Anal. Calcd. for $C_{19}H_{31}BrN_2O$: N, 7.31. Found: N, 7.48.

1-(4-Nitrophenacyl)-4-(1-hexyl)-piperidine (V).—Ten grams (0.0246 mole) of 4-nitrophenacyl bromide was dissolved in 100 ml. of acetone and a large crystal of potassium iodide added. The solution was cooled to −5° and 10 g. (0.0585 mole) of 4-(1-hexyl)-piperidine was added dropwise at such a rate as to keep the temperature below 0°. The solution was immediately placed in the ice-box and allowed to sit overnight. The reaction mixture was filtered, washed with water and then with a small amount of acetone and then ether. This procedure gave 1.5 g. (18%) of the desired product as a yellow powder, m.p. 134–136°.

Anal. Calcd. for $C_{19}H_{28}N_2O_3$: N, 8.43. Found: N, 8.29, 8.34.

Catalytic reduction of compound V gave compound III as the free base in 82% yield, m.p. 95–96°.

DENTON, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

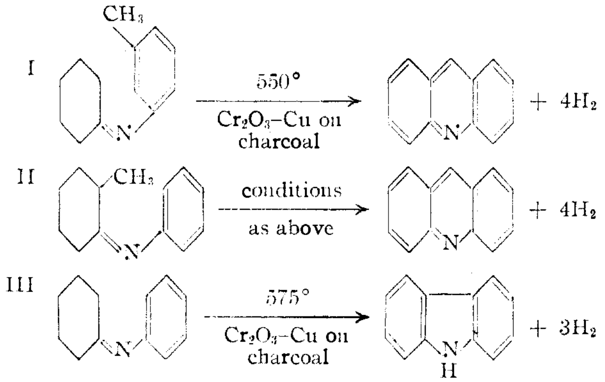
Catalytic Synthesis of Heterocycles. VII.[1] Dehydrocyclization of Anils to Acridine and Carbazole

BY CORWIN HANSCH, FELIX GSCHWEND AND JACK BAMESBERGER

RECEIVED MARCH 22, 1952

The preparation and vapor phase catalytic dehydrocyclization of N-2-methylcyclohexylideneaniline and N-cyclohexylidene-*o*-toluidine to acridine and of N-cyclohexylideneaniline to carbazole is described. The catalytic dehydrogenation of 2-methylcyclohexanol to 2-methylcyclohexanone is also discussed.

Recent work shows[2] that suitable aromatic anils may be easily dehydrocyclized to give nitrogen heterocycles. The work presented in this paper is an extension of this reaction to the synthesis of acridine and carbazole according to the equations



Although a large number of methods[3] have been devised for the synthesis of acridine and its derivatives, very little attention has been given to catalytic procedures. Graebe[4] reported the formation of some acridine and methylacridine by the pyrolysis of *o*-tolylaniline and di-*o*-tolylamine. It had been shown that N-benzylaniline[5] may be pyrolytically dehydrogenated to give acridine. The dehydrocyclization of anils appears to offer considerable advantage over that of the dehydrocyclization of the secondary aromatic amines in that mixed anils are more easily prepared than the mixed secondary amines. It is interesting to note in reactions I and II above that where the possibility for cyclization to occur either through a methyl group to a ring or directly from ring to ring, the bond forms preferentially through the methyl group, acridine being the product rather than methylcarbazole. In reaction III carbazole is the only possibility, but it is formed with greater difficulty and lower yield by ring to ring dehydrocyclization.

The 2-methylcyclohexanone used was found to be most smoothly prepared by the vapor phase dehydrogenation of the commercially available 2-methylcyclohexanol. This ketone was then condensed with aniline, using anhydrous $ZnCl_2$ as the catalyst, to give the anil.

Among the various methods for the preparation of carbazole one vapor phase catalytic method (using Pt-on-charcoal) has been reported[6] for the dehydrocyclization of diphenylamine. This same reaction has also been accomplished pyrolytically.[5,7]

Experimental

2-Methylcyclohexanone.—This substance was prepared by the dehydrogenation of 2-methylcyclohexanol. For the preparation of the dehydrogenation catalyst, the wire form of cupric oxide was reduced *in situ* with a slow stream of hydrogen at 150° for 1/2 hour. The temperature was then raised to 325° and the stream of hydrogen regulated so that the exothermic reduction did not raise the temperature of the catalyst above 350°. The catalyst was then reduced (about 45 minutes) until its temperature showed no tendency to rise in a fast stream of hydrogen. If the catalyst is reduced too long, or the reduction allowed to become too exothermic, the activity of the catalyst is greatly reduced.

