and a separate red liquid phase was present at the bottom of the flask. After warming to room temperature, water and ether were added and the layers separated. Distillation of the ether under reduced pressure left a yellow glass which was recrystallized from an ethanol–water mixture to give 0.15 g. of yellow needles melting over the range 90–94°. A mixture melting point with the starting material was depressed. The analysis of the product indicated 9.21 and 9.29% of nitrogen present.

Acknowledgment.—All infrared spectra were obtained by use of the Baird double beam infrared spectrophotometer of the Institute for Atomic Research, Iowa State College. The writers express their appreciation to Robert McCord and E. Miller Layton for the preparation of the spectra.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

1,5-Diaryl-2,3-pyrrolidinediones. XI. Observations on Synthetic Methods and the Effect of 4-Substituents on Chemical Properties

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A number of 1,5-diphenyl-2,3-pyrrolidinediones with substituents in the 4-position have been prepared and examined. Unlike the parent member of the series, these compounds appear to be extensively, if not fully, enolized and thus also may be characterized as 4-substituted-1,5-diphenyl-Δ^3-2-pyrrolinones. Methods of synthesis are described and contrasted with those for 1,5-diphenyl-2,3-pyrrolidinedione. The thermal decomposition of two of the 4-substituted compounds is described and the major product from each is characterized.

In an earlier paper[2] reference was made to unpublished work by one of us wherein 4-carbomethoxy-1,5-diphenyl-2,3-pyrrolidinedione was decarbomethoxylated to give what was then thought to be 1,5-diphenyl-2,3-pyrrolidinedione (I) but what has recently been unequivocally identified as the isomeric 3-anilino-5-phenyl-2(5H)-furanone.[3] In a later publication[4] reference was made to the unsatisfactory state of this reaction. Subsequently, sporadic investigation of the reaction was intensified with the following results; while the carbomethoxy group readily affords carbethoxy with ethanol (and *vice versa*) attempts at hydrochloric and hydrobromic acid induced hydrolysis lead to not readily characterizable products[5]; basic hydrolysis under mild conditions is essentially without effect, and under drastic conditions affords at best a poor yield of the 3-anil of the desired I. Thus the reported[2] isolation of I was a purely fortuitous isolation of 3-anilino-5-phenyl-2(5H)-furanone.

When it appeared that resistance to hydrolysis coupled with reluctance of the alkali enolates to be alkylated ruled out the 4-carbalkoxy-1,5-diphenyl-2,3-pyrrolidinediones as convenient sources of either I or its 4-substituted analogs, attention was directed to the previously reported "decarboxylation" of the 4-carbalkoxy-1,5-diphenyl-2,3-pyrrolidinediones.[4] The major reactant of their thermal decomposition had not been identified; and since we were working with an enolized β-ketoester, the reaction might well be another instance of thermal "decarbalkoxylation," as first studied by Meerwein[6] (and very recently elegantly applied in steroid synthesis by Johnson and his collaborators[7]).

The reported quantitative evolution of carbon dioxide was observed upon heating 4-carbethoxy-1,5-diphenyl-2,3-pyrrolidinedione (II) in nitrobenzene,[4] with no water known to be present. Consequently, the analogy to Meerwein's reaction was not complete, and an attempt was made to see if ethylene were also produced, and if so, what was produced from the analogous methyl ester. However, collection of the evolved gas over 50% potassium hydroxide, as for a Dumas nitrogen determination,[8] afforded completely negative results. Thus ordinary ester pyrolysis was ruled out, and in spite of the apparent absence of water it appeared that the reaction must resemble Meerwein's, the necessary water being present in the solvent and adsorbed on the solute. The nitrobenzene was removed in an air stream leaving a substance which melted at 166–167° and which showed infrared absorption at 1710 and 1760 cm.$^{-1}$ but none in the hydroxyl region. The same substance was obtained from the analogous methyl ester. Analytical data and a resemblance of the infrared spectrum to those of authentic 2,3-pyrrolidinediones[9] suggested that thermal "decarbalkoxylation" had indeed occurred with production of I. Characterization of the resulting product and details of the "decarbalkoxylation" already have been reported.[10] Thus with the parent member of the series (I) in hand, attention was turned to non-functional 4-substituents.

