THE FORMATION OF CYCLIC COMPOUNDS FROM DERIVATIVES OF DIPHENYL. PART III. OPTICAL RESOLUTION OF 6-NITRO-6'-ACETAMIDODIPHENIC ACID, AND FORMATION OF 5-NITROPHENANTHRIDONE-4-CARBOXYLIC ACID THEREFROM.

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Received July 19th, 1934. Published September 28th, 1934.

In Parts I(1) and II(2) of this series, an account was given of the experiments showing that, whilst formation of five- or six-membered rings through the 2- and 2'-positions of optically active diphenyl compounds leads always to inactive products, no such disappearance of activity takes place when seven- or eight-membered rings are formed by linking the 2- and 2'-positions. The importance attached to these observations from the point of view of structure of the substances concerned is that they afford very convincing evidence for the coplanar structure of compounds containing five- or six-membered rings on the one hand, and for the non-coplanar structure of such substituted diphenyls and in substances containing seven- or eight-membered rings on the other. It will be noticed that, in the experi-

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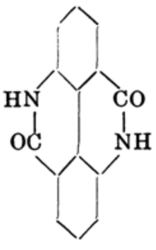
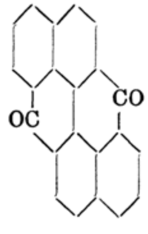
(1) Sako, *Mem. Coll. Eng., Kyushu Imp. Univ.*, **6** (1932), 263.

(2) Sako, this Bulletin, **9** (1934), 55.

ments referred to above, it is only in the formation of six-membered rings, namely, in that of compounds (I)⁽³⁾ and (II)⁽⁴⁾ from 6,6′-diacetamidodiphenic acid and 2,2′-dicarboxy-1,1′-dinaphthyl respectively, that two rings, one on either side of the diphenyl molecule, are formed, a result which is natural for diphenyl-compounds having such structures as the two just mentioned. The present investigation was instituted with the object of obtaining information regarding a compound which, as in those possessing five-, seven-, or eight-membered rings, has only one six-membered ring formed through the 2- and 2′-positions of 2,2′,6,6′-substituted diphenyl.

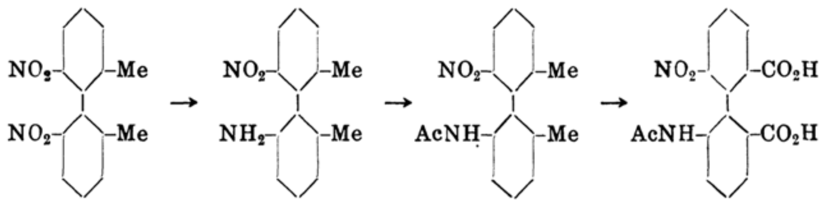


(I)



(II)

As the compound capable of producing only one six-membered ring, 6-nitro-6′-acetamidodiphenic acid was chosen, which was prepared from 2,2′-dimethyl-6,6′-dinitrodiphenyl by the following series of processes :



(III) (IV) (V) (VI)

The conversion of 2,2′-dimethyl-6,6′-dinitrodiphenyl (III) into 2,2′-dimethyl-6-amino-6′-nitrodiphenyl (IV) has been effected by Angeletti,⁽⁵⁾ who used alcoholic ammonium sulphide as the reducing agent. It has now been found that this conversion can be accomplished more conveniently by the use of sodium sulphide in place of ammonium sulphide. However, it should be added that sodium sulphide can act in a way other than the above-mentioned partial reduction which occurs when the reaction is carried out under mild conditions. Under somewhat more drastic conditions, there occurs the formation of a cyclic azoxy-compound, 4,5-dimethyl-phenazone oxide (VII), a reaction which recalls the formation of (VIII) and (IX) from 2,2′-dinitro-diphenyl and 4,4′-dimethyl-2,2′-dinitro-diphenyl respectively under similar circumstances.⁽⁶⁾

