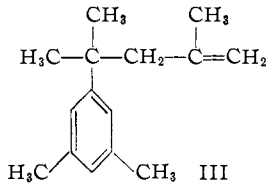


III

formed into the corresponding substituted indan IV.

These conclusions are drawn from the infrared spectrometric data and from the different values of the refractive index.

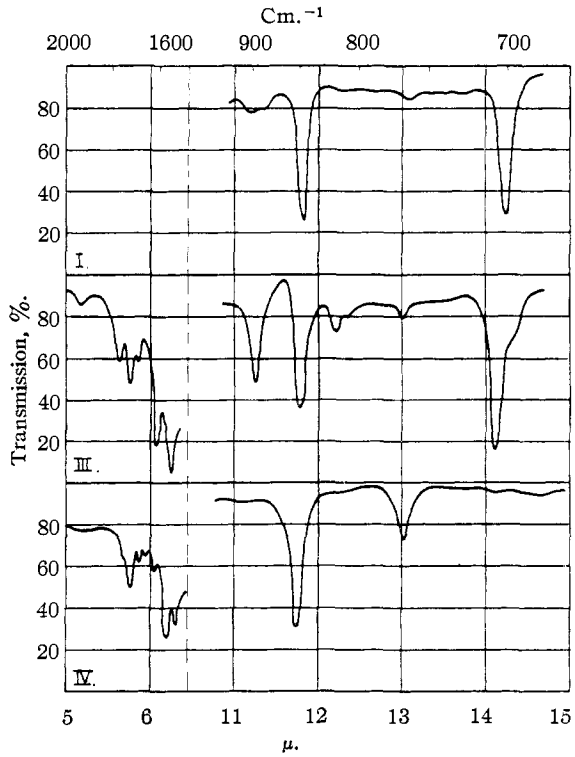
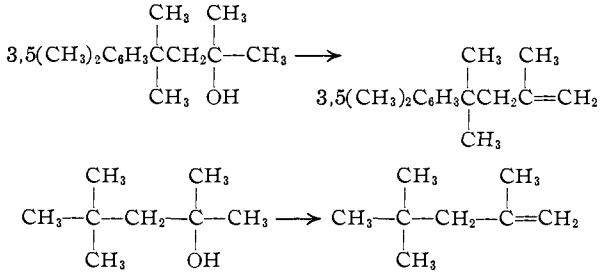


Fig. 1.

In the region of the strong absorption bands due to the aromatic C–H vibrations, compounds I and III show a similar spectrum with two strong bands at 11.80–11.85 and 14.20 μ which are characteristic of a 1,3,5-trisubstituted aromatic ring. Both bands disappear in the spectrum of IV, in which a strong band appears at 11.73 μ, characteristic of a 1,2,3,5-tetrasubstituted ring.[3,4] In the 5–6 μ region a group of sharp overtone bands is present, which are also characteristic of this tetrasubstitution.[5] Only compound III shows a typical olefinic absorption band at 6.09 μ (C=C stretching vibration).[3,6] This olefinic bond is a disubstituted terminal vinyl group RR'C=CH_2, as established by the typical absorption band at 11.25 μ (–CH out-of-plane deformation vibration).[3,7] By cyclization in presence of aluminum chloride, the same absorption band disappears.

The refractive index of compound III ($n^{28.5}$D 1.5056) is very different from that of compound IV ($n^{28.5}$D 1.5101), which shows the same value as that given by Smith and Spillane (1.5100).

This type of dehydration of 4-methyl-4-(3,5-dimethylphenyl)-2-methylpentanol-2 is completely analogous to that of dimethylneopentylcarbinol as given by Whitmore,[8] and must be related to the steric influence of the substituents.[9]



Experimental Part

The infrared spectra were measured with a single-beam Perkin–Elmer spectrometer, model 112; 10% carbon disulfide solutions between 10 and 15 μ, and pure hydrocarbons between 5 and 6.5 μ, were used (cell thickness, 0.1 mm.).

