ceding runs. One and thirty-one hundredths grams of analytically pure 2-bromo-3,5-dimethyl-4-carbethoxypyrrole prepared according to Corwin and Viohl,[5b] 2.0 g. of technical zinc cyanide and 55 ml. of dry ether (filtered from sodium) were used. Dry hydrogen chloride was passed through the reaction mixture for a total of 70 minutes, the temperature being held below 16°. After the reaction mixture had stood for a few additional minutes, the ether was removed *in vacuo* leaving a viscous red-brown sirup which was subsequently heated to 90° with 70 ml. of water, then cooled to 15°. The crude brown product was filtered, taken up in warm ethanol, then poured with stirring into 70 ml. of aqueous 2% sodium hydroxide. A bright red precipitate formed, and stirring was continued for some time to effect coagulation. The red substance was filtered off by gravity, suspended in a few ml. of ethanol and re-extracted twice more in the same manner with 2% sodium hydroxide solution. All three filtrates upon acidification with acetic acid to a *p*H of 6 to 7 gave precipitates of the aldehyde. After refrigeration the three crops were combined during filtration; weight of crude 2-formyl-3,5-dimethyl-4-carbethoxypyrrole (XIV), 385 mg. or 37% yield of material melting at 158–164.5°[20] with previous softening. Recrystallization from ethanol–water, then from isoöctane raised the melting point to 165.5–166°[21]; mixed melting point with authentic XIV prepared by the method of Corwin and Andrews,[15] 165–166°.[21]

2-Formyl-3-methyl-4-carbethoxy-5-chloropyrrole (XII).—To a solution of 1.34 g. of 2-formyl-3-methyl-4-carbethoxypyrrole in 6 ml. of glacial acetic acid at room temperature was added dropwise with stirring a solution of 0.65 ml. of sulfuryl chloride in 3 ml. of glacial acetic acid. The addition was carried out during 5 minutes, and the mixture was stirred for 5 more minutes, then poured cautiously with stirring into a solution of 20 g. of sodium bicarbonate in 100 ml. of water. After refrigerating briefly the light orange precipitate which had separated was filtered off, washed and pressed. To remove any starting aldehyde still present the crude product was taken up in minimum boiling ethanol, then poured with stirring into a solution of 5.1 g. of sodium carbonate monohydrate in 83 ml. of water. After a few minutes stirring the mixture was filtered to remove the reddish precipitate. The crude chloroaldehyde separated from the filtrate upon neutralization to a *p*H of 7 with acetic acid. After refrigerating for a short time the product was filtered off and washed. Repeated recrystallization from ethanol–water afforded the analytically pure chloroaldehyde XII melting at 173.5–174.5° with previous sintering at 169–170°.[21]

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68; C_2H_5O, 20.90. Found: C, 50.12; H, 4.63; C_2H_5O, 20.85.

2-Iodo-3-methyl-4-carbethoxy-5-formylpyrrole (XVII).—Two and five-tenths grams of 2-carboxy-3-methyl-4-carbethoxy-5-formylpyrrole was heated with 10 ml. of methanol to the boiling point. Three grams of sodium bicarbonate was then added, and the mixture was shaken to complete neutralization of the acid. Two and eight-tenths grams of iodine was then added, and the mixture was boiled for several minutes. Upon pouring into 100 ml. of ice-water a brown gummy mass separated. After addition of 1 g. of potassium iodide, the mixture was reheated to near boiling with frequent shaking, then cooled and allowed to stand overnight at room temperature. In order to effect purification of the crude brownish solid which had separated out, this material was filtered off and stirred for about one-half hour with 150 ml. of aqueous 1% sodium hydroxide, then filtered. Acidification of the filtrate with glacial acetic acid to a *p*H of 5 produced a precipitate of the iodoaldehyde. After filtration the crude product was dried *in vacuo*; yield 2.3 g. or 67%. One recrystallization from ethanol followed by two more from toluene–isoöctane gave the analytically pure iodoaldehyde melting at 178–179°[21] with previous sintering.

Anal. Calcd. for $C_9H_{10}O_3NI$: C, 35.20; H, 3.28; C_2H_5O, 14.67. Found: C, 35.20, 35.05; H, 3.31, 3.33; C_2H_5O, 14.42.