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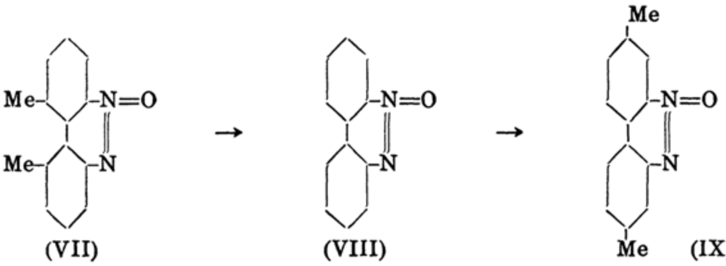
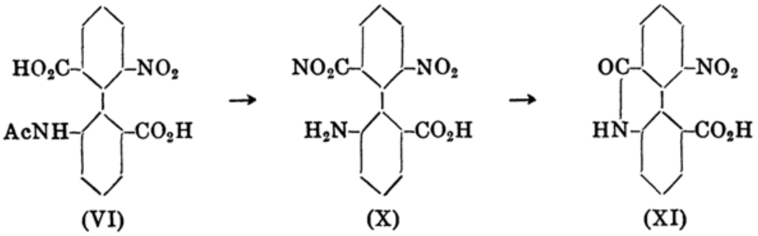
(3) Meisenheimer and Höring, *Ber.*, **60** (1927), 1433.
(4) Kuhn and Albrecht, *Ann.*, **465** (1928), 282.
(5) *Gazz. chim. ital.*, **61** (1931), 651.
(6) Ullmann and Dieterle, *Ber.*, **37** (1904), 23.


(VII) (VIII) (IX)

Attempted resolution of *dl*-6-nitro-6′-acetamidodiphenic acid (VI) with brucine has been fruitless. An almost quantitative resolution, however, has been realized by the use of strychnine, the acid strychnine salt of the *l*-acid and both the acid and neutral strychnine salts of the *d*-acid being obtained easily. The active acids freed from strychnine have $[\alpha]_D = \pm 122.1^0$ in a slightly ammoniacal solution. The ammonium as well as sodium salt of the active acids are stable to heat, but the free acids dissolved in concentrated hydrochloric acid appear to racemize even in the cold.

6-Nitro-6′-acetamidodiphenic acid (VI), on heating with sulphuric acid, yields 4-carboxy-5-nitrophenanthridone (XI). The phenanthridone derivative (XI) produced from the active acids has been found to be optically inactive. It has not been possible to isolate the intermediate amino-acid (X), and yet, compared with the formation of the dilactam (I) from 6,6′-diacetamidodiphenic acid which was stated to take place easily, (VI) is converted into (XI) with greater difficulty.


(VI) (X) (XI)

Since the active forms of 6-nitro-6′-acetamidodiphenic acid do not appear stable in the presence of concentrated hydrochloric acid as already stated, the disappearance of optical activity when the phenanthridone derivative (XI) is formed from the active acids in the presence of concentrated sulphuric acid can scarcely be regarded as providing evidence in favour of the coplanar structure for (XI). Nevertheless, it seems not unreasonable to suppose that this question of structure should depend on the

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(7) Kenner and Stubbings, *J. Chem. Soc.*, **119** (1921), 593.

size of two atoms which participate in forming a six-membered ring through the 2- and 2′-positions. If the distance between the centres of two atoms in question is smaller than, or nearly equal to, that of the aromatic carbon atoms (1.45Å), as is the case when the atoms are -C-C-, -C-N-, or -N-N-, etc. as in the compounds (I), (II), (VII), and (XI), such a six-membered ring should be uniplanar, for, if so, there is little or no strain. If, on the other hand, it is much larger than 1.45Å as in -S-S- or -As-As-, etc., it is doubtful whether such a compound has normally a coplanar structure, for, if so, it should be accompanied by the production of strain.

Experimental.

(A) Preparation of *dl*-6-Nitro-6′-acetamidodiphenic acid.

2,2′-Dimethyl-6-amino-6′-nitrodiphenyl (IV). This compound has been obtained by Angeletti(5) by the reduction of 2,2′-dimethyl-6,6′-dinitrodiphenyl with alcoholic ammonium sulphide. The following method, which has been evolved after a large number of comparative experiments, and in which sodium sulphide is employed in place of ammonium sulphide, is not only more convenient but gives a better yield than Angeletti's : a yield of 73 per cent. is obtained by the present method, but 56 per cent. by his method, although allowance has to be made for the unchanged original dinitro-compound which is stated to be recovered to the extent of 33 per cent. by Angeletti's method. Another advantage of the present method is that a large quantity, and indeed any desired amount, of the dinitro-compound can be treated in one experiment with equally good result. The success of the reduction is dependent essentially upon the quantity of the reducing agent and, in a lesser degree, upon temperature, the use of an amount less than given in the direction below leading to incomplete reaction and the use of a more amount at a higher temperature to the production of the cyclic azoxy-compound as described elsewhere.

