

at 156-7° (a second crystallization would doubtless have raised the melting point) and a mixture of this product and 2-benzoylamino-4-bromo-5-methylphenylacetate (m. p. 157-8°) described above melts between 156° and 158°, which indicates that they are identical, and that in the benzoylation of 2-acetylamino-4-bromo-5-methylphenol the benzoyl radical attached itself to nitrogen while the acetyl migrated to oxygen.

Summary

When the acetyl and benzoyl radicals are introduced into the *o*-aminophenols obtained from *o*- and *m*-cresols, respectively, the benzoyl radical is found attached to nitrogen in each case, regardless of the order of introduction. This confirms the observations previously reported.

The work was done while the junior author held the Du Pont scholarship in chemistry at the State University of Iowa, and our thanks are due to E. I. Du Pont de Nemours and Company for this assistance in our work.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

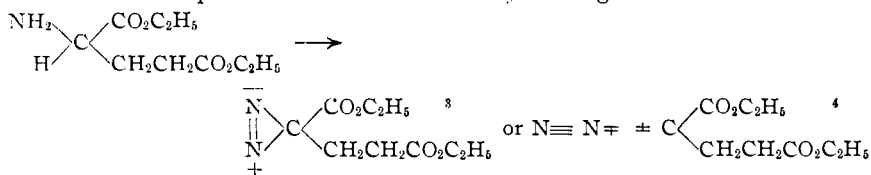
OPTICALLY ACTIVE DIAZO COMPOUNDS. II

BY H. M. CHILES WITH W. A. NOYES

Received June 2, 1922

In a previous paper C. S. Marvel¹ with one of us has given an account of unsuccessful experiments undertaken in the hope of preparing optically active aliphatic diazo compounds in which the only asymmetric carbon atom is combined with the two nitrogen atoms. After that paper was published Levene and Mikeska² reported that they had obtained diethyl-diazosuccinate in an active form. We have now succeeded in preparing 6 such active compounds. The failure of the former experiments was due to the fact that such compounds racemize very easily. It is necessary to carry through all operations very carefully and to distil the compounds under a very low pressure.

The first compound obtained was diethyl-diazoglutarate.



It seems to be impossible to reconcile the Curtius formula for these active compounds with the ideas of atomic structure and of non-polar valence proposed by G. N. Lewis and Irving Langmuir. The Angeli-

¹ C. S. Marvel with W. A. Noyes, *THIS JOURNAL*, **42**, 2259 (1920).

² Levene and Mikeska, *J. Biol. Chem.*, **45**, 593 (1921); **52**, 485 (1922).

³ The Curtius formula.

⁴ The Angeli-Thiele formula.

Thiele formula may be reconciled with those theories if we assume that the polar valence between an ammonium group and another atom is a definite bond located in a fixed position in the compound. R. S. Potter with one of us has given very positive evidence⁵ that this is true.

The only pure diazo esters prepared in this work were obtained by the Curtius method and purified by the vacuum distillation of the thoroughly washed and dried crude samples.

The following active diazo esters were prepared.

Diethyl- α -diazoglutarate, $[\alpha]_D +0.85^\circ$ to $+1.86^\circ$.

Dimethyl- α -diazoglutarate, $[\alpha]_D +0.89^\circ$.

Diethyl- α -diazosuccinate, $[\alpha]_D -1.23^\circ$.

Ethyl- α -diazo-*n*-caproate, $[\alpha]_D -1.89^\circ$.

Ethyl- α -diazo-*n*-caproate, $[\alpha]_D +1.84^\circ$.

Ethyl- α -diazo-*isocaproate*, $[\alpha]_D -1.52^\circ$.

These diazo esters upon treatment with dil. sulfuric acid all gave a mixture of an unsaturated ester and hydroxy ester with the same direction of rotation as the amino esters and diazo esters from which these were prepared, and of the same order of magnitude as the diazo ester.

The mixture of *d*-hydroxy glutaric esters and unsaturated ester upon saponification gave sodium salts with the same direction of rotation as the amino acid, but the rotation corresponded to only about 10 to 13% of the pure active sodium salt.

The acid hydrolysis products from the other diazo compounds upon saponification gave sodium salts which had the same direction of rotation but in some cases the salts were not identified, due to lack of material.

Diethyl- α -diazoglutarate upon reduction gave *d*-diethyl-glutamate, but the activity corresponded to only about 12% of that of the pure active amino ester.

The rotation of the diazoglutaric esters prepared cannot be due to the presence of the amino ester, as this product was specifically tested for by the Van Slyke nitrous acid method, after treatment with dil. acid to destroy the diazo ester, and the total amount of nitrogen obtained calculated as the amino ester. The amounts obtained were negligible; moreover, the amino ester gives only a normal increase in rotation when added to the diazo ester. The rotation cannot be due to the presence of an hydroxy ester, as the rotations of the hydroxy ester prepared by treatment of the amino ester with nitrous acid so as to decompose the diazo esters without isolation, were of the same order as those of the diazo esters. This, of course, might suggest that the same impurity caused the rotation in the two cases, but it is hard to see how, even if this supposed impurity escaped removal by distillation, it should give both an active hydroxy acid upon saponification and an active amino acid upon reduction, and

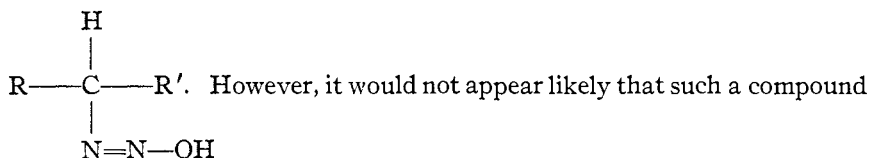
⁵ R. S. Potter with W. A. Noyes, *THIS JOURNAL*, 37, 189-203 (1915).

that the rotation obtained, although of a different amount, should correspond at least approximately to the same percentage of the active compound in the two cases.

