sodium bicarbonate according to known procedures: **2,4,6-triphenylpyrylium pseudo-base** (IVa), buff needles from alcohol, melted at 115–116° (reported,[2a] m.p. 119°); **2,6-diphenyl-4-*p*-anisylpyrylium pseudo-base** (IVc), pale-yellow needles from ethyl acetate–methanol, melted at 122–122.5° (reported[13] m.p. 122°).

4,6-Diphenyl-2-*p*-anisylpyrylium pseudo-base (IVb) was obtained as pale-yellow needles from ether. Although the literature[10] reports m.p. 105°, in our hands the m.p. remained constant at 89.5–90° after the substance had been recrystallized five times.

Anal. Calcd. for $C_{24}H_{20}O_2$: C, 80.90; H, 5.66. Found: C, 80.97; H, 5.48.

The "methyl ether" of **IVa** (IIId), hard, heavy, white prisms from benzene–Skellysolve A, melted at 140–141° (reported 142–143°).

The ultraviolet spectra (Beckman model DU spectrophotometer) of freshly-prepared 95% ethanol solutions of these substances were determined using material which had been recrystallized to constant melting point and dried *in vacuo*. Although the photodimerization of benzalacetophenone has been reported[4] to cause a rapid diminution in intensity of its absorption maximum, no such changes were observed with any of the pseudo-bases.

The infrared spectra of benzalacetophenone, the "methyl ether" (IIId) and the pseudo-base (IVa) were determined in chloroform solutions with the Perkin–Elmer spectrometer, Model 12-B. The relevant portions of the spectrum were plotted by a point-by-point analysis of the sample and solvent curves.

Alkaline Hydrolysis of the "Methyl Ether."—A solution of 0.37 g. of the methyl ether and 0.30 g. of potassium hydroxide in 10 cc. of 90% methanol was heated under reflux. The solution immediately turned bright-red. After an hour, the mixture was evaporated. The residue was taken up in water and the aqueous solution, after having been washed with ether, was acidified with hydrochloric acid. The precipitated acidic material was extracted with chloroform and dried (sodium sulfate). Evaporation of the chloroform solution left 0.11 g. (85%) of benzoic acid, m.p. and mixed m.p. 117–119°.

LOS ANGELES 7, CALIF.

RECEIVED JULY 16, 1951

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[13] W. Dilthey, *Ber.*, **53** 252 (1920).

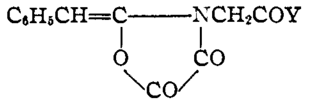
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Condensation Products of Oxalyl Chloride with Monosubstituted Amides: Structure and Reactions

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

An investigation has been made of the structure of the reaction products of oxalyl chloride with phenylacetamides and the methods by which the resulting heterocyclic system can be degraded to the original monosubstituted amides. The correctness of the 2-benzylidene-3-oxazolidine-4,5-dione structures assigned to the condensation products has been established unequivocally by, *inter alia*, the preparation of the isomeric pyrrolidine-2,3,5-triones, which represent the alternative formulation. The pyrrolidine-2,3,5-triones appear to be formed readily only by base catalyzed cyclization. It is concluded that aminolysis represents the most practical procedure for obtaining phenylacetamides from 2-benzylidene-3-oxazolidine-4,5-diones. The possible application of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride in the indirect synthesis of benzylpenicillin and its analogs is discussed.

Compounds containing the 2-benzylidene-3-oxazolidine-4,5-dione nucleus appear to be promising intermediates in the synthesis of β-lactamthiazolidines bearing the 6-phenylacetylamino substituent characteristic of benzylpenicillin. For example, the successful use of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (II)[2] in the acid chloride–thiazoline reaction previously disclosed,[3] followed by removal of the oxalyl grouping from the heterocyclic ring, would lead to structures like that of benzylpenicillin.



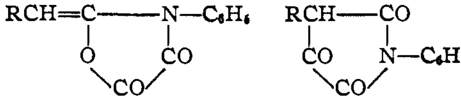
I, Y = OH III, Y = NHC_6H_5

II, Y = Cl IV, Y = $OCH_2C_6H_5$

Treatment of II with aniline or benzyl alcohol resulted in formation of the corresponding anilide (III) or benzyl ester (IV). The benzyl ester IV could be obtained more readily and in 91% yield by treatment of benzyl phenaceturate with oxalyl chloride. The infrared spectra of I–IV exhibit bands in the double bond region at 5.50, 5.73 and 5.95 μ which are highly characteristic of the heterocyclic system.

At the beginning of the present work the available information concerning the conversion of oxazolidinediones to acylamino compounds was meager. An investigation of the chemistry of these compounds with particular emphasis on ring-cleavage reaction was therefore undertaken.

