166. *The Coupling of Diazonium Salts with Derivatives of Cyclic β-Ketonic Acids.*

By R. P. Linstead and Abel Bao-Lang Wang.

Fifty years ago, Japp and Klingemann found that benzenediazonium chloride coupled with ethyl methylacetoacetate in alkaline solution to give the phenylhydrazone of ethyl pyruvate with elimination of acetic acid; if, on the other hand, the ketonic ester was first hydrolysed by standing with alkali and then coupled, the product was the monophenylhydrazone of diacetyl, carbon dioxide being eliminated (*Ber.*, 1887, **20**, 2942, 3284, 3398; *Annalen*, 1888, **247**, 190):

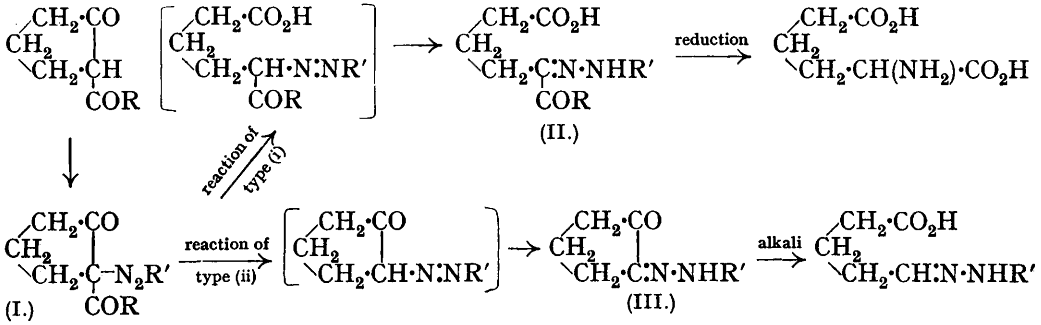
$$\text{(i)}\quad CH_3\cdot CO\vdots CHMe\cdot CO_2Et \longrightarrow CH_3\cdot CO_2H + CH_3\cdot C(CO_2Et){:}N\cdot NHPh$$

$$\text{(ii)}\quad CH_3\cdot CO\cdot CHMe\vdots CO_2Na \longrightarrow CH_3\cdot CO\cdot CMe{:}N\cdot NHPh + CO_2$$

These reactions resemble the acidic and ketonic fissions of β-ketonic esters.

Dieckmann obtained a parallel to reaction (ii) in the alicyclic series by preparing *cyclo*pentane-1 : 2-dione monophenylhydrazone from ethyl *cyclo*pentanone-2-carboxylate (*Annalen*, 1901, **317**, 27), a process which has been extended by Lions (*J. Proc. Roy. Soc. N. S. Wales*, 1932, **66**, 516). Reaction (i), which now involves a fission of the ring, was realised for alicyclic compounds independently by Kalb, Schweizer, and others (*Ber.*, 1926, **59**, 1858, 1860) and by Manske and Robinson (J., 1927, 240; compare Jackson and Manske, *J. Amer. Chem. Soc.*, 1930, **52**, 5209). This modification is of particular interest in connection with the synthesis of physiologically important indole derivatives. We have made a general investigation of the reaction of diazonium salts with derivatives of cyclic β-ketonic acids, with the object of determining the mechanism of these two degradations which follow the coupling reaction. In the summary which follows, we shall refer only to the compounds obtained from benzenediazonium chloride, except where other diazonium salts gave substances of special interest.

The structures of the products obtained from ethyl *cyclo*pentanone-2-carboxylate by the two processes were first confirmed. When coupling immediately followed the dissolution of the ester in alkali, the main product was ethyl hydrogen α-ketoadipate phenylhydrazone (II; R = OEt, R′ = Ph), the structure of which followed from its conversion into α-aminoadipic acid by reduction and hydrolysis. A small amount of *cyclo*pentane-1 : 2-dione monophenylhydrazone (III, R′ = Ph) was formed in this coupling. The nature of this was proved by its conversion into the corresponding osazone, which was independently synthesised. Similar dione monophenylhydrazones were the sole products when the keto-ester was first allowed to stand with alkali and then coupled. These products are insoluble in aqueous alkali, but alcoholic potash causes ring fission. Thus, cyclo*pentane*-1 : 2-*dione mono*-o-*nitrophenylhydrazone* (III, R′ = $C_6H_4{\cdot}NO_2$) yielded the o-*nitrophenylhydrazone of ω-aldehydovaleric acid.*