The rotation cannot be due to the hydroxy acid, as this compound in the first place is levorotatory;⁶ moreover, it certainly would be separated by distillation. The rotation cannot be due to the presence of pyrrolidone carboxylic ester, as this compound besides being levorotatory⁷ has a much higher boiling point.

The arguments which have been advanced in the case of the glutaric esters in the main hold good for all of the other diazo esters prepared. Though in some cases the diazo compounds prepared were not as pure as those obtained in the case of the glutaric esters, it was found in all cases that purification had only a small effect on the rotation, presumably due to the fact that the chief active impurity, the hydroxy esters, in all cases had rotations of the same order as those of the corresponding diazo compounds.

It has been a rather common observation that in the distillation of diazo esters, even of those that have been carefully dried, a part and in some cases nearly all of the diazo ester is decomposed with the production of a large amount of hydroxy ester.⁸ The behavior of the diazo esters prepared in this work makes it appear possible that these compounds as ordinarily prepared and dried may consist in part of the hydrated form



would distil without complete decomposition. Also, to account for the amount of the active hydroxy ester formed by the decomposition of the diazo ester, about 12% of this compound would be necessary. The analytical results for carbon seem to exclude this possibility.

Experimental Part

The first attempt made was the preparation of ethyl-diazovalerate by the treatment of nitrosomethyl-2-pyrrolidone with an ethereal solution of sodium methylate according to Oppe's method.⁹

γ -Aminovaleric acid was prepared by reduction of the phenylhydrazone of levulinic acid with aluminum amalgam according to the method of

⁶ Ritthausen, *J. prakt. Chem.*, [1] **103**, 239 (1868); [2] **5**, 354 (1872). Fischer, *Ber.*, **45**, 2447 (1912).

⁷ Fischer, *ibid.*, **44**, 1332 (1911).

⁸ Curtius, *J. prakt. Chem.*, [2] **38**, 477 (1888). Ref. 1, p. 2262.

⁹ Oppe, *Ber.*, **46**, 1095 (1913).

Fischer and Groh,¹⁰ Nitrosomethyl-2-pyrrolidone was prepared from the lactam of the amino acid according to the method of Tafel.¹¹ The treatment of this nitroso compound with sodium methylate or ethylate gave a very unstable compound which evolved nitrogen even in contact with the air of the laboratory, and the crude product almost completely lost its color when treated with dry carbon dioxide according to Oppe's method.

As no method could be found for purification, the work on this series was discontinued.

Derivatives of *d*-Glutamic Acid

d-Glutamic Acid has been prepared by the hydrolysis of a large number of protein products including gliadin. For this work it was prepared by the hydrolysis of the crude flour protein obtained by simply washing flour with water to remove the starch.

Eleven kg. of hard wheat flour in the original muslin sack was soaked for 30 minutes in a sink filled with water and then vigorously kneaded with frequent changes of water until very little more starch passed through the sack and all lumps were broken up. The crude wet gluten, weighing about 4500 g., was then hydrolyzed by heating on the water-bath with 4 liters of conc. hydrochloric acid until the purple coloration had disappeared, and the hydrolysis was then completed by heating to boiling under a reflux condenser for 24 hours. The humus matter was removed by filtration and washed by decantation through a filter. The combined filtrate and wash waters were then concentrated under diminished pressure to a volume of about 2000 cc. and the glutamic acid hydrochloride precipitated by saturating the cooled solution with hydrogen chloride and allowing the mixture to stand in the ice-box for several hours. The crude product was filtered on a "Filtros" plate and thoroughly washed with ice-cold alcoholic hydrochloric acid and finally with ether.

The product was redissolved and reprecipitated as above until it was perfectly white, which usually required three reprecipitations. The filtrates from the reprecipitations were reconcentrated and reprecipitated to recover the considerable amount of glutamic acid which they contained. The product from the mother liquors was further purified by washing with alcohol, esterifying in the usual manner and filtering from any unesterified matter. The crude ester was hydrolyzed by heating on the water-bath for 5 hours with 10 volumes of 10% hydrochloric acid, concentrated under diminished pressure and reprecipitated in the usual manner.

The total yield of *d*-glutamic acid hydrochloride amounted to 285-310 g. The pure product was dried in a desiccator over sulfuric acid and calcium carbonate; 0.6013 g., when dissolved in 10.00 cc. of water gave a rotation of +1.47° in a 1dm. tube at 22° with sodium light; $[\alpha]_D^{22} + 24.44^\circ$.

Analyses. Subs., 0.2542, 0.2479: 13.55 cc., 13.03 cc., 0.1040 *N* H₂SO₄. Calc. for C₅H₁₀O₄NCl: N, 7.63. Found: 7.65, 7.66.

d-Diethyl-glutamate Hydrochloride was prepared by a modification of Fischer's method¹² which was found to give equally good results with considerably smaller amounts of alcohol.

¹⁰ Fischer and Groh, *Ann.*, **383**, 363 (1911).

¹¹ Tafel, *Ber.*, **19**, 2414 (1886).

¹² Fischer, *ibid.*, **34**, 438 (1901).

Fifty g. of *d*-glutamic acid hydrochloride was heated on the water-bath with 100 cc. of absolute alcohol which had previously been saturated with dry hydrogen chloride until the acid all dissolved and then 200 cc. of absolute alcohol was added and the heating continued for 1 hour. The mixture was then concentrated under diminished pressure, 100 cc. of absolute alcohol was again added and the heating and concentration repeated. Upon cooling, the ester hydrochloride sometimes solidified. Whether it solidified or not the crude product was dissolved in an equal weight of chloroform on the water-bath and then, after cooling, about 30 cc. of dry ether was added, which precipitated a gummy mass containing some diethyl-glutamate and all of the impurities and colored materials. The clear solution was then filtered and the diethyl-glutamate hydrochloride precipitated as fine white needles by the addition of ether. The gummy, slightly colored mass obtained upon the first addition of ether was purified by redissolving in chloroform and reprecipitating. Yield, 47–55 g. (72.5–85% of the calculated amount); m. p. 96–98°. For analysis the product was dried *in vacuo* over sulfuric acid and calcium carbonate.