Structures involving the oxazolidinedione nucleus were first postulated by Stollé and Luther[4] as the products of the reaction of oxalyl chloride with anilides. These investigators considered the product of the reaction of oxalyl chloride with acetanilide as being best represented by the oxazolidinedione structure V rather than the isomeric pyrrolidinetrione structure VI, because it reacted readily with water to form acetic acid and oxanilic acid. The compound also gave no coloration with ferric chloride solution. Additional support for the oxazolidinedione structure for these products may be drawn from the work of Wislicenus and Sattler,[5] who prepared the pyrrolidinetrione VII by the base-catalyzed condensation of ethyl oxalate with propionanilide. The structure was inferred from analytical data and from the fact that the compound



V, R = H VI, R = H

VIII, R = CH_3 VII, R = CH_3

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[1] Bristol Laboratories Fellow, 1948–1950.

[2] Prepared in high yield by interaction of phenaceturic acid and oxalyl chloride in dioxane followed by phosphorus pentachloride, G. B. Brown, *Arch. Biochem.*, **24**, 429 (1949).

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

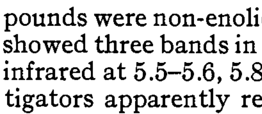
[4] R. Stollé and M. Luther, *Ber.*, **53**, 314 (1920).

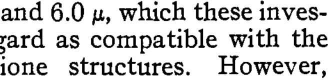
[5] W. Wislicenus and W. Sattler, *ibid.*, **24**, 1245 (1891).

showed all the properties expected of an enol. An isomeric compound was prepared by Figee,[6] who made the first study of the action of oxalyl chloride on amides, by reaction of oxalyl chloride with propionic acid anilide. This compound showed no signs of being an enol and, as pointed out by Stollé and Luther, is best represented by the oxazolidinedione structure VIII rather than VII which had been proposed by Figee.

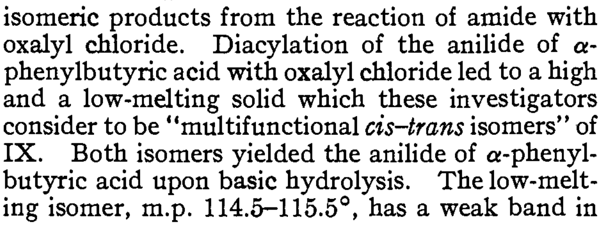
Recently Skinner and Perkins[7] have prepared a series of twenty-five compounds by the action of oxalyl chloride on amides and have proposed structures with pyrrolidinetrione nuclei rather than oxazolidinedione nuclei for the products. The compounds were non-enolic, easily cleaved by alkali and showed three bands in the double bond region of the infrared at 5.5–5.6, 5.8 and 6.0 μ, which these investigators apparently regard as compatible with the assigned pyrrolidinetrione structures. However, the results of present work indicate (*vide infra*) that the spectra of the products obtained by Skinner and Perkins are in much better agreement with the oxazolidine-4,5-dione formulation than with the pyrrolidinetrione structure. In our work oxazolidine-4,5-diones have been found to exhibit strong bands at 5.5, 5.75 and 6.0 μ, while the isomeric pyrrolidinetriones manifest a very weak band at 5.6 μ, a strong band at 5.8 μ and no band at 6.0 μ.

In one case Skinner and Perkins have isolated two isomeric products from the reaction of amide with oxalyl chloride. Diacylation of the anilide of α-phenylbutyric acid with oxalyl chloride led to a high and a low-melting solid which these investigators consider to be "multifunctional *cis–trans* isomers" of IX. Both isomers yielded the anilide of α-phenylbutyric acid upon basic hydrolysis. The low-melting isomer, m.p. 114.5–115.5°, has a weak band in the infrared at 5.65 μ and a strong band at 5.8 μ and is probably the pyrrolidinetrione IX. The high-melting isomer, m.p. 129–130°, absorbs strongly at 5.6, 5.8 and 6.0 μ and seems best represented as the oxazolidinedione X.[8]

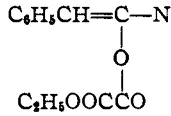

IX


X

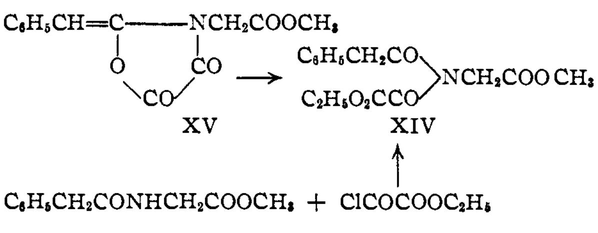
It should be noted that there are two possible end products in the hydrolysis of oxazolidinediones, one the parent acylamino compound XI and the other an oxalylamino derivative XII. Hydrolysis of V apparently leads to cleavage of the intermediate N,N-diacyl compound by route B, while hydrolysis of XIII has been reported as taking place by route A.[9] Unfortunately, in the latter case the yield of N-benzylphenylacetamide was not reported, so that it is not possible to tell whether cleavage occurred appreciably by reaction B. Although the general statement has been made that "2-benzylideneoxazolidine-4,5-diones revert on mild hydrolysis to the parent phenylacetamides,"[9] no further examples of the hydrolysis of these compounds appear in the literature.