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[1] Abstracted from the Ph.D. Dissertation of Irene Shuster Covey, University of Michigan, 1957.

[2] W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 382 (1953).

[3] (a) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98 (1957); (b) **22**, 1560 (1957).

[4] W. R. Vaughan and D. I. McCane, *ibid.*, **20**, 143 (1955).

[5] See, however, H. H. Wassermann and R. C. Koch, *Chemistry & Industry*, 428 (1957), who appear to have hoped for effective hydrolysis by means of hydriodic acid, but actually achieved hydrolysis, decarboxylation and *reduction* of the 3-carbonyl owing to the hypophosphorous acid present in commercial concentrated hydriodic acid, a most interesting result which has recently been repeated in this Laboratory (W. L. Meyer, private communication).

[6] (a) H. Meerwein, *Ann.*, **398**, 242 (1913); (b) in this study enolizable β-ketoesters were heated at 200° with water in sealed tubes.

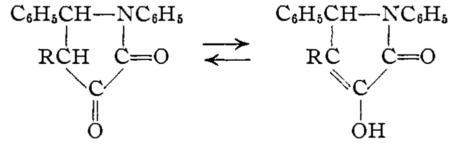
[7] (a) W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, THIS JOURNAL, **78**, 6354 (1956); W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956); (b) these authors appear to favor a direct, homolytic or heterolytic decomposition and propose to study the mechanism.

[8] W. R. Vaughan, W. T. Boyd, D. I. McCane and G. J. Sloan, *Anal. Chem.*, **23**, 508 (1951).

[9] Very kindly furnished by Professor Phillip L. Southwick; *cf.* P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

[10] W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 1554 (1957).

Of a series of such compounds comprising 4-methyl-(III), 4-ethyl-(IV), 4-benzyl-(V) and 4-phenyl-(VI) 1,5-diphenyl-2,3-pyrrolidinedione (Fig. 1), compounds V[11] and VI[12] had been previously reported; but since the reaction employed for their synthesis involved heating benzyl- or phenylpyruvic acids with aniline and benzaldehyde, and since V and VI obtained in this manner showed strong absorption in the OH–NH region of their infrared spectra, reminiscent of the pseudo-2,3-pyrrolidinediones (3-arylamino-5-aryl-2(5H)-furanones[3]) produced when the same type of reaction is applied to pyruvic acid itself,[2] no confidence could be placed in the previous assignment of structure.

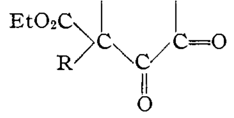


	Ferric chloride color	Hydroxyl absorption, cm.$^{-1}$
I, R = H	None	None
II, R = $CO_2C_2H_5$	Red	3260 ± 10
III, R = CH_3	Olive-green	3280 ± 10
IV, R = C_2H_5	Blue	3270 ± 10
V, R = $C_6H_5CH_2$	Brown-green	3250 ± 10
VI, R = C_6H_5	Emerald	3160 ± 10

Fig. 1.

The original procedure of Borsche was altered to improve yields by substituting benzylideneaniline (*cf.* ref. 2) for benzaldehyde and aniline, and the same products were obtained; and when the reaction was extended to ethylpyruvic acid (α-ketovaleric acid) a similar product was formed. The infrared spectra of all three compounds were very similar; all three produced color with ferric chloride and formed acetates with acetic anhydride (*unlike* the pseudo-2,3-pyrrolidinediones); and all three reacted with aniline to produce "anils" whose infrared spectra and behavior on melting resembled those of the "anil" of I. However, when methylpyruvic acid (α-ketobutyric acid) was used in the same reaction, and indeed when other modifications of this synthesis[2] were attempted, the only product appeared to be the "anil."