Analyses. Subs., 0.2671, 0.2871: 11.09, 11.92 cc. of 0.1040 *N* H₂SO₄. Calc. for C₉H₁₃NO₄Cl: N, 5.85. Found: 5.86, 5.86.

Diethyl- α -diazoglutamate was prepared from the recrystallized amino ester hydrochloride.

Fifty g. of *d*-diethyl-glutamate hydrochloride was dissolved in 100 cc. of water. To this was added 25 g. of sodium acetate, and the mixture was cooled to -10° ; 25 g. of sodium nitrite and 300 cc. of ether were then added and the mixture was gently stirred by a mechanical stirrer. Then during the course of 1 hour 50 cc. of 10% sulfuric acid was added and the stirring continued thereafter for 1 hour. The ether layer was separated and washed first with five 25cc. portions of ice-cold *N* sulfuric acid, then with saturated sodium hydrogen carbonate solution and finally with 5% sodium carbonate solution until the carbonate layer was distinctly colored. The ether solution was dried, first over calcium carbonate containing a little anhydrous barium hydroxide, and then over fused calcium chloride. The ether solution was diluted with anhydrous ether to a volume of exactly 1 liter. Exactly 10 cc. of this solution was drawn off by means of a pipet and the ether evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide. This sample was then analyzed for nitrogen by the sulfuric acid method. The difference between the theoretical amount of nitrogen and that found was considered to be due to the hydroxy ester and the calculated amount of a *N* ether and methyl alcohol solution of sodium methylate was added to combine with the hydroxy ester. The sodium methylate solution was made by dissolving 2.30 g. of sodium in 21 g. of absolute methyl alcohol and diluting to 100 cc. with anhydrous ether. After the addition of the sodium methylate the mixture was allowed to stand for 2 hours and then filtered. The ether solution was washed with water and again dried over fused calcium chloride, the ether evaporated *in vacuo* and the diazo ester dried by evacuating the flask to 2 mm. and drawing a stream of carefully dried air through the product for 5 hours. The product was filtered from a solid precipitate, probably diethyl-azoglutamate, as it appears exactly like the product formed under similar circumstances from diethyl-diazosuccinate. The ether solution of this product was inactive. The crude diazo ester which analysis showed to be, in different runs, from 92 to 96% pure, was then distilled in a vacuum, using a pressure at least as low as 0.2 mm. The purified ester boils at 92–93° at 0.1 mm. The yield of crude diazo ester before treatment with sodium methylate varied in different runs between 15 and 21 g. The yield of pure ester amounts to 8–12 g. when the distillation goes well. Sometimes, however, without apparent reason, decomposition takes place even with a vacuum of 0.1 mm. When this occurs, even lowering the vacuum to 0.01 mm. or less fails to yield a pure product, and the distillate contains, besides diazo ester, hydroxy ester and probably the unsaturated ester, as the

product after destroying the diazo ester by treatment with dil. acid decolorizes permanganate solution but has no action in the cold with a solution of bromine in carbon tetrachloride. Thirty preparations of this diazo ester were made, using both sulfuric acid and acetic acid for the diazotization, and the only cases in which an inactive diazo ester were obtained were when a good vacuum for distillation was not available. In three preparations that were distilled under a vacuum of 1.0–3 mm. the products were not pure due to decomposition, and were, furthermore, inactive. Of the preparations which were distilled with a vacuum of 0.2 mm. or less, the rotation of the samples varied from $[\alpha]_D +0.87^\circ$ to $+1.68^\circ$. Three preparations were made which the analysis showed to be 98.5–99% pure and the rotations varied in these cases from $[\alpha]_D +1.38^\circ$ to $+1.68^\circ$. These preparations, as well as the others, showed substantially the same rotation in the pure state as in the crude state (before distillation). Six other preparations were made which the analysis showed to be 95–98% pure, and these preparations all had rotations of $[\alpha]_D +0.87^\circ$ to $+1.68^\circ$. A typical set of data on one sample is given. d_4^{20} , 1.124; rotation in a 1dcm. tube in sodium light at 20° , $+2.01^\circ$; $[\alpha]_D^{20} = +1.68^\circ$; $n_D^{20} = 1.4730$.

Analyses. Subs., 0.117, 0.1088: 13.25 cc. of N_2 (24° and 747 mm.). Calc. for $C_9H_{14}O_4N_2$: N, 13.08. Found: 13.00, 12.92 (H_2SO_4 method).

Subs., 0.2280, 0.2047: CO_2 , 0.4206, 0.3785; H_2O , 0.1399, 0.1250. Calc. for $C_9H_{14}O_4N_2$: C, 50.44, H, 6.59. Found: C, 50.35, 50.40; H, 6.86, 6.78.

Subs., 0.2117, 0.1989: 25.22 cc. of N_2 (Dumas method) (25° and 744 mm.) 23.80 cc. (24° and 739 mm.). Calc. for $C_9H_{14}O_4N_2$: N, 13.08. Found: 13.15, 13.21.

Larger samples were run with particular effort to determine hydrogen more accurately.

Analyses. Subs., 0.5283, 1.0013: H_2O , 0.3148, 0.5994. Calc. for $C_9H_{14}O_4N_2$: H, 6.59. Found: 6.62, 6.65.

The residues from the sulfuric acid nitrogen determination were neutralized with sodium hydroxide, concentrated under diminished pressure, made up to a volume of 5.00 cc. and analysis of 2cc. samples were made with a micro Van Slyke apparatus.