By coupling 2 : 4-dinitrobenzenediazonium sulphate with *cyclo*pentanonecarboxylic ester in acetic acid, the intermediate *azo-ester* [I; R = OEt, R′ = $C_6H_3(NO_2)_2$] was isolated. This was very unstable to alkali, the ring being broken even by cold aqueous sodium carbonate to yield the 2 : 4-*dinitrophenylhydrazone* of *ethyl hydrogen α-ketoadipate* [II; R = OEt, R′ = $C_6H_3(NO_2)_2$]. From this were prepared the corresponding *di-ester, di-acid,* and α-aminoadipic acid. Kalb, Schweizer, Zellner, and Berthold (*Ber.*, 1926, **59**, 1863) describe the preparation of a similar azo-ester by coupling *p*-nitrobenzenediazonium chloride with the same keto-ester in aqueous sodium acetate, but we were never able to isolate azo-esters from couplings in aqueous media.

When *cyclo*pentanone-2-carboxyanilide was used in place of the ester as the second component, the same dione hydrazones (type III) were isolated, but the principal products were azo-anilides * (type I; R = NHPh, R′ = substituted phenyl). These azo-anilides were stable to cold aqueous alkali, and were in fact prepared in this medium. Dieckmann (*loc. cit.*) was unable to obtain 1-*phenyl*-3 : 4-cyclo*pentano*-5-*pyrazolone* (IV), but this has now been prepared, although in such poor yield that its coupling with diazonium salts was not investigated.

These reactions were paralleled in the *cyclo*hexane series. In this case an intermediate *azo-ester* (V) was isolated by coupling *p*-nitrobenzenediazonium sulphate with ethyl *cyclo*hexane-2-one-1-carboxylate in acetic acid.

This on treatment with sodium carbonate gave the p-*nitrophenylhydrazone* of *ethyl hydrogen α-ketopimelate* (VI), identical with material obtained by direct coupling in alkali. Hydrolysis and reduction of (VI) yielded α-aminopimelic acid. As in the homologous series, the *azo-anilide* corresponding to (V) was stable and showed no tendency to ring fission. The hydrolysis of these azo-esters yields only products corresponding to an acidic fission and

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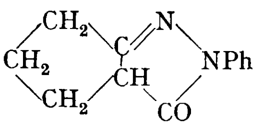
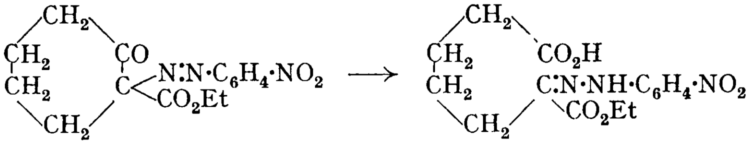
* These are the cyclic analogues of the technically valuable " Hansa Yellows " (for which see Rowe, Burr, and Corbishley, *J. Soc. Dyers and Col.*, 1926, **42**, 80; Burr and Rowe, *ibid.*, 1928, **44**, 205; Fierz-David and Ziegler, *Helv. Chim. Acta*, 1928, **11**, 776).

not to a ketonic fission, even when very weak alkali is used. This falls into line with the fact that substited β-ketonic esters are hydrolysed by weak alkali to ketones only when the



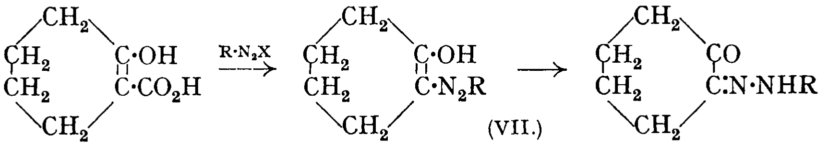
(IV.)



(V.) (VI.)

substituents are small alkyl groups. When the substituent groups are large or negative, acids are the almost exclusive fission products (Fittig, Claisen). These decompositions of azo-esters establish the mechanism of reactions of type (i).

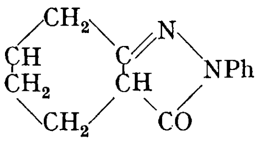
It was next necessary to justify the hypothesis that it is the free ketonic acid, formed by preliminary hydrolysis, which yields the diketone monohydrazone (reaction ii). When pure *cyclo*hexanone-2-carboxylic acid was treated with diazonium salts, even in acetic acid solution, no azo-acid could be isolated : carbon dioxide was at once evolved and the products were dione monohydrazones (VII). The reaction recalls the coupling of *p*-hydroxybenzoic acid with diazonium salts, in which the carboxyl group is eliminated.

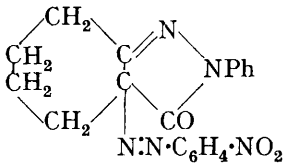


(VII.)