It was discovered during the course of the penicillin program that oxazolidinediones are susceptible to alcoholysis in the presence of small amounts of pyridine. The preparation of methyl N-ethoxalylphenaceturate (XIV) by the ethanolysis of the oxazolidinedione XV was described without mention of yield.[9] The assignment of structure XIV to the alcoholysis product was based upon an independent synthesis of the same compound from methyl phenaceturate and ethoxalyl chloride.[10] The facile alcoholysis of the heterocyclic ring was interpreted as evidence establishing the validity of the assigned oxazolidinedione structures. It may be argued, however, that the pyrrolidinetrione ring might undergo alcoholysis, since it represents an especially reactive 1,3-dicarbonyl system.


$C_6H_5CH{=}\underset{\substack{|\\ O\\ |\\ C_2H_5OOCCO}}{C}{-}NHCH_2COOCH_3$

XVI



One example of the preparation of an N-substituted phenylacetamide by aminolysis of an oxazolidinedione is described in the penicillin monograph. Treatment of the oxazolidinedione XV with benzylamine furnished a 30% yield of methyl phenaceturate. Another example of the cleavage of oxazolidinediones by benzylamine has been reported by Brown,[2] who prepared N-(N-phenylacetylglycyl)-D,L-valine in 74% yield.

Since no definite conclusions can be drawn from these data concerning the relative efficiencies of hydrolysis, alcoholysis or aminolysis procedures in regenerating phenylacetamides from the corresponding oxazolidinediones, a study of each of these methods was made.

An examination of the base-catalyzed hydrolysis

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(6) T. Figee, *Rec. trav. chim.*, **34**, 301 (1915).

(7) G. S. Skinner and J. F. Perkins, THIS JOURNAL, **72**, 5569 (1950).

(8) There also exists the less likely possibility that the two products are *cis–trans* isomers of X.

(9) During the wartime program of research on penicillin, the reaction of oxalyl chloride with several model N-monosubstituted amides and benzylpenicillin itself was investigated as means of detecting and characterizing amides: H. T. Clarke, J. R. Johnson and R. Robinson editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, chapter VIII, p. 239.

(10) The possibility of structure XVI for the alcoholysis product obviously is not excluded rigorously on the basis of this evidence.

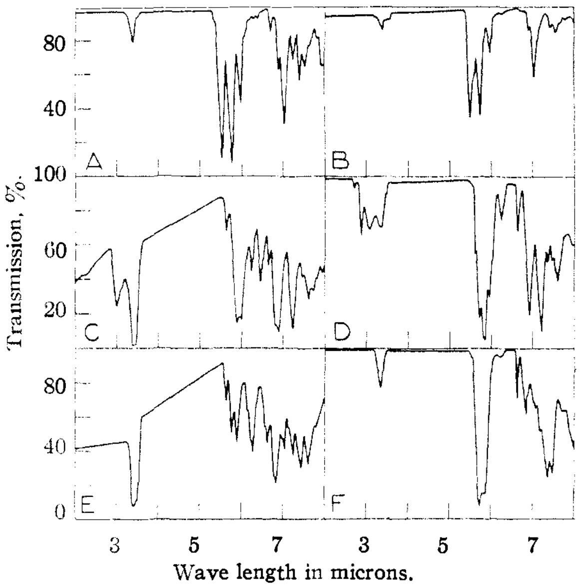
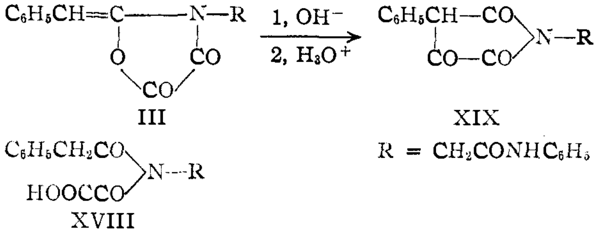


Plate I.—Infrared spectra: curve A, benzyl 2-benzylidene-4,5-diketo-3-oxazolidineacetate (IV), 3% in $Cl_2CHCHCl_2$; curve B, 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (II), 1% in $Cl_2CHCHCl_2$; curve C, 3-phenyl-2,4,5-triketo-1-pyrrolidineacetanilide (XIX) (Nujol mull); curve D, benzyl 4-phenyl-2,3,5-triketo-1-pyrrolidine acetate (XVII), 5% in $Cl_2CHCHCl_2$; curve E, 2,4-dinitrophenylhydrazone of XVII (Nujol mull); curve F, N-ethoxalylphenaceturic acid benzyl ester (XX). 5% in $Cl_2CHCHCl_2$.

of the anilide III and the benzyl ester IV revealed interesting differences. The anilide upon treatment in acetone with three equivalents of 0.1 *N* sodium hydroxide afforded the desired anilide of phenaceturic acid in 39% yield. However, the benzyl ester upon treatment with two equivalents of base yielded no benzyl phenaceturate, but only an acidic, yellow sirup which gradually deposited a very small amount of a yellow, crystalline solid, XVII (*vide infra*). When XVII was treated with ferric chloride a dark green coloration was produced. It was insoluble in water, but dissolved readily in aqueous sodium carbonate with the formation of an orange solution. In both the hydrolysis of the anilide III and of the benzyl ester IV some phenylacetic acid (identified by odor) was produced.