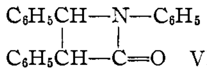
In view of this equivocal situation and in spite of the fact that it had been reported[13] that the addition of ethyl ethoxalylacetate to benzylideneaniline could not be extended to ethyl ethoxalylpropionate, the latter reagents were caused to react, and the reaction was extended to the esters of ethoxalylbutyric and ethoxalyl-γ-phenylpropionic acids with the production of IIIa, IVa and Va, respectively (Fig. 2). The infrared spectra of these compounds exhibit bands falling between 1780 and 1765 cm.$^{-1}$ (ketone) and between 1710 and 1720 cm.$^{-1}$ and thus compare favorably with I and with the 2,3-pyrrolidinediones reported by Southwick.[9] They give negative ferric chloride tests, and upon treatment with one equivalent of methanolic potassium hydroxide, followed by acidification, afford III, IV and V, the latter two being identical with the products obtained from ethyl- and benzylpyruvic acids with benzylideneaniline. The reaction was attempted with ethyl ethoxalylphenylacetate and with ethyl ethoxalylisovalerate with negative results. Like the other members of the series III gave a positive ferric chloride test and afforded an acetate and "anil," and its infrared spectrum was virtually indistinguishable from that of IV. Thus the assignment of structure to III, IV and V is confirmed, and the structure of VI is inferentially settled.



IIIa, R = CH_3
IVa, R = C_2H_5
Va, R = $C_6H_5CH_2$

Fig. 2.

Further support for the structure of VI comes from the similarity in behavior of V and VI on thermal decomposition. Borsche[11] had reported that VI decomposed thermally in the absence of solvent to give stilbene and gaseous products. And in addition he isolated a substance to which he assigned the molecular formula $C_{21}H_{17}NO$ with the unsupported suggestion that it might be the β-lactam VII.



$$\begin{array}{l} C_6H_5CH{-}N{-}C_6H_5 \\ \qquad\quad\ |\quad\ \ | \\ C_6H_5CH{-}C{=}O \end{array}$$

VII

In order to account for the production of VII he postulated carbon monoxide among the decomposition products.

Accordingly VI was decomposed in an atmosphere of carbon dioxide and the resultant gaseous products were collected over 50% potassium hydroxide, as for a Dumas nitrogen determination.[8] The gas collected in this manner was subjected to mass-spectrometric analysis (for which we are indebted to Professor Richard B. Bernstein of this department) and was found to be carbon monoxide, amounting to 85% of the theoretical from one equivalent of VI. Upon purification the residue gave a weak ferric chloride test and analysis indicated a molecular formula of $C_{21}H_{15}NO$ (VIII), which was confirmed by preparation of an acetate, $C_{23}H_{17}NO_2$. An examination of the literature led to the suggestion that VIII might well be 2,3-diphenyl-4-hydroxyquinoline, which was readily accessible[14] by fusing desoxybenzoin with anthranilic acid. Infrared spectra, melting points and a mixture melting point confirmed the suggestion that VIII was in fact 2,3-diphenyl-4-hydroxyquinoline.

Next V was subjected to the same thermal decomposition, and again carbon monoxide was identified while the residue afforded IX, $C_{22}H_{17}NO$, whose infrared spectrum was virtually identical with that of VIII. Thus IX may be assigned the structure 2-phenyl-3-benzyl-4-hydroxyquinoline.

Curiously enough neither III nor IV could be decomposed under similar conditions, both substances being stable well above their melting points. The 4-substituents in these compounds are simple alkyl groups (+I) whereas both phenyl (VI) and benzyl (V) are primarily electron-attracting (−I) (*cf.* ionization constants of phenylacetic, β-

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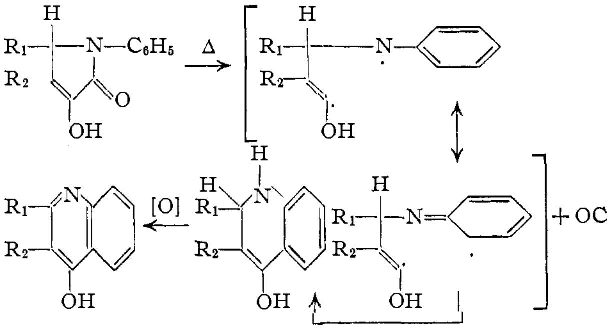
(11) W. Borsche, *Ber.*, **42**, 4072 (1909).