In interesting contrast to the *cyclo*pentane analogue, 1-phenyl-3 : 4-*cyclo*hexano-5-pyrazolone (VIII) is obtainable in excellent yield (compare Dieckmann, *loc. cit.*, p. 45). The difference between the ease of formation of the two dicyclic pyrazolones (IV and VIII) is attributable to the strain in the *cyclo*pentane derivative. The double bond must lie at a bridge head, or possibly in the bridge itself. This can be tolerated in the *cyclo*hexane derivative with little divergence from the tetrahedral arrangement, but the *cyclo*pentane compound is much more strained.

(VIII.)





(IX.)

The pyrazolone (VIII) coupled readily with *p*-nitrobenzenediazonium sulphate in acetic acid. The azo-pyrazolone (IX) could not be isolated in a pure condition, but its presence in the product could be deduced from two striking decompositions. Owing to the stabilisation of the alicyclic ring by the locking in the dicyclic system the general instability associated with structures of type I (or IX) now revealed itself in the ease with which the azo-group was eliminated. Digestion of the reaction product with alcohol regenerated the pyrazolone (VIII) and formed acetaldehyde, nitrobenzene, and nitrogen :

$$\mathrm{R{\cdot}N{:}N{\cdot}C_6H_4{\cdot}NO_2 + C_2H_5{\cdot}OH \longrightarrow RH + N_2 + C_6H_5{\cdot}NO_2 + CH_3{\cdot}CHO}$$

Treatment of (IX) with dimethylaniline in acid yielded *p*-nitrobenzeneazodimethylaniline, a reaction which must be presumed to involve the reversal of the ordinary coupling reaction at an intermediate stage.

EXPERIMENTAL.

cyclo*Pentane Series.*

Intermediates.—The yield of *cyclo*pentanone-2-carboxyanilide obtained from the ester following Blount, Perkin, and Plant (J., 1929, 1983) was 50%. The following process, based on that of Fierz-David and Ziegler for acetoacetic arylamides (*loc. cit.*), gave a 75—80% yield of an identical product. To a mixture of 156 g. of the keto-ester, 300 c.c. of xylene, and 3 c.c. of pyridine at 130—140°, a mixture of 93 g. of aniline, 200 c.c. of xylene, and 2 c.c. of pyridine was added during 3 hours. After a further 2 hours at the same temperature, the solvent was removed under reduced pressure, the residue shaken with 1 l. of 4% aqueous sodium hydroxide, and the solution filtered from the insoluble anil-anilide (below) and acidified with dilute acetic acid. The keto-anilide, isolated by means of ether, crystallised from light petroleum in plates (150 g.), m. p. 103·5—104° (Found: C, 70·8; H, 6·5. Calc.: C, 70·9; H, 6·4%). The anilide is soluble in dilute sodium hydroxide and insoluble in dilute sodium carbonate solution. Concentrated aqueous sodium hydroxide precipitates the sodium salt.

The insoluble product from the above reaction was washed with dilute acid and water and crystallised from alcohol. The *anil* of cyclo*pentanone-2-carboxyanilide* formed colourless prisms, m. p. 128—130° (Found: C, 77·9; H, 6·2. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·4%). The third possible product from the interaction of these reagents, namely, the anil of the keto-ester, was described by Blount, Perkin, and Plant (*loc. cit.*) as an oil. A mixture of 10 g. of the keto-ester, 6 g. of aniline, and a drop of acetic acid was kept over alkali in a desiccator for 10 days. The residue was scratched with light petroleum (b. p. 40—60°) at − 15° and quickly pressed on a tile. The solid on recrystallisation yielded the *anil* of *ethyl* cyclo*pentanone-2-carboxylate* in large prisms, m. p. 58·5° (Found: C, 72·7; H, 7·1. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·3%).

*Bis*cyclo*pentanone-2-carboxybenzidide* was prepared in the same way as the corresponding anilide. The product was repeatedly extracted with a 2% solution of sodium hydroxide in 30% alcohol, in which it dissolved slowly, and reprecipitated with acetic acid until it was white (Found: C, 71·1; H, 5·9; ash, 0·2. $C_{24}H_{24}O_4N_2$ requires C, 71·4; H, 5·9%). It did not melt below 250°.

