4-Acetylaminofluorene-N^{15}[1]

EUGENE SAWICKI, F. E. RAY, AND VERA GLOCKLIN[2]

Received October 7, 1955

4-Acetylaminofluorene, an isomer of the carcinogenic 2-acetylaminofluorene,[3] has been prepared from 2,5-dinitrofluorene[4] and from 4-nitrophenanthraquinone.[5]

Although the main purpose of our research was to prepare the N^{15} compound for eventual metabolic study the procedure can be used for an alternative simple preparation of 4-acetylaminofluorene.

EXPERIMENTAL[6]

Diphenic acid. This acid can be prepared from anthranilic acid[7] but as pure phenanthrene[8] was on hand, it was prepared by a procedure which offers the following two advantages: (1) simplicity of operation and (2) faster preparation of large quantities of pure acid. To a warm stirred solution of 126 g. of *pure* phenanthrene in 1 liter of acetic acid was added 950 ml. of 30% hydrogen peroxide. The temperature was kept at 90–95° for 1–2 hours. Then 200 ml. of acetic anhydride was added (exothermic reaction). The temperature was kept at 90–95° for 3–5 more hours. The mixture was cooled with an ice-salt bath and filtered. Solution of the crystals in aqueous sodium carbonate, followed by filtration and treatment of the cold filtrate with a slight excess of hydrochloric acid gave 95 g. (55%) of white crystals, m.p. 229–232°. Lit. m.p. 226–228°.[7]

4-Carbamylfluorene-N^{15}. The diphenic acid was cyclized with sulfuric acid to 4-fluorenonecarboxylic acid, m.p. 223–224°.[9] The fluorenone was reduced with hydrazine and sodium hydroxide in ethylene glycol solution by the standard procedure to 4-fluorenecarboxylic acid in 65% yield and m.p. 190–191° (toluene). Lit. m.p. 191–192°.[10] Treatment of the latter acid with thionyl chloride formed the 4-fluorenecarbonyl chloride in 95% yield and m.p. 75–76° (hexane). Lit. m.p. 75°.[11]

To a solution of 0.81 g. of ammonium nitrate (containing 64 atoms-% N^{15} as $N^{15}H_4$) in 10 ml. of anhydrous dimethylformamide was added 5 ml. of triethylamine. The flask containing the mixture was stoppered and cooled in an ice-salt bath with frequent shaking for 5–10 minutes. Then a solution of 2.52 g. of 4-fluorenecarbonyl chloride in 10 ml. of dimethylformamide was quickly added. Again the flask was stoppered, cooled, and shaken vigorously for 15 minutes. The mixture was allowed to come to room temperature with occasional shaking over 30 minutes. The addition of 100 ml. of 5% aqueous sodium hydroxide caused an immediate precipitation of product; 1.8 g., (86%), m.p. 216–218°. A small amount, when crystallized from alcohol, yielded colorless needles, m.p. 218–220°. Lit. m.p. 215–216°.[11]

For the preparation of base material in 90–95% yield, an acetone solution of the carbonyl chloride was added to excess, cold, concentrated ammonia (*d.* 0.9).[11] From this amide, base 4-acetylaminofluorene can be obtained readily.

Methyl N-4-fluorenyl carbamate-N^{15}. A hot solution of 1.2 g. of 4-carbamylfluorene-N^{15} in 60 ml. of methanol was added to a cold stirred solution of 1.6 g. of sodium in 100 ml. of methanol. To the cold mixture 0.64 ml. of bromine was added dropwise. The liquid was refluxed for 20 minutes, evaporated to $^2/_3$ volume and poured into 800 ml. of water. Filtration gave 1.25 g. (91%) of colorless crystals, m.p. 121–123°. A small amount, when crystallized from hexane, gave colorless needles, m.p. 124–125°.

Anal. Calc'd for $C_{15}H_{13}N^{15}O$: C, 75.0; H, 5.4. Found: C, 75.3; H, 5.4.