Upon slow titration of the anilide III with only one equivalent of base and acidification of the reaction mixture, there was produced a yellow, acidic solid. The analysis indicated that it was not the expected acid XVIII, but rather, a compound isomeric with the starting material. This product, obtained in 30% yield, was insoluble in water, but soluble in base with formation of a deep yellow-orange color. A dark green coloration similar to that obtained from XVII was formed upon treatment of the product with ferric chloride. These facts, together with the infrared spectrum of the compound, indicated that it is actually 4-phenyl-2,3,5-triketo-1-pyrrolidineacetanilide (XIX) in equilibrium with the corresponding enol. The infrared spectrum of solid XIX exhibits a weak band at 5.62 μ and a stronger band at 5.88 μ which together are characteristic of the succinimido ring. No bands appear which are assignable to the enol form of XIX.



III

XIX

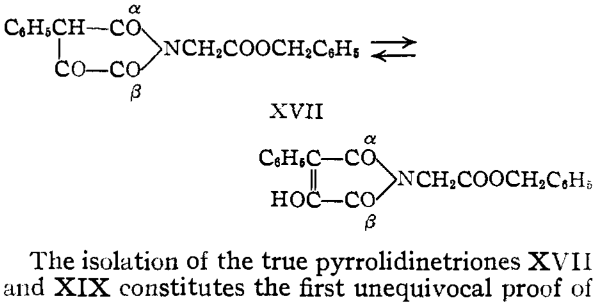
XVIII

R = $CH_2CONHC_6H_5$

The rather unusual transformation of the oxazolidinedione III to the pyrrolidinetrione XIX occurs to a very small extent if at all under the conditions previously described for the conversion of III to phenaceturic acid anilide, *i.e.*, using three equivalents of base. This fact renders untenable the assumption of a reaction path involving simple O to C migration of the oxalyl grouping. If the reaction proceeds *via* the free acid XVIII, as seems likely, the presence of a large amount of base could have two effects: (a) cause loss of the oxalyl group by cleavage of the diamide with resulting formation of phenaceturic acid anilide before cyclization could occur or (b) completely convert the acid to its salt, which would undergo cyclization at a very slow rate or not at all. Either effect would explain the experimental observations.

In view of these results hydrolytic procedures for the formation of phenylacetamides from 2-benzylideneoxazolidinediones seemed unsatisfactory, the main side reactions involved being loss of the phenylacetyl group during hydrolysis and the formation of intractable yellow oils, probably by competing condensations of the intermediate hydrolysis products.

The possibility of preparing the desired phenyl acetamides by a combination of alcoholysis to diamides, such as XIV, and further hydrolysis was also studied. The benzyl ester IV was allowed to react with warm ethanol containing a trace of pyridine to form the alcoholysis product, XX, which without isolation was treated with one equivalent of aqueous sodium hydroxide. There was obtained by extraction of the basic solution a 15% yield of the desired product, benzyl phenaceturate. Acidification of the orange-colored aqueous phase gave a yellow, insoluble solid which was isomeric with IV and identical with the solid obtained earlier (XVII) in low yield. The product, which was obtained in 47% yield, seems best represented as the pyrrolidinetrione XVII in equilibrium with the corresponding enol. Treatment of XVII with 2,4-dinitrophenylhydrazine afforded the dinitrophenylhydrazone, while diphenyldiazomethane reacted to form the enol ether.

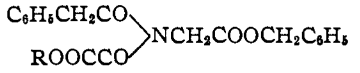


XVII

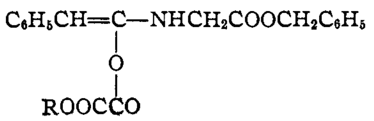
The isolation of the true pyrrolidinetriones XVII and XIX constitutes the first unequivocal proof of the correctness of the oxazolidinedione formulation, rather than the pyrrolidinetrione structure, for the reaction products of substituted phenylacetamides with oxalyl chloride.

The infrared spectrum of XVII in solution exhibited a weak band at 5.62 μ and a strong band at 5.85 μ as did the pyrrolidinetrione XIX. The presence of the enol form of XVII is also indicated by the infrared spectrum. There appear unassociated and associated O–H stretching bands at 2.97 and 3.08 μ in addition to a band at 6.22 μ which is probably due to the α-carbonyl group of the enol. The latter assignment is supported by the occurrence of a similar shift in the spectra of β-amino-α,β-unsaturated ketones.[11] The band at 5.98 μ probably arises from the β-imide carbonyl of the enol present. The spectrum of the dinitrophenylhydrazone of XVII shows the 5.63 and 5.88 μ bands which arise from the succinimido carbonyls, but it has no 5.95 or 6.22 μ band.