(12) W. Borsche, *ibid.*, **41**, 3884 (1908).

(13) L. J. Simon and A. Conduché, *Ann. chim. phys.*, [8] **12**, 5 (1907).

(14) A. K. Das and B. N. Ghosh, *J. Chem. Soc.*, **115**, 817 (1919).

phenylpropionic, acetic and propionic acids[15] which decrease in that order). Thus it may be argued that if phenyl and benzyl facilitate bond rupture between the oxygen-carrying carbons of the ring, methyl and ethyl should inhibit it. The decarbonylation thermally engendered may be considered to lead to an intermediate biradical which cyclizes and rearranges to a 1,2-dihydroquinoline, which then suffers autoxidation or disproportionation (only somewhat less than 50% quinoline is obtained), *e.g.*



It remains to comment upon salient differences between I and its 4-substituted derivatives. First, in the matter of synthesis it would appear that I and III cannot be obtained except as their "anils" from benzylideneaniline with pyruvic acid or methylpyruvic acid whereas IV, V and VI are readily produced by the addition of substituted pyruvic acids to benzylideneaniline. It seems reasonable to infer that the reason for this is steric: in each reaction the addition to the carbon–nitrogen double bond occurs and is followed by cyclodehydration to the lactam system, which then may or may not react rapidly with more benzylideneaniline (or free aniline), depending upon the bulk of the 4-substituent, to give the "anil."

Only in the case of I does there seem to be any tendency to produce the pseudo-2,3-pyrrolidinedione system, and then only by the expedient of adding aniline to benzylidenepyruvic acid to obtain the intermediate anil which cyclizes to the lactone.[3b] It is possible that this route to the cyclic "anil" of III passes through the open-chain anil of β-benzylidene-α-ketobutyric acid (*cf.* Experimental, the yellow, lower-melting primary reaction product from β-benzylidene-α-ketobutyric acid and aniline), which either fails to lactonize or lactonizes to the pseudo-2,3-pyrrolidinedione which then disproportionates to the cyclic "anil" as this type of compound is known to do on heating.[16]

Further differences between I and its 4-substituted derivatives appear in the properties of the compounds themselves. First, I is extraordinarily subject to dimerization of the type described by Southwick.[9] Even the nature of the solvent for recrystallization seems to be significant in this connection, and a previous publication from this Laboratory describes the difficulty in obtaining a pure sample of I by another route.[10] No such sensitivity is encountered with any of the 4-monosubstituted derivatives of I, which for the most part appear to be soluble in alkali from which they may be reprecipitated by acidification. Indeed, like other 4-carbalkoxy-2,3-pyrrolidinediones,[17] II and its methyl ester analog are sufficiently acidic to react with bicarbonate.

Finally, I exhibits no enolic properties, either chemically or spectroscopically; and whereas the β-ketoester structure of II and its analogs would be expected to produce appreciable enolization, the phenolic properties, chemical and spectroscopic, of III, IV, V and VI are unexpected. Electronic considerations cannot be invoked, since only in VI is there a group (phenyl) capable of conjugating with an enolic double bond; and in III and IV the electron-repelling effect of methyl and ethyl should render the 4-carbon more negative and thus less prone to transfer its proton to oxygen. Thus one is confronted with the phenomenon of three electronically different types (methyl, ethyl (+I), benzyl (−I) and phenyl (−I, ±T)) producing the same structural change: extensive, if not virtually complete enolization. It is not a function of preference of endocyclic carbon–carbon conjugation with the lactam carbonyl over exocyclic carbonyl conjugation with the lactam carbonyl, as might seem to be true for the "anil" of I, which exists preferentially in the enamine structure,[18,19] since I is not enolized; and consequently one is left with a steric effect as the alternative. Interference between the 4-substituent and the 5-phenyl group by itself is not sufficient, since in one of the potential epimeric pairs, these can be *trans* and thus not interfere. Consequently, in addition, the phenyl group on the ring-nitrogen must bulk large enough to force the 4-substituent to take up a more nearly coplanar position with the heterocyclic ring.