3-Methyl-4-carbethoxy-5-formylpyrrole (XVI).—Three hundred eighty-three milligrams of 2-iodo-3-methyl-4-carbethoxy-5-formylpyrrole, 156 mg. of magnesium oxide, 309 mg. of 5% palladium-on-carbon and 5 ml. of methanol were placed in a semi-micro hydrogenation vessel. Shaking was begun at a pressure of 17.5 lb. of hydrogen (2.8 lb. gage). Twenty-two hours later the hydrogen uptake had ceased and the reaction mixture was filtered to remove the catalyst. The catalyst was washed with 2 ml. of methanol, and a few drops of aqueous 0.1 *N* sodium thiosulfate were added to the filtrate to prevent reoxidation of iodide ion. Fifty milliliters of water was then added and the mixture was refrigerated. The crude aldehyde was filtered off and dried *in vacuo*; weight of product 83 mg. An additional 30 mg. separated from the filtrate on long standing; total yield 50%. The first crop of aldehyde was recrystallized for analysis from isoöctane, m.p. 143–144°.[21]

Anal. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; C_2H_5O, 24.87. Found: C, 59.49, 59.54; H, 6.03, 6.06; C_2H_5O, 24.68.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND THE STERLING-WINTHROP RESEARCH INSTITUTE]

Synthesis of N-Methylmorphinane

BY C. F. KOELSCH AND N. F. ALBERTSON

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Isoquinoline has been converted to N-methylmorphinane by the reaction sequence outlined below.

The synthesis of N-methylmorphinane from isoquinoline as outlined below was begun by the senior author (C.F.K.) in March, 1947, and carried as far as the betaine, VI, before learning of Grewe's successful synthesis of X.[1] Experimental work was discontinued until the junior author became interested in this field and undertook to try the remaining steps. Because the recent successes of others[2] have made this synthesis chiefly of academic interest, time was not spent in improving yields. However, some of the steps may be of general interest.

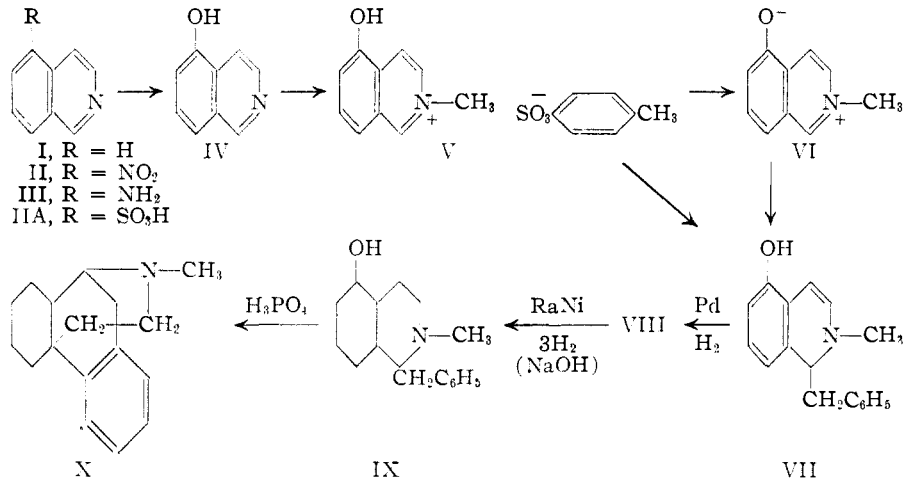
The 5-hydroxyisoquinoline was prepared in 56% over-all yield from isoquinoline *via* the nitro and amino intermediates, but on a larger scale the preparation *via* the sulfonic acid, IIA, in 48% over-all yield was more convenient. Also it proved to be simpler to prepare VII directly from V rather than to prepare the betaine, which forms a hydrate that cannot be dehydrated without decomposition.[3]

Reduction of 1-benzyl-2-methyl-5-hydroxy-1,2,-3,4-tetrahydroisoquinoline (VIII) with hydrogen in the presence of Adams platinum oxide in acetic acid led to reduction of the unsubstituted benzene

(1) R. Grewe, *Naturwissenschaften*, **33**, 333 (1946). See also R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

(2) (a) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950). (b) R. Grewe, H. Pohlmann and M. Schnoor, *Ber.*, **84**, 527 (1951). A convenient synthesis of N-methylisomorphinane has also been reported by M. Gates, R. Woodward, W. Newhall and R. Kunzli, THIS JOURNAL, **72**, 1141 (1950). The method has been applied to the synthesis of morphine by M. Gates and G. Tschudi, *ibid.*, **74**, 1109 (1952).