Analyses. Subs., 0.0447, 0.0447: 0.01 cc. of N (24° and 747 mm.) 0.015 cc. (24° and 747 mm.). Found: diethyl-glutamate: 0.10%.

Molecular Weight by Boiling Point Method in Ether.—0.6494 g. of diazo ester raised the boiling point of 68.4 g. of ether 0.091° , 0.093° ; mol. wt., 220, 215.5; 0.9788 g. of diazo ester raised the boiling point of 69.8 g. of ether 0.136° ; mol. wt., 218. Calc., for $C_9H_{14}O_4N_2$: 214.13.

Samples of the diazo ester were tested for halogen both by the Beilstein copper-wire method and sodium fusion, and showed no halogen.

Treatment of Diethyl-diazoglutamate with Dil. Sulfuric Acid.—Fifteen g. of the optically active diazo ester, $[\alpha]_D +1.56^\circ$, was added to 100 cc. of 20% sulfuric acid and the mixture shaken at intervals until it lost its yellow color; it was then extracted with ether, the ether solution dried over anhydrous sodium sulfate and the ether evaporated on the water-bath. Yield, 7 g. The crude product was filtered and the rotation taken in a 1dcm. tube in sodium light was $+3.30^\circ$. The product was then distilled in a vacuum and 5 g., boiling at 90 – 95° at 0.2 mm., was obtained; d_4^{20} 1.072; rotation in a 1dcm. tube in sodium light, $+1.28^\circ$. The product was again distilled in a vacuum and 4 g. boiling at 90.5 – 91.5° at 0.2 mm. was obtained; d_4^{20} 1.072; n_D^{20} 1.4484; rotation in a 1dcm. tube in sodium light at 20° was $+1.29^\circ$; $[\alpha]_D^{20} +1.07$. The product had no action with a solution of bromine in carbon tetrachloride in the cold, but readily reacted with a 1% permanganate solution. The product prepared by using *N* sulfuric acid for the hydrolysis gave identical results, and the purification by steam distillation also gave identical results.

Analyses. Subs., 0.1731, 0.1749: CO₂, 0.3445, 0.3493; H₂O, 0.1156, 0.1168. Calc. for C₉H₁₄O₄: C, 58.10; H, 7.57; calc. for C₉H₁₆O₅: C, 52.91; H, 7.90; calc. for C₇H₁₀O₄: C, 53.10; H, 6.33. Found: C, 54.38, 54.47; H, 7.35, 7.42.

The analysis, reaction with potassium permanganate and the decrease in rotation upon distillation which does not change with further distillation, indicate that the product is a mixture of diethyl-glutaconate and the lactone ester (ethyl tetrahydro-5-keto-2-furancarboxylate).

Saponification of the Acid Hydrolysis Products of Diethyl- α -diazoglutarate.—Two g. of the acid hydrolysis products from the preceding experiment was treated with 19.5 cc. of pure *N* alcoholic sodium hydroxide (from sodium) and the mixture allowed to stand at room temperature until the solution was neutral to phenolphthalein.

The sodium salt commences to precipitate immediately after mixing. After the saponification was completed the sodium salt was filtered off, washed with alcohol and then with ether, and the product dried in a desiccator over sulfuric acid. Yield, 0.9 g. (50% of the calculated amount).

0.5850 g. of the sodium salt dissolved in water and made up to 5.00 cc. had a rotation of +0.14° in a 1dcm. tube in sodium light at 23°; $[\alpha]_D^{23} +1.20^\circ$. Fischer and Warburg¹³ give the rotation of *l*-sodium- α -hydroxyglutarate as $[\alpha]_D -8.65^\circ$; therefore the salt prepared was about 13% active. Three other preparations of this salt were made and the rotation was always between $[\alpha]_D^{20} +1.0^\circ$ and $+1.20^\circ$.

The product was tested for amino nitrogen in a micro Van Slyke apparatus and showed none. It gave no test for nitrogen after a fusion with sodium peroxide.

Analyses. Subs., 0.5833, 0.4461: Na₂SO₄, 0.4329, 0.3342. Calc. for C₅H₆O₅Na₂: Na, 23.97. Found: 24.14, 24.21.

Subs., 0.1876, 0.1422: CO₂, 0.2260, 0.1708; H₂O, 0.0507, 0.0384. Calc. for C₅H₆O₅Na₂: C, 31.25; H, 3.15. Found: C, 32.87, 32.75; H, 3.00, 3.00.

The analyses show that the product probably contains some of the unsaturated sodium salt. The salt was thrice recrystallized from dil. alcohol; 0.5819 g. of the recrystallized salt dissolved to make 5.00 cc. of solution gave a rotation in a 1dcm. tube in sodium light at 24° of 0.50°; $[\alpha]_D^{24} +4.29^\circ$.

Analysis. Subs., 0.3824: Na₂SO₄, 0.2840. Calc. for C₅H₆O₅Na₂: Na, 23.97. Found: 24.06.

It is necessary to use pure sodium hydroxide for the saponification, as the addition of sodium carbonate causes a great increase in the rotation.

For comparison with the product obtained by the hydrolysis of the diazo ester, the amino ester hydrochloride was diazotized in such a way that the diazo ester was decomposed without being isolated.

Thirty g. of *d*-diethyl-glutamate hydrochloride was dissolved in 320 cc. of *N* sulfuric acid and the solution cooled at 0°. To this solution was added slowly 18 g. of sodium nitrite dissolved in 45 cc. of water. The mixture was allowed to stand at 0° for 1 hour thereafter, then removed from the cooling bath, and allowed to stand at room temperature for 5 hours, and finally warmed to 40° for 1 hour. It was then extracted with ether, the ether solution dried over anhydrous sodium sulfate, the ether evaporated on a water-bath and the product distilled in a vacuum; the fraction boiling at 90–95° at 0.2 mm. was collected; yield, 5 g. This fraction was redistilled, and the portion boiling at 90.5–91.5° and 0.2 mm. collected; yield, 5 g.; d_4^{20} , 1.072; n_D^{20} , 1.4485; rotation in a 1dcm. tube in sodium light at 23°, +2.04°; $[\alpha]_D^{23} +1.90^\circ$.