1-*Phenyl*-3 : 4-cyclo*pentano-5-pyrazolone* (IV).—A mixture of ethyl *cyclo*pentanone-2-carboxylate (10 g.), phenylhydrazine (10 g.), acetic acid (5 c.c.), and a few drops of sulphuric acid was heated for 16 hours on a steam-bath. The residue was poured into 100 c.c. of ether and extracted thrice with 50 c.c. portions of 2*N*-hydrochloric acid. (The ethereal layer yielded the phenylhydrazone of the keto-ester, m. p. 90·5°, in agreement with Dieckmann; *loc. cit.*) The acid layer was made alkaline and extracted with ether. The alkaline solution was carefully acidified with acetic acid, and the small amount of voluminous precipitate was filtered off, separated from tarry matter, and crystallised from 50% alcohol. The *pyrazolone* separated in lustrous needles (10 mg.), m. p. 177—178° (Found: C, 71·9; H, 5·9; N, 14·2. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0%), sparingly soluble in organic solvents and soluble both in acid and in alkali. Attempts to prepare the pyrazolone by cyclising the corresponding phenylhydrazone were unsuccessful.

Coupling Reactions.—(i) *Ester*. A solution of aniline (10 g.) in hydrochloric acid (20 c.c.) and ice-water (30 c.c.) was diazotised with a solution of 7 g. of sodium nitrite in 50 c.c. of water, and 10 g. of sodium acetate were added. The mixture was added slowly at 0° with stirring to a fresh solution of ethyl *cyclo*pentanone-2-carboxylate (16 g.) in 2·5% aqueous sodium hydroxide (400 c.c.). The brownish-red precipitate of *cyclo*pentane-1 : 2-dione monophenylhydrazone (III, R′ = Ph) was collected after 16 hours and crystallised from alcohol, giving 1 g. of yellow-orange plates, m. p. 201—203° (decomp.), soluble in caustic alkali to give a green solution, insoluble in sodium carbonate (Found: C, 70·1; H, 6·4. Calc.: C, 70·2; H, 6·4%). The mother-liquor on the addition of sodium chloride gave a semi-solid sodium salt, yielding a red oil on acidification. This was purified through sodium carbonate and then solidified on long standing. Crystallisation from benzene yielded ethyl hydrogen α-ketoadipate phenylhydrazone (II; R = OEt, R′ = Ph), m. p. 120° (compare Kalb *et al.*, *loc. cit.*). On hydrolysis with cold alcoholic potash this yielded the corresponding acid, m. p. 141°, in agreement with Gault (*Bull. Soc. chim.*, 1912, **11**, 387). The acid so prepared from 4 g. of the half-ester was reduced with tin (10 g.) and warm hydrochloric acid (50 c.c.) until colourless. After dilution to 200 c.c. the tin was removed by means of hydrogen sulphide, and the filtrate basified and evaporated. Aniline was identified in the distillate as the tribromo-derivative. α-Aminoadipic acid, isolated from the residue through the copper salt, had m. p. 205—206°.

The dione monophenylhydrazone described above was converted by means of phenylhydrazine in alcoholic acetic acid into the corresponding osazone, which formed brownish-yellow needles (from alcohol), m. p. 144°. The same substance (m. p. and mixed m. p.) was obtained by the action of alcoholic phenylhydrazone on *cyclo*pentane-1 : 2-dione, prepared (1·5 g., b. p. 117°/18 mm.) by oxidizing 25 g. of *cyclo*pentanone with 28 g. of selenium dioxide, following Riley, Morley, and Friend (J., 1932, 1898).

Using *o*- or *p*-nitroaniline in place of aniline in the above process, we were unable to obtain solid half-ester hydrazones; but the corresponding dione hydrazones were readily made in good yields by the following procedure, a modification of that of Lions (*loc. cit.*). Ethyl *cyclo*pentanone-2-carboxylate (8 g.) was kept for 16 hours at 0° with a solution of sodium hydroxide (2·2 g.) in 50% alcohol (100 c.c.). Diazotised *p*-nitroaniline (7 g. of base) was added in one portion, and the mixture stirred with 10 g. of sodium acetate. After 20 minutes the gummy product was collected and washed.

cyclo*Pentane*-1 : 2-*dione mono*-p-*nitrophenylhydrazone* (III; R′ = $C_6H_4{\cdot}NO_2$) crystallised on standing, and separated from alcohol in yellow needles, m. p. 242°. It is insoluble in sodium carbonate; the solution in sodium hydroxide is blood-red (Found : C, 56·3; H, 4·7. $C_{11}H_{11}O_3N_3$ requires C, 56·6; H, 4·6%). The corresponding *mono*-o-*nitrophenylhydrazone*, prepared similarly from *o*-nitroaniline, is dimorphous. When crystallised from acetic acid, it forms long golden-yellow needles, unchanged on being dried in a vacuum desiccator (Found : C, 56·6; H, 4·7%). When the yellow form, contaminated with a trace of acetic acid, is dried at 100°, it changes completely into stout orange needles; but is unchanged if first dried and then heated to 100°. Both forms, and a mixture of the two, melt at 176—177° (slow heating) or 172—177° (rapid heating).