The formation of XVII may have occurred by a number of routes: (a) base-catalyzed cyclization of the alcoholysis product XX during the alcoholysis, (b) base-catalyzed cyclization of XX during the basic hydrolysis or (c) cyclization of the acid XXI which may have been formed during the hydrolysis. It should be pointed out that the formation of XXI



XX, R = C_2H_5
XXI, R = H



XXII, R = C_2H_5

is not unlikely since esters of oxalic and oxamic acids are saponified with great rapidity.[12]

Alcoholysis of the benzyl ester IV in hot, absolute ethanol containing a trace of pyridine provided in addition to the expected product (the diamide XX) the pyrrolidinetrione XVII. The relative amounts of XX and XVII formed depend on the length of the heating period. When heating was carried on only until all of the starting material has been dissolved (13 minutes) the yield of XX was 74% and that of XVII was 12.8%. After a 25-minute heating period the yields of the diamide XX and the pyrrolidinetrione XVII were 35 and 44%, respectively, while after three hours the yields were 0 and 84%, respectively. It should be mentioned that XX represents the correct structure of the alcoholysis product of the benzyl ester IV rather than XXII. The substance is non-basic and possesses an infrared spectrum which is clearly inconsistent with XXII. The spectrum exhibits no N–H stretching bands and shows bands at 5.72, 5.80 and 5.85 μ which are assignable to the ester and diamide carbonyls.[13]

It is evident that the pyrrolidinetrione XVII is formed not by O to C migration of an acyl group, but through the intermediate diamide XX. Furthermore, O to C migration could not be effected even under forcing conditions. The benzyl ester IV could not be induced to rearrange to the pyrrolidinetrione XVII by heating either with sodium hydride or pyridine in dioxane. Treatment of the diamide XX, however, with sodium hydride in dioxane gave a 68% yield of XVII. Hydrolysis of the diamide XX with one equivalent of sodium hydroxide produced only a 27% yield of benzyl phenaceturate.

Treatment of the benzyl ester IV with two equivalents of benzylamine resulted in rapid formation of benzyl phenaceturate in 68% yield along with the second cleavage product, N,N′-dibenzyloxamide. Use of phenylhydrazine as the base led to a 69% yield of benzyl phenaceturate, while the less reactive methylamine gave a 53% yield. Aniline and piperidine were found to be unsatisfactory. The anilide III formed phenaceturic acid anilide in 61% yield upon treatment with benzylamine. These results strongly indicate that aminolysis represents the most practical procedure for the conversion of 2-benzylidene-3-oxazolidine-4,5-diones to the parent phenylacetamides.

Experimental[14]

2-Benzylidene-4,5-diketo-3-oxazolidineacetanilide (III).—To 1.50 g. (0.00565 mole) of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (II) in 10 ml. of dry dioxane and 10 ml. of dry benzene at 5° was added dropwise a solution of 1.05 g. (0.0113 mole) of aniline in 5 ml. of benzene. The mixture was allowed to stand at room temperature for 20 minutes and filtered. The yellow solid was washed with carbon tetrachloride, dried, and suspended in 50 ml. of water. The water-insoluble solid, m.p. 258–261°, weighed 1.55 g. (85.2%). Recrystallization from 40 ml. of dioxane and 40 ml. of benzene yielded 1.30 g. of fine, yellow needles, m.p. 260–262° (in bath at 250°).

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.88; H, 4.54; N, 8.52.

Benzyl 2-Benzylidene-4,5-diketo-3-oxazolidineacetate (IV).—To a solution of 8.49 g. (0.030 mole) of benzyl phenaceturate in 30 ml. of dry dioxane was added 6.0 ml. of oxalyl chloride. After two hours the mixture was evaporated to dryness, treated with benzene, and the yellow solid (8.7 g.) was collected by filtration. The solid was recrystallized by dissolving in 50 ml. of hot dioxane and adding a hot solution of 30 ml. of ligroin. The heterocycle crystallized as fine, yellow needles, m. p. 178–179°, and amounted to 8.30 g. (91%). A small portion of the substance (0.100 g.) was recrystallized from hot benzene (6.5 ml.) to yield analytically pure IV, m.p. 178.0–179.0°.

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.39; H, 4.61; N, 4.23.

The benzyl ester IV could also be obtained from the acid chloride II. A mixture of 0.100 g. (0.377 millimole) of the acid chloride, 0.0406 g. (0.377 millimole) of benzyl alcohol and 0.0298 g. (0.377 millimole) of pyridine was allowed to react in 20 ml. of dry benzene. After 15 minutes the mixture was filtered and 40 ml. of petroleum ether was added to the yellow filtrate. The flocculent, yellow solid which precipitated was collected by filtration and recrystallized from benzene–methylcyclohexane to give 0.070 g. of IV, m.p. 177.5–180°.

Hydrolysis of III. A.—To 0.200 g. (0.620 millimole) of the anilide III suspended in 10 ml. of acetone was added 17.34 ml. of 0.1074 *N* sodium hydroxide. The solid completely dissolved after a few minutes, and the resulting

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(11) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, THIS JOURNAL, **71**, 3337 (1949).

(12) A. Skrabal and G. Muhry, *Monatsh.*, **42**, 48 (1921).

(13) J. C. Sheehan and E. J. Corey, THIS JOURNAL, in press.