(3) A. Claus and C. Gutzeit, *J. prakt. Chem.*, [2] **52**, 10 (1895).



ring to give 1-cyclohexylmethyl-2-methyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline; the phenolic ring was not reduced. However, reduction of VIII in sodium hydroxide solution with Raney nickel catalyst led to the desired reduction of the phenolic ring.

Dehydration and cyclization of IX in phosphoric acid[4] gave a mixture of $C_{17}H_{25}N$ isomers from which no crystalline picrate, picrolonate or hydrochloride could be obtained. A pharmacological test showed high analgesic potency.[5] A sample chromatographed on alumina gave three fractions, the second and third of which crystallized to N-methylmorphinane. Presumably the isomer removed by chromatography is largely, if not entirely, 1-benzyl-2-methyl-Δ^5-octahydroisoquinoline.

The identity of the N-methylmorphinane was confirmed by a mixed melting point of the picrate with a sample of Dr. Grewe's N-methylmorphinane picrate.

Experimental

5-Nitroisoquinoline (II) was obtained in 93–95% yield by the method of LeFevre and LeFevre.[6]

5-Aminoisoquinoline (III) was prepared in 78% yield by reduction of 5-nitroisoquinoline with a palladium catalyst according to the procedure of Misani and Bogert.[7] The nitro compound was also reduced with tin and hydrochloric acid.[8] To a solution of 105 g. of the nitro compound in 500 ml. of hydrochloric acid and 300 ml. of water there was added 120 g. of tin in portions. The temperature was kept near 100° by slight cooling. The mixture was then poured into a solution of 350 g. of sodium hydroxide in 1500 ml. of water, and the product was removed and distilled, b.p. 200° at 15 mm. The yield was 72.7 g. or 76% of pale yellow crystals. A second experiment gave identical results. The crystals melted at 125–127° when recrystallized from ligroin.

5-Hydroxyisoquinoline (IV) **(from amine)** was obtained by the following modification of the method of Claus and Gutzeit.[3] A mixture of 15 g. of 5-aminoisoquinoline, 20 ml. of water and 25 ml. of concentrated hydrochloric acid was heated in a sealed tube at 240° for five hours. The contents of four such tubes were combined and poured into 100 ml. of concentrated ammonia, diluted with some water. The black precipitate was coagulated by boiling, then washed and dried, giving 57.5 g., or 96% of crude product. A second series of four similar tubes gave 57.1 g. The crude phenol was purified by distillation at 25 mm. in an apparatus consisting of two bulbs connected by a wide tube; 10 g. of crude material gave an average of 8 g. of nearly colorless product, m.p. *ca.* 225–228°.

5-Hydroxyisoquinoline was also obtained in 30% yield by heating 3 g. of 5-aminoisoquinoline with 20 ml. of 85% phosphoric acid for 20 hours at 165°.

Isoquinoline-5-sulfonic acid (IIA) was prepared by a modification of the method of Weissgerber[9] in which high yield was sacrificed for simplicity of preparation. To 183 g. of concentrated sulfuric acid was added 221 g. of practical grade isoquinoline. The product was broken up into lumps which were added to 561 g. of 65% fuming sulfuric acid with swirling in a Dry Ice–chloroform-bath to keep the temperature below 40°. The solution was allowed to stand at room temperature for 24 hours and poured onto 1930 g. of ice. The product separated as white needles in yields of 200 to 210 g. (56–59%).

5-Hydroxyisoquinoline (IV) **(from sulfonic acid).**—The following modification of the method of Robinson[10] gave considerably higher yields. A mixture of 210 g. of potassium hydroxide and 210 g. of sodium hydroxide was heated to 170° and 126 g. of sulfonic acid was added while the temperature rose to 200°. The temperature was maintained at 210 to 230° for 10 minutes while the color of the mixture turned from yellow to brown. There was some foaming. The reaction mixture was added to 1200 ml. of water and 440 ml. of acetic acid. The crude product, 80.5 g., was dissolved in 200 ml. of water and 58 ml. of concentrated hydrochloric acid, filtered and reprecipitated with 58 ml. of concentrated ammonium hydroxide. The yield amounted to 73.2 g. Other experiments gave yields of 81–83%, except in one case in which the heating period was extended. This experiment gave a considerable amount (332 g. from 685 g. of sulfonic acid) of 1,5-isoquinolindiol,[9] readily separated from the product by its insolubility in hydrochloric acid.