Ring fission. *cyclo*Pentane-1 : 2-dione mono-*o*-nitrophenylhydrazone (2 g.) was kept with an excess of aqueous alcoholic potassium hydroxide. The dark red solution deposited a brown precipitate, which changed to yellow crystals. After 5 days the mixture was diluted and acidified; the acidic product was purified through sodium bicarbonate and crystallised from acetone–light petroleum. ω-*Aldehydovaleric acid* o-*nitrophenylhydrazone* formed thin yellow needles (0·8 g.), m. p. 170—172° (Found : C, 52·6; H, 5·1. $C_{11}H_{13}O_4N_3$ requires C, 52·5; H, 5·2%).

6 C.c. of sulphuric acid were added to a solution of 9·2 g. of 2 : 4-dinitroaniline in hot acetic acid (60 c.c.), the mixture quickly cooled to 15°, and 9 c.c. of butyl nitrite added with stirring below 20° (cf. Hantzsch, *Ber.*, 1901, **34**, 3337). The diazonium salt was precipitated with 200 c.c. of ether, washed with ether, and redissolved in 50 c.c. of acetic acid. To the solution was added ethyl *cyclo*pentanonecarboxylate (10 c.c.) in acetic acid (50 c.c.), followed by sodium acetate (10 g.). After 16 hours, water precipitated 12 g. of crude azo-ester. Three crystallisations from 50% acetic acid yielded 5 g. of *ethyl* 2-(2′ : 4′-*dinitrobenzeneazo*)cyclo*pentanone*-2-*carboxylate* [I; R = OEt, R′ = $C_6H_3(NO_2)_2$] in lustrous, light yellow needles, m. p. 162—164° (decomp.), insoluble in sodium bicarbonate, soluble with difficulty in sodium carbonate, readily soluble in sodium hydroxide solution with a blood-red colour (Found : C, 47·7; H, 4·2. $C_{14}H_{14}O_7N_4$ requires C, 48·0; H, 4·0%).

Acidic fission of the azo-ester. 5 G. of the above compound were shaken in the cold with 200 c.c. of 2% aqueous sodium carbonate and 50 c.c. of ether until carbon dioxide was no longer evolved. The ethereal layer was separated and acidified with hydrochloric acid, and the yellow precipitate taken up in more ether and purified through sodium bicarbonate solution. Removal of ether and crystallisation from benzene and ethyl acetate yielded *ethyl hydrogen α-ketoadipate* 2 : 4-*dinitrophenylhydrazone* [II; R = OEt, R′ = $C_6H_3(NO_2)_2$] in yellow needles (4 g.), m. p. 168—170° (decomp.), moderately easily soluble in alcohol and ether, soluble in acetone, appreciably soluble in water (deep yellow solution) and readily soluble in sodium bicarbonate (orange solution). It could be titrated with $N/10$-baryta, acting as a self-indicator, but the end-point was not sharp (Found : C, 45·2; H, 4·3. $C_{14}H_{16}O_8N_4$ requires C, 45·6; H, 4·3%). The presence of the carbethoxy-group was proved by hydrolysis of 2 g. with 5% sodium hydroxide solution and fractional distillation. Ethyl alcohol in the final distillate was identified as the 3 : 5-dinitrobenzoate by Henstock's method (J., 1933, 216). For the isolation of the acid, 4 g. of the half-ester were kept with 1·5 g. of potassium hydroxide in 80% alcohol (60 c.c.) for 3 days. The acid was isolated by means of ether and purified through sodium bicarbonate and by crystallisation from water (once) and acetone (twice). *α-Ketoadipic acid* 2 : 4-*dinitrophenylhydrazone* formed powdery yellow crystals (2 g.), m. p. 238—240° (decomp.). The acid was sparingly soluble in organic solvents, and gave a deep yellow solution in water, turned brown by alkali. It gave approximately the correct equivalent on titration, acting as a self-indicator (Found : C, 42·4; H, 3·6. $C_{12}H_{12}O_8N_4$ requires C, 42·4; H, 3·5%). Esterification of the half-ester at room temperature by the Fischer–Speier method yielded the *diethyl* ester, which slowly solidified and formed lemon-yellow needles from light petroleum, m. p. 48—50° (Found : C, 48·1; H, 5·3. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·2%). It yielded the di-acid hydrazone on hydrolysis. 3 G. of the di-acid hydrazone were reduced by the procedure already described, except that the aromatic reduction product (triaminobenzene) was removed by extraction with chloroform instead of distillation in steam. The acidic product was α-aminoadipic acid, identical with that already isolated.