Analyses. Subs., 0.1966, 0.1780: CO₂, 0.3917, 0.3551; H₂O, 0.1341, 0.1189. Calc. for C₉H₁₆O₅: C, 52.91; H, 7.90. Found: C, 54.34, 54.40; H, 7.52, 7.42.

¹³ Fischer and Warburg, *Ber.*, 45, 2447 (1912).

The product was saponified as described in the preceding experiment. From 3 g. of the ester 1.1 g. of sodium salt was obtained.

Analysis. Subs., 0.3242: Na_2SO_4 , 0.2417. Calc. for $\text{C}_5\text{H}_8\text{O}_5\text{Na}_2$: Na, 23.97. Found: 24.18.

0.5672 g. was dissolved in water to make a volume of 5.00 cc.; rotation in a 1dcm. tube in sodium light at $23^\circ +0.21^\circ$; $[\alpha]_D^{23} +1.85^\circ$.

Reduction of Diethyl-diazoglutarate.—Five g. of the diazo ester was dissolved in 30 cc. of ether, and 1.5 g. of aluminum amalgam which had been freshly prepared and washed with alcohol was added. There is a vigorous reaction with a copious evolution of ammonia. If the reaction became too vigorous the contents of the flask were diluted with dry ether. The flask was frequently shaken for 4 hours with the occasional addition of a drop of water. One cc. of water was then added and the flask was allowed to stand overnight. The ether solution was then filtered and the aluminum hydroxide washed with ether. The ether solution was evaporated *in vacuo*, and the residue had the appearance and odor of diethyl-glutarate; 2.7141 g. of residue made up to 5.00 cc. with ether had a rotation of $+0.90^\circ$ in a 1dcm. tube. To the residue was added 20 cc. of 10% hydrochloric acid, and the acid solution extracted with ether to remove the hydroxy ester. The acid solution was then heated on the water-bath for 5 hours and the solution evaporated nearly to dryness under diminished pressure. Upon cooling, beautiful white crystals, which had the characteristic taste of glutamic acid, formed on the walls of the flask. The crystals were washed from the flask with a little alcohol, and ether was added to complete the precipitation. The yield from the different preparations was 0.75–1.1 g. (30–43% of the calculated amount). The product was dissolved in water and reprecipitated by adding alcohol and then ether. 0.2511 g. dissolved in water and made up to a volume of 5.00 cc. had a rotation of $+0.16^\circ$ in a 1dcm. tube in sodium light at 23° ; $[\alpha]_D^{23} +3.20$; 0.5829 g. dissolved in water, volume of solution 5.00 cc., had a rotation of $+0.36^\circ$ in a 1dcm. tube in sodium light at 24° ; $[\alpha]_D^{24} +3.10^\circ$. The rotation of the glutamic acid hydrochloride from three other runs varied from $[\alpha]_D +2.90^\circ$ to $+3.20^\circ$.

The rotation of pure active *d*-glutamic acid hydrochloride is about $[\alpha]_D +24.5^\circ$.¹⁴ Therefore the product prepared is about 12 % active.

Analyses. Subs., 0.1134, 0.1214: 5.89, 6.27 cc. of 0.1040 *N* H_2SO_4 . Calc. for $\text{C}_5\text{H}_{10}\text{O}_4\text{NCl}$: N, 7.63. Found: 7.56, 7.52.

Attempts to Prepare Diethyl- α -diazoglutarate by Oppé's Method. Ethyl-5-pyrrolidone-2-carboxylate.—Fischer and Bolhner¹⁴ have prepared this compound by heating diethyl-glutamate and found that it was not racemized in the preparation, as upon hydrolysis it gives *d*-glutamic acid with full activity.

Fifteen g. of *d*-diethyl-glutamate was heated for 20 minutes on an oil-bath to 160 – 170° under a pressure of 20 mm. with a water pump, the flask was then evacuated with an oil pump when nearly all of the product distilled at a constant temperature; b. p., 137 – 140° , at 0.45 mm. Upon pouring the distillate into an open dish the product crystallized in white needles; yield 9.3 g. (80% of the calculated amount). After recrystallization from ether solution by the addition of petroleum ether the product softens at 49 – 50° and melts at 54° .

Analyses. Subs., 0.4511, 0.3556: 29.01 cc. of 0.09872 *N* HCl (Kjeldahl). Calc. for $\text{C}_7\text{H}_{11}\text{O}_2\text{N}$: N, 8.91. Found: 8.86, 8.84.

2.0013 g. dissolved in water and made up to a volume of 10.00 cc. gave a rotation of -0.49 in a 1dcm. tube in sodium light; $[\alpha]_D, -2.45^\circ$. Neither this product nor the free acid made by heating *d*-glutamic acid in a similar manner gives a nitroso derivative

¹⁴ Fischer and Bolhner, *Ber.*, **44**, 1332 (1911).

when treated with hydrochloric acid and sodium nitrite, sodium nitrite in glacial or 50% acetic acid or in a solution in dry ether when treated with amyl nitrite and dry hydrogen chloride.

***d*-Dimethyl-glutamate Hydrochloride.**—The crude ester hydrochloride was prepared exactly as described for the diethyl compound, but the ester hydrochloride would not crystallize upon cooling nor when precipitated from chloroform solution by means of ether.