4-Aminofluorene-N^{15}. To a refluxing solution of 1.2 g. of methyl N-4-fluorenyl carbamate-N^{15} in 10 ml. of 95% ethanol was added dropwise a solution of 5.6 g. of potassium hydroxide in 20 ml. of water. The mixture was refluxed for 30 minutes and 30 ml. of water was added. Cooling followed by filtration gave 0.87 g. (96%) of colorless needles, m.p. 112–114°. A small amount, when crystallized from hexane, gave a melting point of 115–116°. Lit. m.p. 115–116°,[4] 116–117°.[5]

4-Acetylaminofluorene-N^{15}. A solution of the amine in benzene was acetylated with acetic anhydride.[4] A 90–95% yield of colorless needles, m.p. 197.5–198°, was obtained. Crystallization from heptane-benzene gave an 85–90% yield of long fan-shaped masses of fine needles, m.p. 200–201°. Lit. m.p. 200–201°,[4] 204–205°.[5]

CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

(1) This investigation was supported by research grant C-1066 from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) Physiology Department, Yale University, New Haven, Connecticut.

(3) Wilson, DeEds, and Cox, Jr., *Cancer Research*, **1**, 595 (1941).

(4) Weisburger, Weisburger, and Morris, *J. Am. Chem. Soc.*, **74**, 4540 (1952).

(5) Neish, *Rec. trav. chim.*, **72**, 899 (1953).

(6) All melting points are uncorrected. Analyses are by the Peninsular ChemResearch, Inc., Gainesville, Florida.

(7) Huntress, *Org. Syntheses*, Coll. Vol. I, 216 (1932).

(8) Bachmann, *J. Am. Chem. Soc.*, **57**, 555 (1935).

(9) Graebe and Aubin, *Ann.*, **247**, 257 (1888).

(10) Bachmann and Sheehan, *J. Am. Chem. Soc.*, **62**, 2687 (1940).

(11) Bachmann and Brockway, *J. Org. Chem.*, **13**, 384 (1948).

Quinoxaline Studies. VIII. Decahydroquinoxaline[1]

WARNER CHRISTIE, WILMER ROHDE, AND HARRY P. SCHULTZ

Received October 10, 1955

Mousseron and Combes[2] reported the preparation of 2,3-tetramethylenepiperazine by ammonolysis of 2-(β-chloroethylamino)cyclohexyl chloride. Unfortunately they reported no physical properties for the substance, but only the m.p. of a nitroso derivative. Beck, Hamlin, and Weston[3] prepared decahydroquinoxaline by a ring closure of 2-(β-aminoethylamino)cyclohexanol.

The purpose of this paper is to report the synthesis of decahydroquinoxaline by the stepwise reduction of quinoxaline to tetrahydroquinoxaline and thence to decahydroquinoxaline.

Negative results were obtained when quinox-

(1) Abstracted from theses by W. Christie and W. Rohde in partial fulfillment of requirements for the degree of Master of Science at the University of Miami.

(2) Mousseron and Combes, *Bull. soc. chim. France*, 82, (1947).

(3) Beck, Hamlin, and Weston, *J. Am. Chem. Soc.*, **74**, 607 (1952).

aline was reduced at low pressure in acetic acid over platinum oxide, in hydrochloric acid over palladium chloride on charcoal, and in hydrochloric acid over platinum oxide. Hydrogen uptake corresponded to no definite compound, much tar was formed, and no single pure substance was isolated from any of these runs. When quinoxaline was reduced in an absolute ethanolic hydrogen chloride solution over platinum oxide, only one atom of hydrogen per molecule of quinoxaline was absorbed by the reduction mixture, giving an intensely blue solid whose color faded upon exposure to air. The nature of this possible meroquinoid material is still the subject of investigation. Pure tetrahydroquinoxaline was obtained in 85 to 90% yields when quinoxaline was reduced at low pressure in a basic solution of ethanol over Raney nickel catalyst.

Continuing research demonstrated that tetrahydroquinoxaline could be reduced to decahydroquinoxaline in good yield over platinum oxide in acid solution. Yields of decahydroquinoxaline approaching quantitative were obtained in an absolute ethanolic hydrogen chloride solution; in an ethanolic aqueous hydrochloric acid solution considerable hydrogenolysis occurred to give approximately 65% of decahydroquinoxaline and 35% of N-cyclohexylethylenediamine; in aqueous hydrochloric acid much excess hydrogen was taken up by the reaction mixture, decahydroquinoxaline was obtained in about 50% yield, N-cyclohexylethylenediamine in about 10% yield, and neutral substances were also obtained, one of which was cyclohexanol.