(ii) *Anilide and benzidide.* The diazonium chloride prepared from 13·8 g. of *p*-nitroaniline and 35·5 c.c. of concentrated hydrochloric acid was treated with 10 g. of sodium acetate, and dropped into an ice-cooled, stirred solution of 20·2 g. of *cyclo*pentanone-2-carboxyanilide in 500 c.c. of 3% aqueous sodium hydroxide. A yellow precipitate at once separated from the purple solution. After 2 hours the product was acidified (to assist filtration), and the orange solid filtered off and shaken with 2% sodium hydroxide solution (500 c.c.). The hydrazone (A below) dissolved, leaving a residue of azo-anilide, which was crystallised from alcohol and thrice from glacial acetic acid. 2-p-*Nitrobenzeneazo*cyclo*pentanone*-2-*carboxyanilide* (I; R = NHPh, R′ = $C_6H_4{\cdot}NO_2$) formed short lemon-yellow needles (4 g.), m. p. 242°, sparingly soluble in organic solvents, insoluble in alkali (Found: C, 60·9, 61·1; H, 4·3, 4·1; N, 16·1. $C_{18}H_{16}O_4N_4$ requires C, 61·3; H, 4·5; N, 15·9%). The same compound was prepared in good yield by coupling the anilide with *p*-nitrobenzenediazonium sulphate in acetic acid. The alkaline extract (A) yielded on acidification *cyclo*pentane-1 : 2-dione mono-*p*-nitrophenylhydrazone (1·2 g.), m. p. 242° after crystallisation from alcohol, identical with material prepared from the keto-ester.

2-o-*Nitrobenzeneazo*cyclo*pentanone*-2-*carboxyanilide*, prepared in the same way as the *p*-nitro-compound, in 40% yield, formed yellow needles from acetic acid, turning orange on standing, m. p. 177° (Found: C, 60·8; H, 4·6%). The alkali-soluble by-product from this preparation was *cyclo*pentane-1 : 2-dione mono-*o*-nitrophenylhydrazone, m. p. 177°, not depressed by admixture with material prepared from the keto-ester (above), but depressed to 130—160° by admixture with the corresponding azo-anilide, m. p. 177°.

2 : 4-Dinitroaniline was diazotised as described above and coupled with 10 g. of *cyclo*pentanonecarboxyanilide, dissolved in 100 c.c. of acetic acid. The deposit of yellow crystals was collected after an hour and recrystallised from acetic acid. 2-(2′ : 4′-*Dinitrobenzeneazo*)cyclo*pentanone*-2-*carboxyanilide* formed yellow needles (14 g.), m. p. 206—207°, sparingly soluble in organic solvents, soluble in sodium hydroxide solution with a red colour (Found: C, 54·1; H, 4·0. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8%).

Bis*cyclo*pentanone-2-carboxybenzidide condensed readily with diazotised *o*- and *p*-nitroanilines and 2 : 4-dinitroaniline. The products were, however, extremely difficult to purify owing to their insolubility, and the procedure need not be detailed. *Bis*-2-o-*nitrobenzeneazo*-cyclo*pentanone*-2-*carboxybenzidide* formed vermilion needles from acetic acid, m. p. 265—268° (decomp.) (Found: C, 61·5; H, 4·5%). The corresponding p-*nitro*-compound was an orange powder, m. p. 245—250° (decomp.) (Found: C, 61·5; H, 4·6. $C_{36}H_{30}O_8N_8$ requires C, 61·7; H, 4·7%).

cyclo*Hexane Series.*

Unless otherwise stated, the methods used resembled those already described for the *cyclo*pentane analogues.

Intermediates.—Sen and Basu (*J. Indian Chem. Soc.*, 1929, **6**, 313) described the preparation of *cyclo*hexanone-2-carboxyanilide from the ester, but did not analyse the product, and stated that it was insoluble in alkali. By the method described above for *cyclo*pentanecarboxyanilide, the anilide was obtained in 70% yield. It formed colourless plates from ether–light petroleum, m. p. 106—107° (Sen and Basu, 104—105°) (Found: C, 71·7; H, 6·8. Calc. for $C_{13}H_{15}O_2N$: C, 71·9; H, 6·9%). It was soluble in 1% aqueous sodium hydroxide, but the addition of less dilute alkali precipitated a sparingly soluble sodium compound. This accounts for the reported insolubility in alkali. The only by-product from the preparation was *s*-diphenylurea, m. p. and mixed m. p. 235—236° (compare Oppenheim and Drecht, *Ber.*, 1876, **9**, 1098; Knorr, *Annalen*, 1886, **236**, 69). When the keto-ester (16 g.) was kept with 9 g. of aniline over sulphuric acid in a vacuum desiccator for 4 days, it yielded the anil. This formed large prisms (11 g.) from light petroleum, m. p. 57—58 in agreement with Sen and Basu (*loc. cit.*), who did not analyse their product (Found: C, 73·5; H, 7·8. Calc.: C, 73·5; H, 7·8%).