Dimethyl- α -diazoglutamate.—This diazo compound was prepared from the crude amino ester hydrochloride, exactly as described for the diethyl ester, from 30 g. of the *d*-ester hydrochloride, giving 12 g. of the crude diazo ester. After distillation in a vacuum there was obtained 6 g. of product boiling at 86–87° at 0.5 mm.; d_4^{20} , 1.183; n_D^{20} , 1.4750; rotation in a 1dcm. tube at 22°, +1.04°; $[\alpha]_D^{22}$ +0.88°. The product was redistilled and 5 g. was obtained, boiling at 85–86° at 0.4 mm.; d_4^{20} , 1.185; n_D^{20} , 1.4753; rotation in a 1dcm. tube in sodium light at 22°, +1.06; $[\alpha]_D^{22}$, +0.89°.

Analyses. Subs., 0.2203, 0.2091: 29.87 cc. of N (23° and 739 mm.), 28.33 cc. (22° and 740 mm.). Calc. for $C_7H_{10}O_4N_2$: N, 15.07. Found: 14.78, 14.85.

Another preparation of this diazo ester was made in exactly the same way except that a lower pressure was used in the distillation. The results were exactly the same; b. p., 82–83° at 0.2 mm.

***d*-Isopropyl-glutamate.**—The crude ester hydrochloride was prepared in the same manner as described for the diethyl ester hydrochloride, except that it was necessary to heat the reaction mixture for about 3 times as long. The crude ester hydrochloride did not crystallize upon cooling, and could not be crystallized from chloroform by the addition of ether, so the free ester was liberated in the usual manner and the product distilled in a vacuum. From 50 g. of glutamic acid hydrochloride 22 g. of product was obtained, boiling at 115–117° at 0.15 mm. It is a water-white viscous oil; d_4^{20} , 1.023; n_D^{20} , 1.4402. The rotation in a 1dcm. tube in sodium light at 22° is +5.65°; $[\alpha]_D^{22}$, +5.08°.

Analyses. Subs., 0.2739, 0.2853: 11.49 cc., 11.97 cc., of 0.1040 *N* H_2SO_4 . Calc. for $C_{11}H_{21}O_4N$: N, 6.06. Found: 6.11, 6.10.

***d*-ISOPROPYL GLUTAMATE HYDROCHLORIDE.**—The ether solution of the free ester was treated with dry hydrogen chloride, and the ester hydrochloride was precipitated as a thick, viscous oil. The ether was decanted and the remainder of the ether and hydrochloric acid removed *in vacuo* over sulfuric acid and sodium hydroxide. The yield was practically quantitative.

Di-isopropyl- α -diazoglutamate.—The preparation of this diazo ester was carried out exactly as described for the diethyl ester, using the ester hydrochloride prepared by precipitation of the free ester from ether solution by dry hydrogen chloride. From 20 g. of the ester hydrochloride there was obtained 6 g. of crude product, which was washed and dried as described for the diethyl ester. The crude material had a rotation of +1.24° in a 1dcm. tube in sodium light. It was tested for amino nitrogen by the Van Slyke method; 0.1084 g. was warmed with 50% acetic acid until the yellow coloration was destroyed and then gave only 0.04 cc. of nitrogen when treated in a micro Van Slyke apparatus. An attempt to distil a portion of the product resulted in decomposition.

Di-isopropyl- α -hydroxyglutamate.—The remainder of the crude diazo ester prepared above was shaken with 20% sulfuric acid in the usual manner until the yellow color disappeared. The mixture was then extracted with ether, the ether layer dried over anhydrous sodium sulfate, the ether evaporated on the water-bath and the product distilled with steam; yield, 2 g. The substance is slightly heavier than water; n_D^{20} , 1.4440; 1.4732 g. of substance made up with ether to 5.00 cc., gave a rotation in a

1dcm. tube in sodium light at 24° of +0.33°; $[\alpha]_D^{24}$, +1.12°. It gave no test for amino nitrogen when tested by the Van Slyke nitrous acid method.

Attempt to Prepare *d*-Di-*n*-butyl Glutamate.—Fifty g. of *d*-glutamic acid hydrochloride was treated in the same way as that used for the preparation of the di-*isopropyl* ester. The product after the evaporation of the excess alcohol did not crystallize, but was soluble in ether. The crude material was treated with potassium carbonate and conc. sodium hydroxide in the usual manner to obtain the free amino ester¹¹ which was then distilled in a vacuum; yield, 20 g.; b. p., 151–153° under 0.2 mm. pressure. The product is a colorless, very viscous, sirupy liquid containing a small amount of suspended flaky material. It was redistilled and obtained as a clear oil, which did not crystallize when immersed in a bath of salt and ice; d_4^{20} , 1.1101; n_D^{20} , 1.4773; rotation in a 1dcm. tube in sodium light at 22°, –13.75°; $[\alpha]_D^{22}$, –12.39°.

Analyses. Subs., 0.8499, 0.3201: 46.58, 17.62 cc. of 0.0979 *N* HCl. Calc. for C₁₃H₂₅O₄N: N, 5.40; calc. for C₉H₁₆O₂N; N, 7.56. Found: (Kjeldahl), 7.53, 7.55.

The product did not react when treated with an equivalent amount of hydrochloric acid and sodium nitrite at 0°. The product evidently is butyl-5-pyrrolidone-2-carboxylate. It probably was formed during the esterification and not upon distillation, as the crude esterification mixture after evaporation of the excess alcohol was soluble in ether.

***l*-Diethyl-Aspartate Hydrochloride.**—The crude ester hydrochloride was prepared from *l*-asparagin according to the method of Curtius and Lang¹⁵ and was recrystallized from chloroform solution by means of ether as described for *d*-diethyl-glutamate. From 30 g. of asparagin there was obtained 27 g. of the ester hydrochloride; m. p., 95°.

Diethyl- α -diazosuccinate.—This compound was prepared from the recrystallized amino ester hydrochloride according to the method of Curtius and Müller.¹⁶ From 27 g. of the ester hydrochloride there was obtained after two distillations 7 g. of product, boiling at 77–78° under 0.1 mm. pressure; d_4^{20} , 1.139; rotation in a 1dcm. tube in sodium light at 22°, –1.40°; $[\alpha]_D^{22}$, –1.23°; n_D^{20} , 1.4620. The product was analyzed by the sulfuric acid method.