(14) All melting points are corrected. Infrared spectra were measured with a Baird Infrared Recording Spectrophotometer, Model B. The cell thickness used with solutions was 0.10 mm. The cell thickness in the case of nujol mulls was 0.010–0.025 mm. We are indebted to Mr. S. M. Nagy and associates for the microanalyses and infrared spectra.

yellow solution was warmed on a steam-bath to expel most of the acetone. Upon cooling, a colorless precipitate formed. The mixture was extracted with three 30-ml. portions of chloroform and the chloroform solutions were combined and dried by filtration. Evaporation of the chloroform yielded 0.065 g. (39.2%) of a colorless solid, m.p. 154–156°, mixed m.p. with phenaceturic acid anilide, 156–160°. Upon acidification of the aqueous solution the characteristic odor of phenylacetic acid could be detected easily. Extraction of the acidified solution with methylene chloride and evaporation of the extract furnished a small amount of intractable, yellow oil.

B.—To a solution of 0.400 g. (0.00124 mole) of III in 35 ml. of dioxane at room temperature was added 12.0 ml. of 0.1074 *N* sodium hydroxide over a period of 45 minutes. The orange solution was evaporated under reduced pressure to a volume of 5 ml. The concentrate was taken up in 15 ml. of water, acidified and extracted with ether. The ether extract was evaporated to dryness and the residual yellow solid was recrystallized from ethanol-water to yield 0.118 g. (29.5%) of the pyrrolidinetrione XIX as yellow needles, m.p. 236.5–237.5° (in bath at 230°).

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.99; H, 4.35; N, 8.52.

Treatment of XIX with alcoholic ferric chloride solution resulted in the immediate formation of a dark green coloration.

Hydrolysis of IV.—A solution of 0.500 g. (0.001485 mole) of the benzyl ester IV in 40 ml. of acetone was cooled to 0° and treated with 28.0 ml. of 0.1074 *N* sodium hydroxide. The solution was allowed to warm up to room temperature. After one-half hour the orange solution was concentrated under reduced pressure to remove the acetone and the resulting aqueous solution was extracted with chloroform. Upon evaporation of the chloroform extract there remained a small amount (*ca.* 0.07 g.) of a yellow oil from which no crystalline material could be isolated. Acidification of the aqueous layer and extraction with chloroform afforded, after removal of the chloroform, a yellow oil which was triturated with, and kept under, carbon tetrachloride. After storage for four days a small amount of the oil had crystallized. The solid was separated from the oil and recrystallized from carbon tetrachloride–ligroin. The yield of the pyrrolidinetrione XVII, m.p. 134–136°, was 0.012 g.

Combined Alcoholysis and Hydrolysis of IV.—A mixture of 1.00 g. (0.00293 mole) of IV, 25 ml. of absolute ethanol and one small drop of dry pyridine was heated on a steam-bath until all of the solid had dissolved (13 minutes). To the resulting yellow solution was added *ca.* 20 g. of ice and one drop of phenolphthalein indicator. The cold solution was titrated slowly with 0.1074 *N* sodium hydroxide, fresh portions of base being added when the color of the indicator disappeared. After eight minutes 26.0 ml. (0.0028 mole) of base had been added and the color of the indicator faded at a very slow rate. The cold solution was extracted with chloroform, and the chloroform extract was evaporated under reduced pressure to an oil which partially solidified upon tituration with petroleum ether. The semi-solid residue was triturated further with four 10-ml. portions of methanol-water solution (1.5:1), and the resulting crisp solid, m.p. 88–90° (0.170 g.) was recrystallized from benzene–ligroin to yield 0.125 g. (15%) of benzyl phenaceturate, m.p. 90.0–93.2°, undepressed upon admixture with an authentic sample.

The bright orange solution from the chloroform extraction was acidified with 4 *N* hydrochloric acid and the resulting pale yellow solution was allowed to stand. After two hours the precipitate which had formed was collected by filtration, washed with water and dried *in vacuo* to yield 0.470 g. (47%) of the pyrrolidinetrione, XVII, m.p. 136.8–137.7°. Upon heating, the color of the solid faded to a very pale yellow. A sample which had been placed in a heating bath at 125° melted immediately, indicating slow conversion to the less strongly colored and higher melting keto form of XVII on heating. Recrystallization of the bright yellow solid (0.200 g.) from carbon tetrachloride furnished 0.156 g. of pyrrolidinetrione XVII as pale yellow needles, m.p. 137.8–138.4°.

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15; mol. wt., 337. Found: C, 67.27; H, 4.63; N, 4.10; mol. wt. (Rast), 392.

Treatment of XVII with alcoholic ferric chloride resulted in the formation of a dark green coloration similar to that obtained from the corresponding anilide XIX.