*cyclo*Hexanone-2-carboxylic acid, m. p. 78—80° (decomp.), and 1-phenyl-3 : 4-*cyclo*hexano-5-pyrazolone, m. p. 164—165° (Found: C, 72·7; H, 6·6. Calc.: C, 72·9; H, 6·5%), were made by Dieckmann's methods (*Annalen*, 1901, **317**, 98, 102).

Coupling.—(i) *Ester.* In agreement with Jackson and Manske (*loc. cit.*) diazotised aniline coupled with a freshly prepared alkaline solution of ethyl *cyclo*hexanone-2-carboxylate to give *ethyl hydrogen α-ketopimelate phenylhydrazone*, m. p. 140—141°, in good yield (Found: C, 61·7; H, 6·9. $C_{15}H_{20}O_4N_2$ requires C, 61·6; H, 6·8%). On hydrolysis with alcoholic potash this yielded *α-ketopimelic acid phenylhydrazone*, which formed light yellow needles from ethyl acetate–petroleum, m. p. 153—154° (decomp.) (Found: C, 59·4; H, 6·4. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1%). 2 G. of this compound were reduced by tin and hydrochloric acid to α-aminopimelic acid, isolated through its copper salt. This reacted slowly with hydrogen sulphide, on account of its sparing solubility. The amino-acid formed prismatic needles from water, dissolved in its own water of crystallisation at 100°, and then became anhydrous, m. p. 203—204°. Yield, 0·8 g.

Ethyl hydrogen α-ketopimelate p-*nitrophenylhydrazone*, similarly prepared, formed yellow prismatic needles, from benzene, m. p. 150°; it gave orange solutions in dilute alkali and green solutions in concentrated alkali (Found: C, 53·7; H, 5·7. $C_{15}H_{19}O_6N_3$ requires C, 53·4; H, 5·6%). The corresponding *acid* formed yellow needles from acetone–petroleum, m. p. 174—175° (decomp.) (Found: C, 50·2; H, 4·9. $C_{13}H_{15}O_6N_3$ requires C, 50·5; H, 4·9%).

Ethyl *cyclo*hexanone-2-carboxylate was hydrolysed with alkali at 0° for 24 hours and then coupled with diazotised aniline. In agreement with Lions (*loc. cit.*) the product was *cyclo*hexane-1 : 2-dione monophenylhydrazone, m. p. 183—184°, from which the osazone, m. p. 153—154°, of Coffey (*Rec. trav. chim.*, 1923, **42**, 528) was prepared. The use of *p*-nitroaniline similarly led to the formation of cyclo*hexane*-1 : 2-*dione mono*-p-*nitrophenylhydrazone* (VII, R = $C_6H_4{\cdot}NO_2$) in good yield; it formed orange-yellow needles from amyl acetate, m. p. 245—246° (decomp.) (Found: C, 58·2; H, 5·2. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3%). 2 G. of this compound were heated for 30 minutes in a water-bath with 2 c.c. of phenylhydrazine in alcoholic acetic acid, and the product precipitated with mineral acid. Crystallisation from acetic acid gave remarkably different results according to the rate of cooling. Rapid cooling of a concentrated solution yielded small orange prisms; slow cooling of a more dilute solution yielded long indigo-blue needles. Both were cyclo*hexane*-1 : 2-*dione phenylhydrazone* p-*nitrophenylhydrazone*, and yielded an orange powder, m. p. 243—244 [Found: C, 64·5; H, 5·7 (orange); C, 64·2; H, 5·8 (indigo-blue). $C_{18}H_{19}O_2N_5$ requires C, 64·1; H, 5·6%]. Treatment of *cyclo*hexane-1 : 2-dione monophenylhydrazone with *p*-nitrophenylhydrazine in acetic acid yielded indigo-blue crystals of the same mixed osazone, m. p. and mixed m. p. 243—244°.