In a typical run, 118 g. of 2-methylcyclohexanol was passed over 10 ml. of catalyst at space velocity of 866 (ml. vapor/ml. catalyst/hr. at normal temperature and pressure) at a temperature of 320°. This gave a yield of 86% 2-methylcyclohexanone as calculated from the hydrogen evolved. The gas evolved in this dehydrogenation was 97–98% hydrogen. The methylcyclohexanone was not separated from the unreacted alcohol, but used directly for the preparation of the anil.

N-2-Methylcyclohexylideneaniline.[8]—Crude 2-methylcyclohexanone from the above experiment, calculated to contain 94.5 g. of ketone was added to 80 g. of aniline and 1 g. of powdered anhydrous $ZnCl_2$ in 200 g. of toluene. The mixture was refluxed for 7 hours, the water being removed

---

[1] For the previous paper in this series see THIS JOURNAL, **73**, 3080 (1951).

[2] C. Hansch, D. G. Crosby, M. Sadoski, A. Leo and D. Percival, *ibid.*, **73**, 704 (1951).

[3] A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946.

[4] C. Graebe, *Ber.*, **17**, 1370 (1884).

[5] H. Meyer and A. Hofmann, *Monatsh.*, **37**, 681 (1916).

[6] N. D. Zelinskii, I. N. Titz and M. Gaverdovskaia, *Ber.*, **59**, 2590 (1926).

[7] C. Graebe, *ibid.*, **5**, 377 (1872).

[8] This substance has been previously prepared (J. Hoch, *Compt. rend.*, **199**, 1428 (1934)) by the reaction of 1,1-diethoxymethylcyclohexane with aniline.

as it was formed by a water trap. Most of the toluene was then removed by distillation and the residue fractionated under reduced pressure; yield of anil, 97.5 g., 62%, b.p. 124–126° (5 mm.), $n^{25}D$ 1.5481.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.42; H, 9.09. Found: C, 83.34; H, 9.57.

N-Cyclohexylidene-*o*-toluidine.—In 200 g. of toluene, 89 g. of cyclohexanone, 107 g. of *o*-toluidine and 1 g. of anhydrous, powdered $ZnCl_2$ were allowed to react as above. Yield of the anil was 151.5 g., 81%, b.p. 124–126° (5 mm.) d^{25}_{25} 0.9829, $n^{25}D$ 1.5479.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.42; H, 9.09. Found: C, 83.02; H, 9.44.

N-Cyclohexylideneaniline.[9]—This compound was prepared as above in 51% yield.

Dehydrocyclization of N-2-Methylcyclohexylideneaniline to Acridine.—The catalyst used in all of the dehydrogenations was chromium–copper-on-charcoal catalyst no. 2 reported by Hansch, *et al.*[2] In each run 10 ml. of fresh catalyst was reduced as previously described.[2] In a typical run, 35 g. of the anil was processed at a space velocity of 538 at a temperature of 550°. A total of 11.5 liters of gas was evolved, 92% of which was hydrogen, 2% olefins and 6% saturated hydrocarbons. To the condensate was added 40 ml. of 6 *N* HCl and 15 ml. of acetone and this mixture cooled in the ice-box overnight. The acridine hydrochloride which crystallized out was filtered, washed thoroughly with ether and dried; yield, 11.7 g., 29%. The acridine obtained by treating the hydrochloride with dil. NaOH melted at approx. 108°, and at 109–110°[10] after recrystallization from ligroin. This product showed no melting point depression with an authentic sample of acridine. The picrate melted at the same point as that made from acridine.

Dehydrocyclization of N-Cyclohexylidene-*o*-toluidine to Acridine.—This molecule was dehydrogenated and the product worked up by the same procedure as that described above. Thirty-five grams of the anil gave 6.1 g. of acridine hydrochloride, 15.2%. In this reaction 10.3 liters of gas was evolved which consisted of 78% hydrogen, 5% olefins and 17% saturated hydrocarbons. Thus in this reaction, as indicated by the gaseous hydrocarbons, side reactions occurred to a much greater extent than in the dehydrogenation of N-2-methylcyclohexylideneaniline to acridine. In neither case did runs at 575° or 525° give higher yields of acridines. At the higher temperatures more decomposition occurred which poisoned the catalyst faster. No doubt higher yields could be obtained by using larger amounts of catalyst.