Experimental

Melting points are uncorrected. Microanalyses by Anna Griffen (G), University of Michigan, and Spang Microanalytical Laboratory (S), Ann Arbor, Mich. Infrared spectra obtained from Nujol mulls by means of a Perkin–Elmer double beam recording spectrophotometer, model 21.

2-Carbomethoxy- and 2-Carbethoxy-1,5-diphenyl-2,3-pyrrolidinedione (II).—These compounds were obtained by condensation of the corresponding oxalacetic esters with benzylideneaniline.[20,21] Each is converted readily into the other by refluxing a 0.5-g. sample in the appropriate alcohol (20 ml.) to which is added 5 ml. of the alcohol saturated with dry hydrogen chloride. Complete conversion is achieved in 24–48 hr., as shown by mixture melting point determination and identity of infrared spectra.

1,5-Diphenyl-2,3-pyrrolidinedione (I).—The procedure used for conversion of II into I by refluxing in nitrobenzene has been described in an earlier paper.[10] The conversion of the methyl ester into I was achieved by heating 0.1 g. in 20 ml. of nitrobenzene until the temperature reached 200° and maintaining this temperature for about two minutes. Recovery was by evaporation of the solvent as described for the ethyl ester.[10] The product, I, melted at 164–165°, with softening before melting; no m.p. depression on admixture with an authentic sample.[10] When the decomposition of II was carried out in an atmosphere of carbon dioxide[8] and the reaction flask was swept out with carbon dioxide after cooling, no residual gas was observable.

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[15] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 734–735.

[16] *Cf.* K. Garzarolli-Thurnlackh, *Montash.*, **20**, 480 (1899).

[17] P. L. Southwick and R. T. Crouch, THIS JOURNAL, **75**, 3413 (1953).

[18] W. R. Vaughan, *J. Org. Chem.*, **20**, 1613 (1955).

[19] W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 1565 (1957).

[20] R. Schiff and C. Bertini, *Ber.*, **30**, 601 (1897).

[21] P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2532 (1949). For structure proof *cf.* refs. 4 and 17.

