid precipitate which was formed was undoubtedly the acyl quaternary ammonium salt[5] (II). When a sample of II was placed in aniline the anilide of I was formed. However, II did not eliminate triethylamine hydrochloride under the usual conditions to yield dimethyleneketene (III). A change to higher boiling solvents (benzene and xylene) did not effect elimination. In one run, sodium hydride was added to the reaction mixture in the hope that it would remove the α-hydrogen atom and thus promote the reaction, but this also failed.



The failure to obtain III is an excellent example of I-strain.[6] An exocyclic double bond in III would necessitate the conversion of the cyclopropyl carbon from a tetrahedral to a trigonal configuration. The bond angle in cyclopropane (60°) already imposes a certain amount of strain on the tetrahedral form (60 to 109°) but this strain is greatly increased in going to the trigonal form (60 to 120°). Energy considerations would then account for the failure to obtain III under these conditions.

The above considerations are in direct correlation with the facts that cyclopropanone[7] exists only as the hydrate and that nitrocyclopropane[8] is insoluble in bases.

Experimental

In a three-necked flask equipped with stirrer, dropping funnel and condenser were placed 10 g. (0.1 mole) of I and 50 cc. of dry ether. To this mixture, with stirring, was slowly added 12 g. (0.12 mole) of triethylamine. An immediate precipitate was obtained and the mixture was refluxed for 48 hours.

A sample of the mixture was removed and added to aniline. The resultant anilide gave a m.p. and mixed m.p. 111–112°[9] identical with cyclopropanecarboxanilide. To assure the fact that this was a reaction of II with aniline, 0.4 g. of the acid chloride was mixed with 1 cc. of triethylamine and all excess reagent removed *in vacuo*. The dry solid was washed with ether, dried, and reacted with aniline to yield 0.3 g. of anilide, m.p. and mixed m.p. 111–112°.

The remainder of the mixture was poured into ice-cold 50% sulfuric acid and extracted with ether. The ether extract was dried, stripped and residual oil was distilled *in vacuo* to yield 6.8 g. (0.081 mole, 81%) of cyclopropanecarboxylic acid, b.p. 101–102° (41 mm.). The residue did not contain any ketonic material.

The above experiment was modified by changing the solvent to benzene and xylene and placing a Dry Ice trap in the system to collect the ketene as it was formed. No material was found in the trap and only the acid was isolated from the

(1) C. M. Hill, Ph.D. Thesis, Cornell University, 1941.

(2) Unpublished results.

(3) H. M. Walborsky and E. R. Buchman, A.C.S. Meeting, April, 1950.

(4) A. Staudinger, H. Schneider, P. Shotz and P. M. Strong, *Helv. Chim. Acta*, **6**, 294 (1923).

(5) H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949).

(6) H. C. Brown, R. S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(7) P. Lipp, J. Buchkremer and H. Seeles, *Ann.*, **499**, 1 (1932).

(8) Private communication from Dr. H. Shechter, The Ohio State University.

(9) W. Autenrieth, *Ber.*, **38**, 2549 (1905).