Dehydrocyclization of N-Cyclohexylideneaniline to Carbazole.—Over 10 ml. of catalyst was processed 31.5 g. of anil at space velocity 408 and temperature of 575°. The liquid condensate was crystallized from ligroin, giving 3 g. of carbazole m.p. 243–245°,[6] 10% yield. The product gave a picrate m.p. 186–187° dec.[6] Runs at 550° and 600° gave slightly lower yields.

Acknowledgment.—This research was supported by the Office of Naval Research under contract NR-055-149. The carbon–hydrogen analyses reported were made by C. F. Geiger of Chaffey College, Ontario, California.

CLAREMONT, CALIFORNIA

---

[9] G. Reddelien and O. Meyn, *Ber.*, **53**, 345 (1920).

[10] O. Fischer and G. Korner, *ibid.*, **17**, 102 (1884).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Syntheses and Reactions of Acyclic N,N-Diacylglycines

BY JOHN C. SHEEHAN AND ELIAS J. COREY[1]

RECEIVED APRIL 17, 1951

Three acyclic N,N-diacylglycines have been prepared which represent possible intermediates in the synthesis of penicillin-like compounds. The acids were obtained in each case by hydrogenolysis of the corresponding benzyl esters. Synthesis of the benzyl esters was accomplished by three different routes: (1) acylation of an N-monoacylglycine benzyl ester, (2) alkylation of a diamide with a benzyl haloacetate and (3) formation and rearrangement of an O-acylisoamide. In sharp contrast to cyclic N,N-diacylamino acid chlorides, the acyclic N,N-diacylglycyl chlorides were found to be sufficiently stable to permit easy isolation in pure form *only* when the acyl groups were *aroyl.*

Recently a new method has been reported[2] for the preparation of fused β-lactam-thiazolidines involving interaction of protected amino acid chloride derivatives (such as succinylglycyl chloride) and thiazolines. Extension of the reaction to acyclic N,N-diacylglycyl chlorides and subsequent selective hydrolysis of one acyl group would lead to β-lactam-thiazolidines possessing the 6-acylamino substituent characteristic of the natural penicillins. A selective hydrolysis appears feasible since diamides are hydrolyzed rapidly to amides under mild conditions in the presence of base.[3] We are now reporting the preparation[4] of three acyclic diacylglycines and studies on the synthesis of the corresponding acid chlorides, N,N-diacetylglycyl chloride, N-acetylphenaceturyl chloride and N,N-dibenzoylglycyl chloride.

Catalytic esterification of aceturic acid with benzyl alcohol afforded, in 91% yield, benzyl aceturate (I), which when treated with acetic anhydride under conditions similar to those employed by Wiley and Borum[4] resulted in a 91% yield of N,N-diacetylglycine benzyl ester (II). The infrared spectrum of II (Fig. 1, curve A) contains bands at 5.70 and 5.85 μ due to the ester and diamide carbonyl groups, respectively, and no N–H stretching bands.[5] N,N-diacetylglycine (III) was obtained in 97% crude yield by catalytic hydrogenolysis of II. The acid, which was isolated as a colorless glass, could not be induced to crystallize, and it decomposed upon storage at room temperature. Exposure of III to laboratory air is sufficient to cause hydrolysis to aceturic acid. Attempts to convert III to the corresponding acid chloride led to unstable, noncrystalline products, the infrared spectra of which indicated the absence of the acid chloride function.

---

[1] Bristol Laboratories Fellow, 1948–1950.

[2] J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950).

[3] For example, diacetamide is almost completely hydrolyzed in one minute to acetamide by treatment with 0.1 *N* sodium hydroxide at 15° [A. W. Titherley and L. Stubbs, *J. Chem. Soc.*, **105**, 299 (1914)].

[4] At the time this work was initiated, no acyclic diacylamino acids or the corresponding acid chlorides were known. Recently two N,N-diacylamino acid esters have been described [R. H. Wiley, O. H. Borum and L. L. Bennett, THIS JOURNAL, **71**, 2899 (1949); R. H. Wiley and O. H. Borum, *ibid.*, **72**, 1626 (1950)]

[5] The shift in wave length of absorption of diamide carbonyl groups from the value usually found for acyclic amides (6.0 μ) is quite general, J. C. Sheehan and E. J. Corey, *ibid.*, **74**, 360 (1952).