2,2′-Dimethyl-6,6′-dinitro-diphenyl (136 g.) was dissolved in boiling ethyl alcohol (1300 c.c.) and the solution was allowed to cool. As soon as the temperature reached about 50°C., a solution of $Na_2S.9H_2O$ (240 g.) in water (300 c.c.) previously heated to the same temperature was added with shaking. Some of the separated dinitro-compound disappeared in three to five minutes forming a red solution, meanwhile temperature of the liquid approaching the boiling point of ethyl alcohol. The solution was allowed to stand for an hour or so, at the end of which its temperature was 50°C. Water (450 c.c.) was then added with shaking, when 2,2′-dimethyl-6-amino-6′-nitrodiphenyl began to crystallize at once. The crystals were collected and washed with a mixture of water and alcohol. The substance weighed 80.5 g. By further dilution of the mother liquor with water (650 c.c.) a second crop melting at 121–123° was obtained, which, on one crystallization from alcohol-water gave a material (9.2 g.) having the same purity as the main crop. The substance thus obtained, as indicated by its melting point (123–124.5°), was almost pure and might be used for further experiments. But it was easily purified by recrystallization from alcohol-water. Then it formed lustrous, yellow, thin plates melting at 124–125° (the m. p. recorded by Angeletti is 122–123°) (Found: C, 69.58; H, 5.87; N, 11.81. Calculated for $C_{14}H_{14}O_2N_2$: C, 69.39; H, 5.83; N, 11.57%). 2,2′-Dimethyl-6-amino-6′-nitrodiphenyl can be distilled under reduced pressure without decomposition.

4,5-Dimethylphenazone oxide (VII). A solution of $Na_2S.9H_2O$ (5.0 g.) in water (3.6 c.c.) was added to a solution of 2,2′-dimethyl-6,6′-dinitrodiphenyl (1.4 g.) in ethyl alcohol (14 c.c.), and the mixture was heated on the boiling water bath. A vigorous reaction occurred. After 45 minutes' heating, water (6.0 c.c.) was added and the turbid mixture thus obtained, on standing, gave crystalline product (0.43 g.) melting at 151–152.5°C. On crystallization from ethyl alcohol (4 c.c.) it formed yellow needles (0.37 g.) melting at 153°C. (Found: C, 74.8; H, 5.4. Calculated for $C_{14}H_{12}ON_2$: C, 75.0; H, 5.4%).

2,2′-Dimethyl-6-nitro-6′-acetamidodiphenyl (V). 2,2′-Dimethyl-6-amino-6′-nitrodiphenyl (9.7 g.) dissolved in benzene was heated with acetic anhydride (4.4 g.) for 30 minutes. The solution was then shaken with a sodium carbonate solution in order to remove acetic acid formed, and after concentrated greatly, left to crystallize. It was often found necessary to inoculate or to scratch the wall of the vessel to start crystallization. The yield was quantitative. The light yellow needles thus obtained, when dried in an air bath at 60°C., used to begin softening at 83°, and to melt completely at 92°. But on rare occasions, it occurred that they melted sharply at 103–104°C. after the same treatment. The analysis of the lower melting substance indicated that there was one molecule of benzene for two molecules of the acetyl-compound (Found: C, 70.2; H, 6.1. Calculated for $C_{42}H_{42}O_6N_4$: C, 70.6; H, 5.9%). The higher melting form was found to be free from benzene (Found: C, 67.8; H, 5.8; N, 10.1. Calculated for $C_{16}H_{16}O_3N_2$: C, 67.6; H, 5.6; N, 9.9%). The melting point of the lower melting substance did not change after months' standing at ordinary temperature, which showed that the benzene was firmly held. But on keeping it for some time at 80°C., the solvent was removed, the higher melting substance being obtained. A strange incident observed in this connection was that, when the crystals, just after separated from the mother liquor, were devided into two portions, one half was dried at 60°C. and the other preserved in a vacuum desiccator (4 mm.) at room temperature, it was found that the former, as usual, had m.p. 92°C., while the latter melted sharply at 103–104°C. This phenomenon, however, was not always observed.