The decahydroquinoxaline prepared in this laboratory had the same physical properties as did the substance reported by Beck, Hamlin, and Weston.[3] Based upon the melting points of the nitroso derivatives, however, the decahydroquinoxaline prepared in this laboratory was different from the substance Mousseron and Combes[2] termed tetramethylenepiperazine.

In view of the possibility in the bicyclic fused ring system of decahydroquinoxaline for geometrical isomerism, it may be that the French authors described a geometrical isomer of the decahydroquinoxaline reported in this paper and by Beck, Hamlin, and Weston.[3] Inasmuch as the final reduction of tetrahydroquinoxaline over platinum oxide was done in an acid medium, it may be expected on the basis of Linstead's[4] findings that *cis*-decahydroquinoxaline was obtained in this laboratory. Should such be true, Mousseron and Combes[2] may have prepared the *trans*-decahydroquinoxaline.

EXPERIMENTAL PROCEDURES

Quinoxaline. Quinoxaline, b.p. 230°, was prepared by the procedure of Cavagnol and Wiselogle.[5]

1,2,3,4-Tetrahydroquinoxaline. Into a 500-ml. Parr low pressure reduction flask were placed 35 g. of quinoxaline, 125 ml. of 95% ethanol, 2 g. of potassium hydroxide, and approximately 3 g. of Raney nickel catalyst.[6] The theoretical quantity of hydrogen was absorbed in 4 hrs. at 30° and 80 p.s.i. After the reduction was completed, the contents of the bottle were heated on a steam-bath until all organic material went into solution. The catalyst was filtered off. After evaporation of the solvent to $^1/_2$ the original volume, the filtrate was cooled in ice, filtered, rinsed, and dried to give 32.6 g. of material, m.p. 97–98°.

This product was recrystallized from petroleum ether (b.p. 90–120°) giving 31.2 g. (86%) of white crystals m.p. 99–99.5°. Merz and Ris[7] reported m.p. 96.5–97° for 1,2,3,4-tetrahydroquinoxaline.

Decahydroquinoxaline. Into a Parr reduction flask were placed 9.2 g. of tetrahydroquinoxaline, 75 ml. of 3 *N* absolute ethanolic hydrogen chloride solution, and 0.4 g. of platinum oxide catalyst.[8] Reduction was complete in 4 hrs. at 60° and 50–80 p.s.i. Enough water was added to the reduction mixture to dissolve the salt and the catalyst was filtered off. The filtrate was evaporated to dryness to give 14.5 g. (99%) of crude decahydroquinoxaline dihydrochloride m.p. 320–334°.

This material was transferred to a separatory-funnel and was treated with 40 ml. of water and 9 g. of sodium hydroxide. The light yellow oil which separated was extracted with one 50-ml. and two 20-ml. portions of benzene. The combined benzene extracts were placed in a separatory-funnel and dried over sodium hydroxide for 24 hrs.; water collecting in the bottom of the funnel was removed periodically. After removal of the solvent, the warm residual amine was taken up in 10 ml. of petroleum ether (b.p. 40–60°), cooled, filtered, rinsed, and dried to give 2.6 g. of white crystals m.p. 144–147°. This material was recrystallized thrice more, with charcoal treatment, to give 1.2 g. (12.5%) of decahydroquinoxaline m.p. 152.5–153°. The micro b.p. of this material was 228–228.5°/761.5 mm. Beck, *et al.*[3] reported m.p. 150–151° for decahydroquinoxaline.

Anal. Calc'd for $C_8H_{16}N_2$: C, 68.51; H, 11.50; N, 19.98; N.E. 70.11. Found: C, 68.41; H, 11.68; N, 19.87; N.E. 69.99.

Decahydroquinoxaline dihydrochloride was prepared and recrystallized by solution in 80% ethanol, then addition to absolute ethanol; m.p. 385–390° dec. Beck, *et al.*[3] reported decahydroquinoxaline dihydrochloride m.p. 365° dec.