For the cyclization reaction, 1 g. of aluminum chloride was added slowly with stirring and cooling to 10 g. of compound III. The mixture was kept 48 hr. at 20°, poured in ice-water containing hydrochloric acid and extracted with ether. The ethereal solutions were washed, dried on sodium sulfate and evaporated. The residue yielded 8.1 g. (81%) of 1,1,3,3,4,6-hexamethylindan, b.p. 125–127° (20 mm.).

(3) L. Bellamy, "Infrared Spectra of Complex Molecules," Methuen Co., London, 1954, pp. 64 and 44.

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(9) H. C. Brown and I. Moritani, *ibid.*, **77**, 3623 (1955).

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The Preparation of Substituted Hydrazines. III.[1] A General Method for Preparing N-Substituted Glycines[2]

BY JACK M. TIEN AND I. MOYER HUNSBERGER[3]

RECEIVED AUGUST 26, 1955

Recent papers[1,4,5] from this Laboratory have described the conversion of a variety of primary amines (RNH_2) *via* the corresponding glycine ($RNHCH_2CO_2H$), nitrosoglycine [$RN(NO)CH_2CO_2H$] and sydnone to the corresponding monosubstituted hydrazine ($RNHNH_2$). Our inability to prepare N-(3-pyridyl)-glycine by the conventional condensation of 3-aminopyridine with various halogenated acetic acid derivatives led us to investigate alternate synthetic routes to the N-substituted glycines. The successful preparation of N-(3-pyridyl)-glycine hydrochloride by catalytic

(1) Paper II, J. M. Tien and I. M. Hunsberger, THIS JOURNAL, **77**, 6604 (1955).

(2) This work was sponsored by the Air Forces under Contract No. AF 33(038)-22909, Supplemental Agreement No. 5(54-1875).

(3) To whom inquiries concerning this article should be sent. Present address: Department of Chemistry, Fordham University, New York 58, N. Y.

(4) J. M. Tien and I. M. Hunsberger, *Chemistry & Industry*, 119 (1955).

(5) J. Fugger, J. M. Tien and I. M. Hunsberger, THIS JOURNAL, **77**, 1843 (1955).

reduction of an equimolar mixture of 3-aminopyridine and ethyl glyoxylate in dilute hydrochloric acid already has been reported.[1,4] The present paper describes the extension of this method to the synthesis of N-(*n*-hexyl)-glycine and N-phenylglycine.

Although mixtures of 3-aminopyridine and ethyl glyoxylate were reduced successfully in a variety of solvents (dilute hydrochloric acid, 95% ethyl alcohol and acetic acid), dilute hydrochloric acid appeared to be the best solvent.[1] Furthermore, in hydrochloric acid the glycine hydrochloride was obtained directly from the hydrogenation reaction. Similar reductions using *n*-hexylamine and aniline proceeded best in glacial acetic acid and in 95% ethyl alcohol, respectively, and produced the glycine ethyl ester in each case. The ethyl ester of N-(*n*-hexyl)-glycine was saponified in the usual manner and the N-(*n*-hexyl)-glycine isolated as its hydrochloride salt. The ethyl ester of N-phenylglycine was converted to N-phenylglycine hydrochloride by treatment with hydrochloric acid in a manner similar to that used on the ester of N-(3-pyridyl)-glycine.[1] The yields of glycine hydrochlorides were quite high. Thus, N-(3-pyridyl)-glycine hydrochloride was obtained in 80–90% yield (based on amine),[1] while the over-all yields (based on amines) of the hydrochlorides of N-(*n*-hexyl)-glycine and of N-phenylglycine were 58 and 74%, respectively.

The demonstration that this new process for preparing N-substituted glycines from amines works well in the case of a representative alkylamine, arylamine and heteroarylamine leads us to predict that it will prove to have very general application. However, it seems likely that some experimentation will be required to determine optimum conditions for each specific case.