dl-6-Nitro-6′-acetamidodiphenic acid (VI). A suspension of 2,2′-dimethyl-6-nitro-6′-acetamidodiphenyl (14.5 g.) in a solution of potassium permanganate (46.0 g.) and crystalline magnesium sulphate (33.0 g.) in water (2000 c.c.) was heated on the boiling water bath with efficient agitation for 2.5 to 3.0 hours, at the end of which the colour of the permaganate disappeared. (When heated without agitation, some of the original compound remained unchanged even after 10 hours, when the permanganate was consumed. Further, when the oxidation was effected by heating over a wire gauze, a trace of the phenanthridone derivative (XI) was produced, an impurity difficult to remove in the later purification work.) The reaction mixture was then cooled, filtered, and the filtrate greatly concentrated in vacuo. After treated with animal charcoal the clear solution was acidified with 50 per cent. sulphuric acid (30 c.c.). The greater part of the product separated at once as an oil which slowly crystallized. The mixture was cooled in ice water for two hours and the solidified mass was collected. For purification, the crude product (15.3 g.) was dissolved in acetone (50.0 c.c.), filtered if necessary, and the solution was mixed with an equal volume of chloroform. Crystallization commenced at once, but it took a long time to complete separation. Thus, almost pure light yellow crystals (13.3 g.) was obtained, but they were once recrystallized from acetone alone. The substance decomposed at 227°C. with darkening after sintering at about 130°C. (Found: C, 55.0; H, 3.9; N, 8.2. Calculated for $O_{16}H_{12}O_7N_2$: C, 55.8; H, 3.5; N, 8.1%). The *dl*-acid in the purest state, which was obtained from the purified strychinine salts, decomposed however at 229°C. after softening at about 130°C. It is easily soluble in methyl and ethyl alcohols, less so in acetone, and insoble in chloroform and benzene. It is sparingly soluble in cold water. In boiling water, it is converted though very slowly, into 4-carboxy-5-nitrophenanthridone. This conversion is accelerated by the presence of strong inorganic acids.

(B) **Resolution of *dl*-6-Nitro-6′-acetamidodiphenic acid (VI), and its Conversion into 5-Nitrophenanthridone-4-carboxylic Acid (XI).** Attempts to resolve *dl*-6-nitro-6′-acetamidodiphenic acid with brucine have not been successful. An easy resolution, however, has been accomplished through the strychnine salts.

Acid Strychnine l-6-nitro-6′-acetamidodiphenate. A hot solution of strychnine (6.68 g.) in chloroform (40 c.c.) was added to a boiling solution of *dl*-6-nitro-6′-acetamidodiphenic acid (6.88 g.) in methanol (280 c.c.) and the resulting solution was heated under reflux for 1.0 to 1.5 hours. The acid strychnine *l*-6-nitro-6′-acetamidodiphenate usually began to appear as yellow needles after 20 to 40 minutes′ heating. Most of the salt separated while heating, but it was allowed to stand overnight to complete crystallization. As the yellow needles are very difficultly soluble in cold methanol, the *l*-acid present could be separated almost completely in this form, which, after being filtered, could be thoroughly washed with the solvent. (The mother liquor obtained here was used for the separation of the strychnine salts of the *d*-acid as described later.) The yellow needles obtained in this way were found to be so pure that further purification was unnecessary. No change was observed in the melting point (273° with decomposition), in the analytical results, and in the rotation before and after recrystallization from methanol (Found: C, 66.1; H, 5.8; N, 8.4. Calculated for $C_{16}H_{12}O_7N_2 \cdot C_{21}H_{22}O_2N_2$: C, 65.5; H, 5.0; N, 8.3%. Rotation: 0.0226 g. of the substance made up to 15 c.c. with methanol gave $\alpha^{20}_{D} = -0.22^\circ$ for $l = 2$, hence $[\alpha]^{20}_{D} = -73.0^\circ$). To dissolve one gram of the acid strychnine salt of the *l*-acid, it is necessary to boil it with 300 c.c. of methanol for a considerable time. The yellow needles dried in the desiccator somewhat gain weight on exposure to the moist air.