Anal. Calc'd for $C_8H_{18}Cl_2N_2$: Cl, 33.27. Found: Cl, 33.38, 33.30.

Decahydroquinoxaline dipicrate was prepared from the pure amine; recrystallized from water, m.p. 301–303° dec., darkening at 296°.

Anal. Calc'd for $C_{20}H_{22}N_8O_{14}$: N, 18.73. Found: N, 18.68, 18.66.

N,N'-Dinitrosodecahydroquinoxaline was prepared by treating a cold hydrochloric acid solution of the amine with cold sodium nitrite solution. Crude material of m.p. 109–111° gave a final m.p. 110–111° when recrystallized from 1:1 ethanol-water. Mousseron and Combes[2] reported m.p. 160° for a nitroso derivative of their 2,3-tetramethylenepiperazine.

Anal. Calc'd for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12. Found: C, 48.74; H, 6.74.

N-Cyclohexylethylenediamine. Into a 500-ml. Parr low pressure reduction flask were placed 20 g. of tetrahydroquinoxaline, 120 ml. of 95% ethanol, 35 ml. of hydrochloric acid (*sp. gr.* 1.19), and 0.7 g. of platinum oxide catalyst.[8] Reduction took place in 5 hrs. at 50° and 50 to 80 p.s.i. The warm reaction mixture was filtered, washing the residual catalyst with a few milliliters of water to dissolve any salts that might have crystallized.

To the filtrate was added a solution of 600 ml. of 95%

(4) Linstead, Doering, David, Levine, and Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(5) Cavagnol and Wiselogle, *J. Am. Chem. Soc.*, **69**, 796 (1947).

(6) Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(7) Merz and Ris, *Ber.*, **20**, 1197 (1887).

(8) Bruce, *J. Am. Chem. Soc.*, **58**, 687 (1936).

ethanol containing 80 g. of picric acid (10% water); the precipitate of decahydroquinoxaline dipicrate was left standing at 10° for 12 hrs., filtered, rinsed with alcohol, and dried to give 56 g. (62%) of light yellow granular microcrystals of decahydroquinoxaline dipicrate m.p. 280° dec. The above filtrate was diluted with 2 volumes of water. After 12 hrs. at 10°, the precipitate of N-cyclohexylethylenediamine dipicrate was filtered, rinsed, and dried to give 24 g. (27%) of yellow needles m.p. 183–187°.

The crude dipicrate was recrystallized from 1200 ml. of water, using charcoal and filter-aid. Three such recrystallizations gave 12 g. of long yellow needles m.p. 192–194°.

Into a 1 l. conical flask were placed 12 g. of purified N-cyclohexylethylenediamine dipicrate, 100 ml. of 95% ethanol, and 10 ml. of hydrochloric acid (*sp. gr.* 1.19). The mixture was heated to boiling, cooled to 60°, and 300 ml. of acetone was added to the reaction mixture. After 12 hrs. at 10°, 3.5 g. of dihydrochloride salt m.p. 178–180° was obtained. This material was recrystallized from 175 ml. of absolute ethanol to give 3.0 g. of N-cyclohexylethylenediamine dihydrochloride m.p. 210–215°.

When the *free amine* was liberated from the dihydrochloride salt in the same way as was decahydroquinoxaline, 4.7 g. of amine b.p. 103°/10 mm. was obtained from 10 g. of salt. This product was dried over sodium and redistilled, giving 4 g. of colorless, very hygroscopic distillate b.p. 93°/5 mm. A micro b.p. determination gave b.p. 188–189°/761.5 mm.; d_4^{25} 0.9190; n_D^{25} 1.4800.

Anal. Calc'd for $C_8H_{18}N_2$: C, 67.58; H, 12.73; N, 19.69; N.E. 71.1. Found: C, 67.63; H, 13.00; N, 19.03; N.E. 70.9.

Pearson, Jones, and Cope[9] reported b.p. 101–102°/14 mm.; n_D^{25} 1.4800; n_4^{25} 0.9153 for N-cyclohexylethylenediamine.

N-Cyclohexylethylenediamine dihydrochloride was prepared from the pure amine and was recrystallized from absolute ethanol to give white crystals m.p. 211–213°.