Experimental[6]

N-(*n*-Hexyl)-glycine Hydrochloride.—*n*-Hexylamine[7] (0.765 g., 0.00754 mole) and 1.7 g. of ethyl glyoxylate[8] (62% pure,[9] *i.e.*, 0.0104 mole of pure glyoxylate) were dissolved in 10 ml. of glacial acetic acid, the solution allowed to stand for 2 hours, and then hydrogenated at 3–4 atmospheres by shaking for 2 hours at room temperature with 0.1 g. of 10% palladium–charcoal catalyst. The colorless filtrate obtained on removal of the catalyst was diluted with 20 ml. of water and just neutralized by the addition of solid sodium bicarbonate. The mixture was extracted twice with 60-ml. portions of ether. The residue obtained on evaporation of the ether was refluxed for 10 minutes with 5 ml. of 10% sodium hydroxide. Acidification of the cooled (ice-bath) alkaline solution with 2–3 ml. of concentrated hydrochloric acid caused the separation of 0.86 g. (58%, based on amine) of small, nearly white plates, m.p. 200–206°. This product was heated with 25 ml. of glacial acetic acid on a steam-bath and the sodium chloride removed by hot filtration. On cooling to room temperature the orange-yellow filtrate deposited 0.4 g. of white flakes, m.p. 215–218°, no depression when mixed with authentic N-(*n*-hexyl)-glycine hydrochloride.[5] Although this glycine hydrochloride melts at nearly the same temperature as *n*-hexylamine hydrochloride, no trace of hexylamine could be detected when the glycine hydrochloride was treated with excess base.

The filtrate from the hydrogenation reaction can be made basic directly with dilute sodium hydroxide, refluxed, cooled, acidified with excess concentrated hydrochloric acid, and evaporated to dryness. From this residue the desired glycine hydrochloride may be extracted with hot glacial acetic acid, leaving the sodium chloride behind.

Hydrogenation of a mixture of *n*-hexylamine and ethyl glyoxylate in 2:3 concentrated hydrochloric acid–water produced only a very low yield of the glycine hydrochloride. No glycine was detected from a hydrogenation in 6 *N* hydrochloric acid. Although the yield was increased greatly by the use of 1:1 acetic acid–water as solvent, the best yields were obtained using glacial acetic acid as solvent and the slight excess of glyoxylate given above. It appeared disadvantageous to permit the mixed reactants to stand longer than 2 hours prior to hydrogenation.

Ethyl Ester of N-Phenylglycine.—A solution of 1.00 g. (0.00107 mole) of freshly-distilled aniline in 5 ml. of 95% ethyl alcohol and 1.70 g. of ethyl glyoxylate (62% pure, *i.e.*, 0.00104 mole of pure glyoxylate) was hydrogenated as above for 2.5 hours. The catalyst was removed by filtration and washed with 10 ml. of 95% ethyl alcohol. The filtrate and washings were combined, diluted to the cloud point with water, and cooled. In this way 1.06 g. of the glycine ester was obtained as white plates, m.p. 57–58°. Further dilution of the mother liquor afforded 2 more crops of crystals (0.41 g., m.p. 57–58°; 0.17 g., m.p. 54–56°), the total yield being 1.64 g. (88%). This product gave no depression in m.p. when mixed with an authentic sample of the glycine ester.

Use of dark-colored aniline for the hydrogenation produced a more highly colored hydrogenation product.

N-Phenylglycine Hydrochloride.—The above ethyl ester (0.179 g., 0.001 mole) was refluxed for 10 minutes with 2 ml. of concentrated hydrochloric acid and 4 ml. of water and the resulting solution evaporated to dryness under reduced pressure. The white residue[10] was dissolved in 2 ml. of concentrated hydrochloric acid by warming on a steam-bath. On cooling, the solution deposited a total of 0.157 g. (84%) of the glycine hydrochloride as white flakes (first fraction, 0.116 g., m.p. 172–174°; second fraction, 0.041 g., m.p. 170–173°), which did not depress the m.p. of authentic N-phenylglycine hydrochloride (prepared as given below).

Repeated attempts to prepare this glycine hydrochloride by hydrogenation of ethyl glyoxylate and aniline in dilute and in concentrated hydrochloric acid yielded only gummy, unidentifiable products. Hydrogenation in acetic acid produced a low yield of material which presumably was a mixture of the free glycine and its ethyl ester.