5-Hydroxyisoquinoline metho-*p*-toluenesulfonate (V) was obtained by warming gently 17 g. of the base with 22 g. of methyl *p*-toluenesulfonate. The reaction is exothermic but easily controlled on this scale. The product was recrystallized from alcohol–ether; yield 30 to 31.6 g. of yellow needles, m.p. 184–187° (78–81%). For preparation on a larger scale the ester was added gradually to a refluxing, stirred suspension of the base in methanol. The yields were the same.

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; S, 9.67. Found: C, 61.90; H, 5.03; S, 9.60.

1-Benzyl-2-methyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline (VIII).—To 14.5 g. of magnesium turnings suspended in 750 ml. of ether was added 75.9 g. of benzyl chloride over a 30-minute period. The solution was stirred for ten minutes more and then 66 g. of dry, powdered 5-hydroxyisoquinoline metho-*p*-toluenesulfonate added over a 20-minute period. Stirring was continued for 20 minutes more and the reaction mixture was then poured onto 1 kg. of ice and water containing 105 ml. of concentrated hydrochloric acid. Insoluble material was removed by filtration, the ether layer separated and the water layer extracted again with ether. The addition of 105 ml. of concentrated ammonium hydroxide liberated the product as a pale yellow oil, but it rapidly darkened on exposure to air. The product was taken up in ether and the aqueous phase extracted several times more with ether. The ether extracts were dried, filtered and concentrated *in vacuo* to give 25.3 to 28.6 g. of purple sirup (VII). This was immediately hydrogenated in 100 ml. of acetic acid using a palladium-on-charcoal catalyst and heating to 50° at 50 lb. initial hydrogen pressure. Removal of

(4) It was originally planned to use sulfuric acid, but Grewe's results[1] suggested that phosphoric acid might be preferable.

(5) The authors are indebted to Dr. J. R. Lewis and Mr. W. McKeon for pharmacological data.

(6) C. LeFevre and R. LeFevre, *J. Chem. Soc.*, 1475 (1935).

(7) F. Misani and M. Bogert, *J. Org. Chem.*, **10**, 358 (1945).

(8) Cf. P. Fortner, *Monatsh.*, **14**, 159 (1893).

(9) R. Weissgerber, *Ber.*, **47**, 3175 (1914).

(10) R. Robinson, THIS JOURNAL, **69**, 1942 (1947).

the catalyst and solvent left a red sirup which readily crystallized to a yellow solid when heated with 100 ml. of water and 20 ml. of concentrated ammonium hydroxide. Most of the color could be removed by slurrying with cold ethyl acetate. Three experiments gave 25.2, 23.2 and 26.5 g. of crude product (melting above 146°) suitable for the next step. A sample recrystallized from ethanol melted at 154–155° uncor.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.11; H, 7.44; N, 5.37.

1-Cyclohexylmethyl-5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.—Reduction of 12.7 g. of the above 1-benzyl compound in 100 ml. of acetic acid in the presence of 0.4 g. of Adams platinum oxide catalyst took about eight hours at 50° and 50 lb. initial hydrogen pressure; yield 10.7 g. melting at 147–149° uncor. A sample, recrystallized from methanol, melted at 153.6–154.6° cor. Both the solubility in sodium hydroxide, the melting point and the ultraviolet absorption spectra of this compound indicated that the benzene ring and not the phenolic ring had been reduced.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.40. Found: C, 78.61; H, 9.53; N, 5.28.

The hydrochloride, recrystallized from isopropyl alcohol, melted at 264.0–266.0° cor.

Anal. Calcd. for $C_{17}H_{25}NO \cdot HCl$: C, 69.00; H, 8.86; N, 4.73; Cl, 11.98. Found: C, 68.97; H, 8.58; N, 4.65; Cl, 12.07.