Anal. Calc'd for $C_8H_{20}Cl_2N_2$: Cl, 32.95. Found: Cl, 32.94, 33.08.

N-Cyclohexylethylenediamine dipicrate was prepared from the pure amine; recrystallized from boiling water, m.p. 192–194°.

Anal. Calc'd for $C_{20}H_{24}N_8O_{14}$: N, 18.67. Found: N, 18.84, 18.70.

Using the same method as was used to prepare the nitroso derivative of decahydroquinoxaline, no nitroso derivative of N-cyclohexylethylenediamine could be prepared.

A sample of N-cyclohexylethylenediamine was prepared by the method of Pearson, *et al.*[9] This material gave a dihydrochloride and a dipicrate of the same m.p. and mixture m.p. as were obtained from the N-cyclohexylethylenediamine prepared in this laboratory.

(9) Pearson, Jones, and Cope, *J. Am. Chem. Soc.*, **68**, 1227 (1946).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MIAMI
CORAL GABLES 46, FLORIDA

Alkylation of α-Substituted Acetoacetic Esters

FREDERICK J. MARSHALL AND WILLIAM N. CANNON

Received October 7, 1955

Many α,α-disubstituted acetoacetic esters have been prepared by a variety of methods.[1] In view of this, when it was desired to have ethyl α-methyl-α-phenylacetoacetate it was surprising to find that no such aryl derivatives have been reported in the literature. Initial attempts at the alkylation of ethyl α-phenylacetoacetate, using the commonly employed sodium ethoxide with ethanol as solvent, produced cleavage of the ester to give ethyl phenylacetate. This methylation was carried out successfully when sodium sand in dioxane was employed as the metalating agent and the product was obtained in 51% yield. Further investigation, however, showed the use of sodium hydride in a (1:1) mixture of benzene and dimethylformamide to be the method of choice.[2] This procedure led to yields of 51–80% (Table I). The utility of this method extends also to the preparation of dialkylacetoacetic esters and gives improvements over previously reported yields (Table I).

Unexpected difficulty was encountered in the unsuccessful attempts at the preparation of ethyl α-(*p*-chlorophenyl)acetoacetate. This was particularly surprising in view of the ease with which the *ortho* isomer was prepared. When ethanolysis of α-(*p*-chlorophenyl)acetoacetonitrile was tried using gaseous hydrogen chloride and ethanol, the O-ethyl derivative of the nitrile was obtained. Treatment of this derivative or the original nitrile with sulfuric acid and ethanol at reflux temperature gave an unidentified product whose properties are described in the Experimental Part.

When, in view of the above difficulties, some of the other esters were subjected to infrared and ultraviolet examination for purposes of reference, it was found that the α-ethyl-α-phenyl and α-(*o*-chlorophenyl)-α-methyl derivatives contained perhaps 5–10% of the O-alkyl derivative. This would appear to depend on both the aryl group present and the entering alkyl group since the methylation of ethyl α-phenylacetoacetate produced no enol ether.

Acknowledgment. The authors are grateful to Dr. H. L. Breunig for preparation of some of the starting materials, to Dr. H. Boaz and Mr. James Forbes for physical chemical data, and to W. L. Brown, H. L. Hunter, G. M. Maciak, and Miss Gloria Beckmann for the microanalyses.

EXPERIMENTAL

Ethyl α-phenylacetoacetate. This material was prepared by ethanolysis of α-phenylacetoacetonitrile[3] according to the method of Kimball, Jefferson, and Pike.[4]

(1) For a general reference see Renfrow and Renfrow, *J. Am. Chem. Soc.*, **68**, 1801 (1946).

(2) Burgstahler, personal communication. See also Stork and Burgstahler, *J. Am. Chem. Soc.*, **73**, 3544 (1951).

(3) Julian, *et al.*, *Org. Syntheses*, Coll. Vol. II, 487 (1943). This nitrile is now available from Benzol Products Co., 237 South Street, Newark 5, New Jersey.

(4) Kimball, Jefferson, and Pike, *Org. Syntheses*, Coll. Vol. II, 284 (1943).

(5) Russell and Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951). These authors reported the compound as an "uncrystallizable oil" and gave no physical constants.