Purification of N-Phenylglycine.—The preparation of a pure sample of N-phenylglycine from the commercial material,[7] which is a yellow powder, proved more difficult than was anticipated. Thus, the free glycine cannot be recovered easily by adding aqueous ammonia or sodium acetate to its solution in dilute hydrochloric acid or by neutralizing its solution in aqueous sodium hydroxide. Considerable experimentation finally showed that a solution of 0.1 g. of the commercial glycine and 0.1 g. of sodium chloride in 5 ml. of warm water (about 70°) will deposit large pale-yellow needles after about 2 minutes of cooling. However, it was preferable to add 0.5 ml. of acetic acid to the above hot solution, in which case after about 20 minutes of cooling colorless crystals separated. If sodium chloride is not present in the solution of the glycine, the latter separates much more slowly and is more highly colored. All samples of recrystallized N-phenylglycine melted at 126–127°. Colorless samples of the glycine turned tan in a few hours.

The hydrochloride can be prepared by dissolving the free base in concentrated hydrochloric acid by heating on a steam-bath. After decolorization (Norit A) and cooling, the solution deposited the hydrochloride as colorless transparent plates, m.p. 168–173°, which turned lemon-yellow on standing for several days. No literature m.p. could be located for this material.

Acknowledgments.—The authors take pleasure in thanking Mr. Elwood Shaw for performing a preliminary investigation of the hydrogenation

(6) All m.ps. are uncorrected.

(7) Eastman Kodak Co., White Label grade.

(8) Prepared essentially according to L. Vargha and M. Reményi, *J. Chem. Soc.*, 1068 (1951); *cf.* ref. 1.

(9) Determined by assay with phenylhydrazine. The main impurity presumably was acetic acid.

(10) This residue had an intense yellow color if the concentrated hydrochloric acid was not diluted with water in the previous treatment. This yellow color could be removed, however, by use of Norit A.

reactions and for checking the preparation of the ethyl ester of N-phenylglycine.

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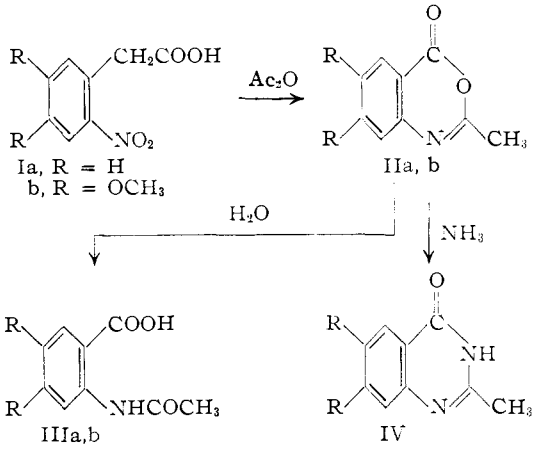
A Novel Rearrangement of *o*-Nitrophenylacetic Acids

BY GORDON N. WALKER

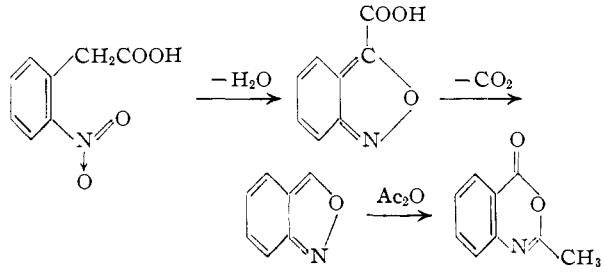
RECEIVED AUGUST 8, 1955

When 2-nitrophenylacetic acid was heated in acetic anhydride an exothermic reaction occurred and carbon dioxide was evolved. A colorless, crystalline substance, m.p. 80–81°, with empirical formula $C_9H_7O_2N$ was formed. This compound reacted readily with a mole of water, giving an acid, $C_9H_9O_3N$, m.p. 182–184°. These characteristics made it apparent that the "acetylation" product was acetylanthranil (IIa) which is hydrolyzed easily[1] to N-acetylanthranilic acid (IIIa). Proof of this assumption was obtained by comparison of the compounds with authentic specimens of IIa and IIIa, respectively, prepared by acetylation of anthranilic acid[1,2] and subsequent treatment with water. The respective materials were identical, as shown by undepressed mixed melting points and two pairs of identical infrared spectra.