Analyses. Subs., 0.2106, 0.2083: 26.94, 26.53 cc. of N₂ (24° and 742 mm.). Calc. for C₈H₁₂O₄N₂: N, 14.00. Found: 13.93, 13.87.

The product was tested for amino nitrogen by the Van Slyke nitrous acid method; 0.10 cc. of the diazo ester after treatment with 50% acetic acid until the yellow color was destroyed gave only 0.02 cc. of nitrogen. The diazo ester was treated with dil. sulfuric acid in the usual manner; 3.0112 g. of crude material was obtained. The product was diluted with ether to a volume of 5.00 cc. and the rotation taken in a 1dcm. tube in sodium light at 24°; α , –0.59°; $[\alpha]_D^{24}$, –0.98°.

α -Amino-*n*-caproic Acid (Nor-leucine).—This amino acid was prepared by the methods previously used¹⁷ and resolved by means of the brucine salt of the formyl derivative.¹⁸ The *d* and *l* ethyl esters were prepared by Fischer's method¹⁹ and the ester hydrochlorides prepared by the method of Noyes and Marvel.¹

Preparation of Optically Active Diazo Esters from the *d*- and *l*-Ester Hydrochlorides of α -Amino-*n*-Caproic Acid.—The diazo esters from these esters have been prepared by Noyes and Marvel¹ and found to be inactive. Using substantially the same method, except that 10% sulfuric acid was used instead of glacial acetic acid and lower pressures for the distillation, optically active diazo esters were prepared. The crude diazo esters

¹⁵ Curtius and Lang, *J. prakt. Chem.*, [2] **44**, 562 (1891).

¹⁶ Curtius and Müller, *Ber.*, **37**, 1261 (1904).

¹⁷ *Z. physiol. Chem.*, **86**, 454 (1913); THIS JOURNAL, **42**, 320 (1920). Ref. 1, p. 2270.

¹⁸ *Ann.*, **362**, 333 (1908).

¹⁹ Ref. 11, p. 433.

obtained were purified in the same manner as already described for diethyl-diazo-glutarate, but the treatment with sodium methylate was omitted. Using 20 g. of the *l*-ester hydrochloride, ($[\alpha]_D^{23}$, -7.27°), 4.6 g. of crude diazo ester was obtained which after one vacuum distillation (boiling point $53-54^\circ$ at 0.35 mm.) had a specific rotation of -1.89° . After a second distillation 2 g. was obtained, b. p., $54-55^\circ$ at 0.35 mm.; $[\alpha]_D$, -1.89° ; n_D^{20} , 1.4535; d_4^{20} , 0.972.

The product was again distilled in a vacuum and 1.1 g. of substance was obtained, b. p., $54-55^\circ$ at 0.35 mm.; n_D^{20} , 1.4543; d_4^{20} , 0.974.

1.0112 g. was dissolved in dry ether and made up to 2.00 cc.; the rotation in a 1dcm. tube in sodium light at 24° was -0.97° ; $[\alpha]_D^{24}$, -1.92° .

Analyses. (Sulfuric acid method). Subs., 0.1567, 0.2243: 24.19 cc. of N_2 (23° and 745 mm.), 33.50 cc. (24° and 745 mm.). Calc. for $C_8H_{14}O_2N_2$: N, 16.47. Found. 16.27, 16.33.

The product gave no test for amino nitrogen when tested by the Van Slyke and nitrous acid method in the usual way. When the product was hydrolyzed with dil. sulfuric acid as described for diethyl-diazoglutarate, the hydrolyzed product was levorotatory and upon saponification a levorotatory sodium salt was obtained. The aqueous solution was acidified and extracted with ether. The ether extract was also levorotatory.

From 12 g. of the *d*-ester hydrochloride ($[\alpha]_D$, $+5.48^\circ$) there was obtained 3 g. of the crude diazo ester, which after vacuum distillation (b. p., $53-55^\circ$ at 0.35 mm.) had a rotation in a 1dcm. tube of $+1.79^\circ$. After a second distillation 1.4 g. of product was obtained, b. p. 54.55° at 0.35 mm.; n_D^{20} , 1.453; d_4^{20} , 0.97; 1.1813 g., dissolved in ether, and made up to 2.00 cc. gave a rotation in a 1dcm. tube in sodium light at 23° of 1.09° ; $[\alpha]_D^{23}$, $+1.84^\circ$.

Analyses. Subs., 0.1843, 0.1663: 26.82, 24.16 cc. of N_2 (24° and 741 mm.). Calc. for $C_8H_{14}O_2N_2$: N, 16.47. Found: 15.82, 15.79.

When the substance was hydrolyzed by dil. sulfuric acid in the manner described for diethyl-diazoglutarate, the ether solution was dextrorotatory. With a volume of ether solution of 5.00 cc. the rotation in a 1dcm. tube in sodium light was $+0.22$; the ether was evaporated, and the residue weighed 0.9211 g., whence $[\alpha]_D$, $+1.19^\circ$.

The crude hydroxy ester was saponified. When this saponification mixture was acidified and extracted with ether, the ether extract was also dextrorotatory.

α -Amino-isocaproic Acid (Leucine).—This amino acid was prepared and resolved by the methods given in the literature.²⁰ The *d* and *l* esters were prepared by Fischer's method,¹³ and the ester hydrochlorides were prepared by dissolving the free ester in ether and passing in dry hydrogen chloride. Ten g. of the *l*-leucine ($[\alpha]_D$, -15.47° in 20% HCl) gave 9.5 g. of ester, b. p., $84-85^\circ$ at 13 mm.; d_4^{20} , 0.92; rotation in a 1dcm. tube in sodium light at 22° , -10.95° ; $[\alpha]_D^{22}$, -11.41° . The yield of the ester hydrochloride was 11.5 g.