The 2,4-dinitrophenylhydrazone of XVII was prepared by heating 0.100 g. (0.296 millimole) of the substance with a solution of 0.200 g. of 2,4-dinitrophenylhydrazine in 15 ml. of hot ethanol (95%) and 0.4 ml. of 12 *N* hydrochloric acid. The crude product, m.p. 235–237°, amounted to 0.060 g. (39.2%). Recrystallization from dioxane (5 ml.) and water (2 ml.) afforded the yellow dinitrophenylhydrazone as a dioxane solvate, m.p. 238.5–240.5°. Upon addition of the first few drops of water to the yellow dioxane solution, a green coloration developed which persisted until the separation of the product was complete.

Anal. Calcd. for $C_{25}H_{19}N_5O_8 \cdot {}^1/_2C_4H_8O_2$: C, 57.75; H, 4.13; N, 12.47. Found: C, 57.53; H, 3.95; N, 12.61.

When the crude product was purified by leaching with hot ethyl acetate, pure, unsolvated material, m.p. 243.2–244.3°, was obtained.

Anal. Calcd. for $C_{25}H_{19}N_5O_8$: C, 58.03; H, 3.70; N, 13.54. Found: C, 58.04; H, 3.88; N, 13.46.

A solution of the dinitrophenylhydrazone in acetone becomes bright blue upon addition of a small amount of water.

The benzhydryl enol ether of XVII was prepared by treatment of 0.050 g. (0.149 millimole) of the heterocycle dissolved in 3 ml. of ether with a solution of 0.030 g. (0.155 millimole) of diphenyldiazomethane in 2 ml. of ether. After 12 hours the ether was evaporated and the residual oil was induced to solidify by trituration with two 5-ml. portions of petroleum ether. Recrystallization of the solid from carbon tetrachloride–petroleum ether furnished 0.040 g. (53.5%) of the enol ether, m.p. 127.0–128.5°. Another recrystallization from the same solvent yielded 0.030 g. of thick, yellow plates, m.p. 128.5–129.5°.

Anal. Calcd. for $C_{32}H_{25}O_5N$: C, 76.32; H, 5.01; N, 2.78. Found: C, 75.67; H, 5.08; N, 2.77.

Alcoholysis of IV.—A suspension of 1.25 g. (0.00372 mole) of IV in 10 ml. of absolute ethanol containing a trace of pyridine was heated on a steam-bath until all the solid had dissolved (13 minutes). The solution was cooled, seeded with the diamide XX and allowed to stand at 5° for one hour. The crystalline precipitate was collected by filtration, washed with a little cold ethanol and dried. The yield of colorless needles, m.p. 99–100° was 1.05 g. (74%). An analytical sample was prepared by two recrystallizations from ethanol, m.p. 100.0–100.7°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.84; H, 5.63; N, 3.51.

The ethanol filtrate was evaporated under reduced pressure to a yellow oil which was taken up in 3 ml. of carbon tetrachloride, seeded with the pyrrolidinetrione XVII and allowed to stand. The yield of XVII was 0.160 g. (12.8%), m.p. 137.0–137.8°.

In similar experiments it was found that the yield of the diamide XX was decreased upon increasing the length of the heating period, while the yield of the pyrrolidinetrione XVII was increased. The products were isolated by the procedure described above.

Alcoholysis of IV occurred much less readily when *t*-butanol was used, and it was necessary to heat the reactants under reflux for eight hours to effect complete reaction. The colorless *t*-butyl ester had a m.p. of 126.3–127.5°.

Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.13; N, 3.14. Found: C, 67.22; H, 6.31; N, 3.51.

Ethanolysis of methyl 2-benzylidene-4,5-diketo-3-oxazolidineacetate, m.p. 188.5–189.0° (reported 186–187°),[9] employing a minimum heating period (15 minutes) also yielded two products, contrary to earlier observations.[9] Both N-ethoxalylphenaceturic acid methyl ester, m.p. 97.3–98.5° (reported 95–97°)[9] and methyl 3-phenyl-2,4,5-triketopyrrolidineacetate, m.p. 134.2–135.3°, (pale yellow needles from carbon tetrachloride) were formed.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.25; N, 5.36. Found: C, 59.50; H, 4.30; N, 5.34.

Reaction of XX with Sodium Hydride.—To a solution of 0.630 g. (0.00174 mole) of the diamide XX in 20 ml. of dry dioxane was added 0.045 g. (0.00187 mole) of finely-powdered sodium hydride, and the mixture was heated to reflux in an atmosphere of nitrogen for 40 minutes. The resulting clear, orange solution was concentrated to an oil which was induced to crystallize by trituration with 10 ml. of water containing six drops of 6 N hydrochloric acid. Recrystallization of the solid (0.50 g.) from carbon tetrachloride provided 0.380 g. (68%) of XVII, m.p. 137.4–138.4°.

In a similar experiment the oxazolidinedione IV was recovered unchanged after treatment with an equimolar amount of sodium hydride in dry dioxane.

Reaction of XX with Aqueous Sodium Hydroxide.—To a solution of 0.100 g. (0.261 millimole) of the diamide XX in 5 ml. of 95% ethanol and 1.5 ml. of dioxane at 0° was added 0.261 ml. of 1.00 N sodium hydroxide. After standing at 0° for five minutes, the solution was diluted with water and extracted with chloroform. The chloroform extract was filtered and evaporated under reduced pressure to a yellow oil which solidified upon trituration with petroleum ether. Further trituration of the solid with water–methanol yielded almost colorless benzyl phenaceturate (0.020 g., 27.1%), m.p. 94–95°.