p-Nitrobenzenediazonium sulphate was prepared from *p*-nitroaniline (13·6 g.) and butyl nitrite (12 g.) in acetic acid by the procedure already described for the 2 : 4-dinitro-compound. A solution of the diazonium salt, well washed with ether, in 50 c.c. of acetic acid was treated successively with 15 c.c. of ethyl *cyclo*hexanone-2-carboxylate and 10 g. of powdered sodium acetate. After 4 hours the solid product was filtered off and repeatedly crystallised from dilute acetic acid. *Ethyl* 2-p-*nitrobenzeneazo*cyclo*hexanone-2-carboxylate* (V) formed yellow needles, m. p. 130—131°, very soluble in organic solvents, insoluble in water and sodium bicarbonate, soluble with decomposition in sodium carbonate and hydroxide solution. Yield, 6 g., crystallisation being wasteful (Found: C, 56·2; H, 5·5. $C_{15}H_{17}O_5N_3$ requires C, 56·4; H, 5·3%). 5 G. of the azo-ester were warmed with 200 c.c. of 1% sodium carbonate solution until carbon dioxide was no longer evolved. The acidic product was isolated by means of ether and purified through sodium bicarbonate. Ethyl hydrogen α-ketopimelate *p*-nitrophenylhydrazone, so obtained, formed yellow needles (2 g.) from benzene, m. p. 150° alone or mixed with the product obtained by coupling in alkali. Hydrolysis yielded the corresponding acid hydrazone, m. p. 173—174° (decomp.).

(ii) *Acid.* Pure, freshly prepared *cyclo*hexanone-2-carboxylic acid (10 g.) was dissolved in alcohol (20 c.c.) and ice-water (200 c.c.) and treated with diazotised aniline (6·5 g.). The addition of 5 g. of sodium acetate caused an immediate evolution of carbon dioxide and separation of a yellow precipitate. This was crystallised from alcohol and identified as *cyclo*hexane-1 : 2-dione monophenylhydrazone, m. p. and mixed m. p. 183—184°. Under similar conditions diazotised *p*-nitroaniline gave the mono-*p*-nitrophenylhydrazone of the dione, m. p. and mixed m. p. 245—246°.

A solution of 5 g. of the pure keto-acid in 50 c.c. of acetic acid was treated with the diazonium sulphate from 4·6 g. of *p*-nitroaniline dissolved in 50 c.c. of acetic acid. The addition of sodium acetate caused an immediate evolution of carbon dioxide and *cyclo*hexane-1 : 2-dione mono-*p*-nitrophenylhydrazone was again formed. An attempt to isolate the azo-acid by dilution, without the addition of sodium acetate, failed.

(iii) *Anilide.* A solution of the diazonium sulphate prepared from 13·6 g. of *p*-nitroaniline in acetic acid (60 c.c.) was added at 0° to one of 21·7 g. of *cyclo*hexanone-2-carboxyanilide in 100 c.c. of acetic acid. After the addition of sodium acetate (10 g.) the mixture was kept overnight and diluted with water, and the solid crystallised twice from acetic acid and twice from alcohol. 2-p-*Nitrobenzeneazo*cyclo*hexanone-2-carboxyanilide* formed rather brownish-yellow needles, m. p. 214°, insoluble in dilute alkali solution (Found: C, 62·0; H, 5·0. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·9%).

(iv) *Pyrazolone.* To a solution of 1-phenyl-3 : 4-*cyclo*hexano-5-pyrazolone (21·4 g.) in acetic acid (100 c.c.) were added an acetic acid solution of *p*-nitrobenzenediazonium sulphate (from 13·6 g. of *p*-nitroaniline) and sodium acetate (10 g.). After standing overnight, the mixture was poured into water, and the product washed and pressed on a porous tile. It gradually changed into a hard cake. All attempts at crystallisation failed, the crude azo-pyrazolone decomposing in hot solvents. Yield of crude material, 30 g., m. p. 85—95° (decomp.). 10 G. were refluxed with 50 c.c. of absolute ethyl alcohol for 2 hours, the solvent distilled through a column, and the most volatile fraction redistilled. Acetaldehyde was identified in the fraction of b. p. $<50°$ (3 c.c.) as the dimedone derivative, m. p. 137—139°. The residue was freed from alcohol and distilled in steam, nitrobenzene being identified in the distillate by the preparation of *m*-dinitrobenzene, m. p. 89—90°. The tarry residue was shaken with dilute hydrochloric acid, and after filtration, the liquid was made alkaline and freed from tar by extraction with benzene. The alkaline solution on cautious acidification with acetic acid yielded the original pyrazolone, m. p. and mixed m. p. 164—165°.

10 G. of the crude azo-pyrazolone were treated successively with 20 c.c. of acetic acid, 20 c.c. of hydrochloric acid, and 10 g. of dimethylaniline. After 16 hours at 50—60°, the original powder had completely disappeared, leaving a paste of red crystals with a metallic reflex. This was poured into water, collected, and crystallised several times from dilute hydrochloric acid. *p*-Nitrobenzeneazodimethylaniline hydrochloride separated in deep red crystals with a metallic lustre. Yield : 12 g. (crude), 5 g. (pure). The substance was identified by conversion into the free azo-base, m. p. and mixed m. p. 228—229°.

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