Acid Strychnine d-6-Nitro-6′-acetamidodiphenate. This salt was obtained by concentrating the mother liquor separated from the yellow needles of the acid strychnine salt of the *l*-acid described above. It was often found necessary to inoculate or to scratch the wall of the vessel to start crystallization. It separated usually as crystals free from methanol, but occasionally it happened that crystals containing one molecule of the solvent was formed, which almost completely melted at 175°, where the other showed no change. Both were decomposed, however, at the same temperature, 263°C. They were both nearly colourless, a property in which they differ from the distinctly yellow salt of the *l*-acid. The separation of the acid strychnine salt of the *d*-acid from a methyl alcoholic solution was so sluggish that it was not complete even after leaving overnight, but by evaporation of the solvent on the water bath a greatly supersaturated solution could be obtained, from which the major part of the salt separated fairly quickly on cooling. Crystallized in this way, it formed clusters of almost colourless plates containing no methanol. (The methanol containing substance lost 4.7 per cent. in weight at 80°. Calculated for $C_{28}H_{34}O_9N_4 \cdot CH_3OH$: CH_3OH, 4.5%. Found for methanol-free substance: C, 65.8; H, 5.6. Calculated for $C_{28}H_{34}O_9N_4$: C, 65.5; H, 5.4%. Rotation: 0.0678 g. of substance not containing methanol made up to 15 c.c. with methanol gave $\alpha^{20}_{D} = +0.33^\circ$ for $l = 2$; hence $[\alpha]^{20}_{D} = +36.5^\circ$.)

Neutral Strychnine d-6-Nitro-6′-acetamidodiphenate. As stated above, the crystallization of the acid strychnine salt of the *d*-acid from the methyl alcoholic mother liquor is very sluggish and, moreover, incomplete, a rather large loss of the material being caused. On the other hand, the neutral strychnine salt of the *d*-acid separates from methanol more completely and more quickly, and, therefore, it is better to isolate the *d*-acid in this form. For this purpose, the boiling methyl alcoholic solution (the filtrate separated from the *l*-acid salt) containing the acid strychnine salt of the *d*-acid was treated with a solution of the required quantity of strychnine in chloroform, and the resulting solution concentrated into one-third the original bulk. On cooling, the neutral salt of the *d*-acid appeared in colourless, voluminous needles. In this way, from 6.88 g. of the *dl*-acid, 9.0 g. of neutral strychnine salt was obtained. One recrystallization from methanol (90 c.c.) sufficed to obtain the salt in pure state. It melted at 175° almost completely and decomposed slowly at 207°. It had two molecules of methanol removable by heating at 80°C. (The substance lost 6.2 per cent. in weight at 80°C. Calculated for $C_{58}H_{56}O_{11}N_6 \cdot 2CH_3OH$: CH_3OH, 6.0%. Found for methanol-free substance: C, 68.3; H, 6.1. Calculated for $C_{58}H_{56}O_{11}N_6$: C, 68.8; H, 5.5%. Rotation: 0.1012 g. of substance freed from methanol made up to 15 c.c. with methanol gave $\alpha_D^{20} = +0.16°$ for $l = 2$; hence $[\alpha]_D^{20} = +11.9°$.)

d- and l-6-Nitro-6′-acetamidodiphenic acids. A mixture of 0.1695 g. of the acid strychnine *d*(or *l*)-6-nitro-6′-acetamidodiphenate (corresponding to 0.0860 g. of the free acid) and a slight excess of ammonia was shaken repeatedly with chloroform until the solution was free from strychnine, and the solution was diluted up to 15 c.c. with water. It had $\alpha_D = \pm 1.40°$ for $l = 2$; hence $[\alpha]_D = \pm 122.1°$. The neutral strychnine salt of the *d*-acid (0.1012 g. which contain 0.0344 g. of the free acid) was treated in the same way with aqueous ammonia and chloroform. The solution made up to 15 c.c. gave $\alpha_D = +0.56°$ for $l = 2$; hence $[\alpha]_D = +122.1°$.