Aminolysis of IV.—To a suspension of 0.350 g. (0.00104 mole) of the heterocycle in 10 ml. of dry benzene was added 0.242 g. (0.00208 mole) of benzylamine. Reaction took place immediately and after ten minutes the colorless solid which had precipitated was collected by filtration. The yield of N,N′-dibenzyloxamide, m.p. 220.5–222.0°, was 0.275 g. (98.5%). Evaporation of the filtrate and trituration of the residue with petroleum ether afforded benzyl phenaceturate as an almost colorless solid (0.200 g., 66%), m.p. 93–94°. Pure material, m.p. 93.6–95.0°, (0.156 g.) was obtained after one recrystallization from benzene-ligroin.

Treatment of IV with phenylhydrazine resulted in the formation of benzyl phenaceturate in 69% yield, while methylamine after a reaction time of twelve days yielded 53% of the theoretical benzyl phenaceturate along with only 71.5% of the theoretical N,N′-dimethyloxamide.

Aminolysis of III.—From 0.300 g. (0.931 millimole) of the anilide III suspended in 10 ml. of dry dioxane and 15 ml. of benzene there was obtained, after treatment with 1.99 g. (1.86 millimoles) of benzylamine for 12 hours, 96% of the theoretical N,N′-dibenzyloxamide, m.p. 220–222°, and 61% of the theoretical phenaceturic acid anilide, m.p. 158.0–162°, undepressed upon admixture with an authentic sample.

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Dicyclic Hydrocarbons. V. Synthesis and Physical Properties of the Diphenyl- and Dicyclohexylbutanes

BY KASPER T. SERIJAN AND PAUL H. WISE

The synthesis and properties are described for fourteen hydrocarbons in the diphenyl- and dicyclohexylbutane series. In addition to the usual properties, heats of combustion and viscosities are presented for these compounds which were prepared in a high state of purity. The methods of preparation and properties for *dl*-2,3-dicyclohexylbutane, *meso*-2,3-dicyclohexylbutane, 1,3-dicyclohexylbutane, 2,2-diphenylbutane and 2,2-dicyclohexylbutane are reported for the first time.

As part of the program being conducted at this Laboratory involving the investigation of possible components of aviation fuel, the hydrocarbons that constitute the structures obtainable by substituting two phenyl or two cyclohexyl groups in the various combinations of positions on a n-butyl chain have been synthesized and purified. Since the *dl*- and *meso*-forms of 2,3-diphenylbutane and 2,3-dicyclohexylbutane were separated, a total of fourteen hydrocarbons are presented.

Previous papers of this series include the dicyclicalkanes through C_{15}[1] and also the α,α- and α,ω-diphenyl- and dicyclohexylpentanes and hexanes.[2]

The methods of preparation for 1,1-diphenyl-1-butanol and 1,2-diphenyl-2-butanol involved the condensation of phenylmagnesium bromide with ethyl n-butyrate[3] and of benzylmagnesium chloride with propiophenone.[4] The Grignard reagent of β-bromoethylbenzene was condensed with acetophenone to give the intermediate carbinol in the preparation of 1,3-diphenylbutane. The synthesis of 1,4-diphenylbutane involved the reaction of γ-phenylpropylmagnesium bromide with benzaldehyde[5] to give 1,4-diphenyl-1-butanol.

The general procedure, where a carbinol was an intermediate, consisted of dehydration, purification of the resulting olefins and hydrogenation to the aromatic hydrocarbon. The dicyclohexylbutanes were prepared by the hydrogenation of the purified aromatic hydrocarbons or by direct hydrogenation of the purified olefin intermediate.

Proof of structure was established by ozonolysis of the intermediate olefins and characterization of the fragments.

1,4-Diphenylbutane was also prepared by the Wurtz reaction using β-bromoethylbenzene and sodium.[4b] The isomers of 2,3-diphenylbutane were obtained from the condensation of α-bromoethylbenzene in the presence of sodium. The *dl*- and *meso*-forms of 2,3-diphenylbutane were also obtained in low yields as rearrangement products from the Friedel–Crafts synthesis of 2,2-diphenylbutane wherein 2-phenyl-2-butanol, benzene and aluminum chloride were used.

The identity of the *dl*- and *meso*-forms of 2,3-diphenylbutane was established by Ott[6] and confirmed by Wessely and Welleba.[7] The melting point reported for the *dl*-isomer as 8°[8] and also 12.5° when pure[7] was not in accord with the results obtained in the present work. Melting points ranging progressively from 10 to −25° were obtained for successive fractions in the initial fractional distillation. Upon further separation of small quantities of the *meso*-isomer by fractional crystallization and azeotropic distillation, the resulting liquid product could no longer be crystallized. This material is believed by the authors to be the *dl*-isomer in a higher state of purity. The saturated compounds obtained from the separate

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