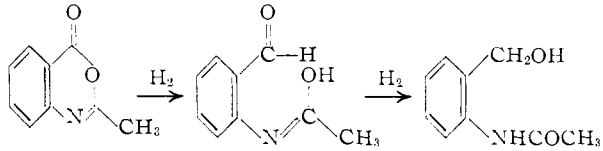
Reaction of 2-nitro-4,5-dimethoxyphenylacetic acid (Ib)[3,4] with acetic anhydride was found to take the same course as with Ia, leading to the corresponding dimethoxyacetylanthranil IIb. This compound was characterized by hydrolysis to amidoacid IIIb, and by reaction with ammonia to form the quinazolone IVb.

Information about the exact course of the rather remarkable change I → II is not available at present. The reaction in any event obviously involves transfer of oxygen from nitrogen to the methylene carbon atom at the adjacent position on the benzene ring. It seems plausible to assume that cyclic intermediates are involved in the change, and evidence in favor of this assumption is the fact that 4-nitrophenylacetic acid does not rearrange in the presence of boiling acetic anhydride, but merely is converted into 4-nitrophenylacetic anhydride. Species such as anthroxanic acid and anthranil might be formed during the rearrangement



This idea is lent support by the following facts: anthroxamic acid is decarboxylated readily,[5] and anthranil is converted into acetylanthranil by acetic anhydride. However, it was found that other compounds, such as ethyl 2-nitrophenylacetate, 2-nitrophenylacetonitriles and 2-nitrotoluene, having a nitro-group and a methylene group in adjacent positions on the benzene nucleus, do not react with acetic anhydride. The reaction appears to be limited to the special case in which a carboxylic acid group is present. The effective driving force in formation of the final product from a complex intermediate may be related to the loss of carbon dioxide. It may be pointed out that the reaction is reminiscent of oxidation–reduction changes with other aromatic nitro-compounds, as for example the formation of anthranils from 2-nitrotoluenes in the presence of alkali,[6] and of the rearrangement of pyridine-N-oxides in the presence of acetic anhydride, which has received attention recently.[7,8] The rearrangement of 2-nitrophenylacetic acid also is in strong contrast with the acetylation of phenylacetic acid, which requires basic catalysis and leads to formation of benzyl ketones.[9]

An interesting hydrogenolytic ring opening was observed during the course of experiments with acetylanthranils. Hydrogenation of IIa in the presence of 10% palladium–charcoal in ethyl acetate resulted in quantitative formation of 2-acetylaminobenzyl alcohol. Thus hydrogen is capable of opening anhydride-like compounds of type II at the same point in the molecule which is sensitive to attack by water, amines and other reagents.



Experimental[10,11]

Acetylanthranil (IIa).—A mixture of 43.8 g. (0.242 mole) of *o*-nitrophenylacetic acid and 300 ml. of acetic anhydride

(1) R. Anschütz and O. Schmidt, *Ber.*, **35**, 3470 (1902).
(2) M. T. Bogert and H. A. Seil, THIS JOURNAL, **29**, 529 (1907).
(3) R. K. Callow, J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 658 (1929).
(4) G. N. Walker, THIS JOURNAL, **77**, 3844 (1955).
(5) E. Bamberger, *Ber.*, **42**, 1664 (1909).
(6) *Cf.* R. Scholl, *Monatsh.*, **34**, 1011 (1913).
(7) V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).
(8) O. H. Bullitt and J. T. Maynard, *ibid.*, **76**, 1370 (1954).
(9) J. A. King and F. H. McMillan, *ibid.*, **73**, 4911 (1951).
(10) Melting points are corrected.
(11) I am indebted to Dr. William C. Alford and his staff for microanalytical data and to Mrs. H. F. Byers of the Instrument Laboratory for spectra.