The rotation of the active acids had to be examined in the way described above because of the difficulty in isolating the active forms in pure crystalline state. Unlike the *dl*-form, the active forms are very soluble in water and, moreover, when forced to separate from a solution, they tend to form an oil which crystallizes with difficulty. These properties rendered the isolation of the active acids in pure state impossible. Thus, for instance, when a concentrated aqueous solution of the ammonium salt of the active acid, obtained by shaking the strychnine salt with ammonia and chloroform, was acidified with a large quantity of sulphuric acid, only a small portion of the active acid crystallized, which, for the above-mentioned reasons, could not be purified by crystallization.

The decomposition of the ammonium salt of the *l*-acid, obtained by drying its aqueous solution in vacuo, with the calculated amount of oxalic acid in acetone met with rather better success. On mixing an acetone solution of oxalic acid with that of the ammonium salt of the *l*-acid, ammonium oxalate separated, which was filtered off. The filtrate, on concentration followed by addition of chloroform, deposited a small quantity of an oil which, on being left overnight, formed light yellow thin needles (resembling the *dl*-acid in colour) melting at 93°C. with slight decomposition after softening at 85°C. It was readily soluble in acetone and methanol and insoluble in chloroform. It was not quite pure as indicated by the rotation (0.0344 g. of substance made up to 15 c.c. with methanol gave $\alpha_D = -0.33°$ for $l = 2$, while α_D for the *l*-acid, calculated from those of the three strychnine salts obtained under the same conditions as already described, is $-0.50°$). The yield of the crystals, 17 per cent. of the theoretical, proved, however, to be too small for purification, and the matter was no further pursued.

The active acid appeared to racemize easily in concentrated hydrochloric acid at low temperatures. When a solution of the ammonium salt of the *d*-acid in 5 c.c. of water, obtained from the neutral strychnine salt (3.0 g.), was saturated with hydrogen chloride in a freezing mixture bath, ammonium chloride (0.2 g.) separated first. On filtration, the hitherto yellow solution suddenly turned brown in colour, a small quantity of brownish crystals separating. The brown colour, however, disappeared after a time. Evidently, this must have been the indication that at least a part of the substance had racemized, for the crystals (0.30 g.) collected after some time had α_D in methanol about one-fourth the value expected. The aqueous solution of the ammonium salt of the active acid is stable to heat, no change in optical activity being observed by heating on the water bath for a long time.

5-Nitrophenanthridone-4-carboxylic acid (XI). This substance is produced by heating 6-nitro-6′-acetamidodiphenic acid with sulphuric acid. This change takes place, though not without difficulty, even when an aqueous solution of the diphenic acid derivative is boiled over a free flame in absence of mineral acids. Still, in order to complete the change, the nitroacetamidodiphenic acid has to be heated for a long time with concentrated sulphuric acid. Thus, for instance, when a solution of the diphenic acid derivative in 75 per cent. sulphuric acid was heated on the boiling water bath the crystalline phenanthridone derivative commenced to separate in 30 minutes, but the crystals increased very slowly and the reaction was not complete after 7 hours' heating.

The best yield of the phenanthridone derivative was obtained as follows: a solution of 6-nitro-6′-acetamidodiphenic acid (0.69 g.) in concentrated sulphuric acid (5 c.c.) was heated on the boiling water bath for 8 hours. It was then cooled, diluted with 3.5 c.c. of water (this caused the product to precipitate), and heated again at 100°C. for an hour. After cooling, the yellow powdery crystals were filtered, and washed first with water and then with acetone. The compound does not melt at 330°C. The yield was 0.54 g. or 94.7 per cent. of the theoretical (Found: N, 9.6. Calculated for $C_{14}H_8O_5N_2$: N, 9.8%). It is insoluble or practically insoluble in usual organic solvents. It dissolves sparingly when boiled with nitrobenzene but the solution darkens at the same time. It is soluble in concentrated sulphuric acid and in alkali or sodium carbonate solution. These solutions become gradually dark on standing.

5-nitrophenanthridone-4-carboxylic acid produced from the active 6-nitro-6′-acetamidodiphenic acids was optically inactive.

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