Ethyl- α -diazoisocaproate.—The ester hydrochloride was diazotized in the usual manner. From 11.5 g. of the hydrochloride there was obtained 2.0 g. of the diazo ester boiling at $47-50^\circ$ under 0.5 mm. pressure; d_D^{20} , 0.958; n_D^{20} , 1.4310; 1.8360 g. made up to 5 cc. with ether gave a rotation in a 1dcm. tube in sodium light of -0.56° ; $[\alpha]_D$, -1.52° . The product was redistilled and 1.2 g. was obtained, b. p., $49-50^\circ$ at 0.50 mm.; d_4^{20} , 0.961; n_D^{20} , 1.4333.

1.1138 g. made up to 5 cc. with ether gave a rotation in a 1dcm. tube in sodium light at 24° of -0.34° ; $[\alpha]_D^{24}$, -1.52° . The product was analyzed by the sulfuric acid method.

Analyses. Subs., 0.1438, 0.1518: 21.33, 22.30 cc. of N_2 (24° and 7.41 mm.). Calc. for $C_8H_{14}O_2N_2$: N, 16.47. Found: 16.12, 15.97.

²⁰ Fischer and Warburg, *Ber.*, **38**, 3997 (1905).

Summary

1. Diazo esters were prepared from the following amino ester hydrochlorides by the Curtius method: *d*-diethyl-glutamate hydrochloride, *d*-dimethyl-glutamate hydrochloride; *l*-ethyl- α -amino-*n*-caproate hydrochloride, *d*-ethyl- α -amino-*n*-caproate hydrochloride; *l*-ethyl- α -amino-*iso*-caproate hydrochloride, *l*-diethyl-aspartate hydrochloride.

2. The diazo esters prepared from all of the above amino esters were found to be optically active in the same sense as the original amino esters.

3. When these diazo esters are decomposed by dilute acids the products are optically active, in the same sense and to a similar degree.

4. The products obtained by the treatment of diazo esters with dilute acids are strongly unsaturated, indicating the presence of considerable amounts of the corresponding unsaturated esters.

5. When the amino esters are treated with nitrous acid under conditions by which the diazo esters are decomposed without being isolated the products are optically active, in the same sense but to a slightly higher degree than those obtained from the decomposition of the purified diazo esters.

6. The products obtained under these conditions have exactly the same physical constants as those obtained by the decomposition of the purified diazo ester, except for a slightly higher optical activity.

7. Vacuum distillation of the hydrolysis products of diethyl- α -diazoglutarate decreases the activity on the first distillation but subsequent distillation causes no further change in activity. Analysis, density and molecular refraction indicate that the product is a constant-boiling mixture of the unsaturated ester and ester lactone.

8. The product obtained by steam distillation shows exactly the same properties and constants.

9. Upon saponification of the hydrolysis products of the diazo esters, optically active sodium salts are obtained which rotate in the same direction as the original amino acids.

10. When the sodium salts are acidified and the mixture extracted with ether the ether extract is optically active in the same sense as the original amino acids.

11. Upon reduction with aluminum amalgam in moist ether solution diethyl-diazoglutarate, followed by acid hydrolysis, gives glutamic acid with a rotation corresponding to approximately 13% of the active acid.

12. Impure di-*isopropyl*- α -diazoglutarate was prepared, which was optically active but it was largely decomposed upon distillation.

13. Impure ethyl- and methyl- γ -diazovalerates were prepared from the lactam of γ -aminovaleric acid by Oppé's method.

14. An attempt to prepare *d*-dibutyl-glutamate by the usual method

resulted in the production of butyl-5-pyrrolidone-2-carboxylate; $[\alpha]_D^{23}$, -12.39° .

15. The production of partially active hydroxy esters by the treatment of diazo esters with dilute acids, together with the production of partially active amino esters by their reduction, may indicate the existence of two forms of diazo ester, possibly corresponding to the compounds indicated by the Curtius and Angeli-Thiele formulas, respectively.

16. It seems impossible to reconcile the Curtius formula for active diazo esters with the ideas of atomic structure and of non-polar valence proposed by G. N. Lewis and Irving Langmuir. The Angeli-Thiele formula may be reconciled with those theories if we assume that the polar valence between an ammonium group and another atom is a definite bond located in a fixed position in the compound.

URBANA, ILLINOIS

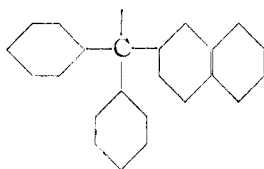
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TRIPHENYLMETHYL. XXX. DIPHENYL-BETA-NAPHTHYLMETHYL AND THE COLOR OF FREE RADICALS¹

BY M. GOMBERG AND F. W. SULLIVAN, JR.

Received June 5, 1922

Our purpose in the present investigation has been to prepare the free radical, diphenyl- β -naphthylmethyl



and to study it with regard to the characteristic chemical reactions and physical properties of free radicals; as a later development, because of the peculiar adaptability of this radical to the problem, it was studied especially from the standpoint of the relation between color and chemical constitution. The characteristic phenomena investigated included the absorption of oxygen, the reaction with iodine, the effects produced by light and acids, the conductivity, the dissociation of the hexa-aryl ethane, the formation of additive compounds, and finally, the effect of dilution and temperature changes upon the color of solutions of the free radical.

The striking fact that triphenylmethyl, although a hydrocarbon, is colored when in solution has given rise to many explanations in order to account for this phenomenon. The principal theories regarding the re-

¹ The material here presented is from the thesis submitted by F. W. Sullivan, Jr., to the Faculty of the University of Michigan in partial fulfillment of the requirements for the degree of Doctor of Philosophy (1921).