1-Benzyl-2-methyl-5-hydroxydecahydroisoquinoline (IX).—A solution of 26.5 g. of 1-benzyl-2-methyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline in 150 ml. of 2 *N* sodium hydroxide to which Raney nickel catalyst had been added was shaken with hydrogen at an initial pressure of 825 lb. The temperature was raised until reduction started (at 175°) and then gradually increased to 195°. Reduction was continued for six hours. The product separated as a separate phase. It was extracted with benzene and distilled at 0.4 mm. to give 14.8 g. boiling from 120 to 143°. Since not all of this material was soluble in dilute hydrochloric acid, 6.6 g. of the product was taken up in benzene and washed with 8 ml. of phosphoric acid in water. Addition of potassium carbonate yielded 3.7 g. of oil which was distilled; b.p. 141–146° (0.3 mm.). The product, though not analytically pure, was used for the last step without further purification.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.40. Found: C, 79.95; H, 10.20; N, 5.93.

N-Methylmorphinane (X).—A solution of 2.7 g. of the decahydro compound in 25 ml. of 85% phosphoric acid was refluxed for 70 hours and then poured onto ice. The aqueous phase was extracted with ether and the product then salted out with potassium carbonate. It was taken up in ether, dried and distilled to give 1.0 g. of pale yellow oil boiling at 130–132° at 0.7 mm. The odor was quite similar to several derivatives of the 1-azabicyclo[3.3.1]nonane ring system which have been prepared by one of us.

Anal. Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.33; H, 9.50; N, 5.51.

Failure to form a crystalline derivative (picrate, hydrochloride, picrolonate) indicated that the product was a mixture. A test showed high analgesic activity for the mixture. The product decolorized permanganate readily suggesting the presence of 1-benzyl-2-methyl-Δ^5-octahydroisoquinoline.

The material was chromatographed by pouring a solution of 0.484 g. in 3.7 ml. of low boiling petroleum ether onto the top of 30 g. of aluminum oxide in a 50-ml. buret. The column was eluted with 20-ml. portions of low boiling petroleum ether to which was added 0, 0, 0, 1, 3, 5, 5 and 5 ml. of ether, respectively. The last three solvents eluted 0.10, 0.12 and 0.12 g. The latter two samples crystallized; m.p. 50–54°. They gave a picrate melting at 172–174°, not depressed when mixed with a sample of Dr. Grewe's N-methylmorphinane picrate kindly furnished to us by Dr. Nolte. The first fraction gave a picrate which, after one recrystallization, softened at 171° and melted at 178°. It gave a large melting point depression with N-methylmorphinane picrate and was not further investigated.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

N-Substituted Lactamides

BY M. L. FEIN AND E. M. FILACHIONE

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N,N-Disubstituted lactamides that are difficult to obtain by aminolysis of methyl lactate with secondary amines were readily prepared by dehydration of the lactic acid-secondary amine salt. The preparation and properties of various dialkyl, alkyl aryl, aralkyl and hydroxyalkyl lactamides are reported.

Previous papers from this Laboratory reported that N-monosubstituted lactamides can be prepared in excellent yields by aminolysis of methyl lactate with primary aliphatic amines.[2,3] The reaction is simple, proceeds readily at room temperature, and in most instances results in almost quantitative yields of the substituted lactamide. With a few exceptions, the N,N-disubstituted lactamides, however, were extremely difficult to prepare by such an aminolysis reaction. The notable exceptions were aminolysis of methyl lactate with dimethylamine, piperidine, morpholine, pyrrolidine and diethanolamine, in which instances the yields of N,N-disubstituted lactamide were extremely high.[4,5,6] Thus, N,N-dimethyllactamide was obtained in 90% yield, whereas N,N-dibutyllactamide was virtually unobtainable by aminolysis of methyl lactate with the appropriate secondary amine.

In the study reported here, the preparation of dialkyl lactamides by dehydration of the lactic acid-secondary amine salt was investigated. This general method for the preparation of amides has been applied previously in making aromatic derivatives such as lactanilide.[7,8] N,N-Dibutyllactamide has been suggested as a plasticizer for

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

(3) W. P. Ratchford and C. H. Fisher, *ibid.*, **15**, 317 (1950).

(4) W. P. Ratchford and C. H. Fisher, THIS JOURNAL, **69**, 1911 (1947).

(5) W. P. Ratchford, J. H. Lengel and C. H. Fisher, *ibid.*, **71**, 647 (1949).

(6) W. P. Ratchford, *Ind. Eng. Chem.*, **42**, 1565 (1950).

(7) Leipen, *Monatsh.*, **9**, 45 (1888).

(8) C. A. Bischoff and P. Walden, *Ann.*, **279**, 71 (1894).