TABLE I

4-SUBSTITUTED-1,5-DIPHENYL-2,3-PYRROLIDINEDIONES

Compound	Procedure	Yield, %	Recrystn. solvent	M.p., °C.	Formula	Analyses, %	
						Calcd.	Found[a]
III	A (from IIIa' and IIIa")	31	Abs. ethanol	213.0–213.5	$C_{17}H_{15}NO_2$	C, 76.96	76.99
						H, 5.70	5.61
						N, 5.28	5.28
Acetate			Methanol–water	129.5–130.0	$C_{19}H_{17}NO_3$	C, 74.25	74.18
						H, 5.58	5.51
						N, 4.56	4.64
"Anil"[b]			Ethanol or gl. acetic acid	220–221	$C_{23}H_{20}N_2O$	C, 81.15	80.94, 81.02
						H, 5.92	5.79, 6.02
						N, 8.23	8.43(G), 8.12(G)
IV	A[c]	3	Ethanol–water	198.5–199.0[d]	$C_{18}H_{17}NO_2$	C, 77.39	77.43(S)
						H, 6.13	5.99(S)
						N, 5.01	4.96
	B (from IVa' and IVa")	67	Ethanol–water	198–199[d]			
Acetate			Methanol	126–127	$C_{20}H_{19}NO_3$	C, 74.74	74.78
						H, 5.96	5.78
						N, 4.36	4.37
"Anil"			Abs. ethanol	130.5–131.5	$C_{24}H_{22}N_2O$	C, 81.32	81.16
						H, 6.26	6.10
						N, 7.90	7.86
V	A[e]	12	Acetic acid–water	219–220 d.[d]			
	B (from Va)	59	Abs. ethanol	220–221 d.[d]	$C_{23}H_{19}NO_2$	C, 80.91	80.71, 81.22
						H, 5.61	5.74, 5.68
						N, 4.10	4.06, 41.2
Acetate			Abs. ethanol	159.5–160.5	$C_{25}H_{21}NO_3$	C, 78.31	78.47(S)
						H, 5.52	5.45(S)
						N, 3.65	3.68
"Anil"			Abs. ethanol	204.0–204.5	$C_{29}H_{24}N_2O$	C, 83.63	83.56
						H, 5.80	5.54
						N, 6.73	6.73
VI	A	50	Gl. acetic acid	243–246	Known[f]		
Acetate				184–185	Known[g]		
"Anil"			Ethanol–water	170.0–171.5	$C_{25}H_{22}N_2O$	C, 83.55	83.56
						H, 5.51	5.40
						N, 6.96	6.82

[a] Carbon and hydrogen analyses by Anna Griffen, University of Michigan (unless marked S); nitrogen analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. (unless marked G). [b] The use of α-ketobutyric acid [W. Tschelinzeff and W. Schmidt, *Ber.*, **62**, 2210 (1929); E. Arnold, *Ann.*, **246**, 329 (1888)] as in method A, in glacial acetic acid at 5° or in ether at 5° afforded only the "anil," m.p. 214–215°, as shown by mixture melting point and identical infrared spectra. β-Benzylidene-α-ketobutyric acid (see below) with aniline in absolute ethanol containing a trace of 10% hydrochloric acid held at reflux for 6 hr. afforded a crude *yellow* product, m.p. 173–180° (softening at 160°), which lost its color on several recrystallizations from absolute ethanol and finally melted at 221–222°. This, too, proved to be the "anil." [c] α-Ketovaleric acid [F. Adickes and G. Andreson, *Ann.*, **555**, 41 (1943); R. Fittig, *ibid.*, **331**, 129 (1904); the former reference is for procedure only, the latter for physical properties with which we concur] was used in procedure A. Since no reaction took place, an additional hour of reflux was employed, whereupon the poor yield reported was obtained. [d] Mixture melting point with product from alternate procedure undepressed. Infrared spectra identical. [e] Benzylpyruvic acid was prepared according to W. Wislicenus, *Ber.*, **31**, 3133 (1898). Borsche[11] previously reported V from warming an alcoholic solution of benzaldehyde, aniline and benzylpyruvic acid on the steam-bath for 5 hr. to melt at 196°. [f] Previously reported to melt at 250°.[11] [g] Previously reported to melt at 184–185°.[11]

4-Carbethoxy-4-methyl-1,5-diphenyl-2,3-pyrrolidinedione (IIIa).—An ethereal solution of 10.0 g. (0.05 mole) of ethyl ethoxalylpropionate[22] and 9.1 g. (0.05 mole) of benzylideneaniline was refluxed for 6 hr. and then was allowed to stand in the refrigerator for two days. The crude precipitate melted at 135–155° and it was accordingly recrystallized from absolute ethanol to give 9.3 g. (56%) of white needles, m.p. 165–166° (IIIa').

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.91; H, 5.53 (G); N, 4.10 (S).

On evaporation of the mother liquors there was obtained a second product in the form of yellowish platelets, which were recrystallized from absolute ethanol to give 1.9 g. (12%) of IIIa", m.p. 119–120°. Infrared spectra of chloroform solutions of these two dimorphic products were identical.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.28; H, 5.63; N, 4.13 (S).

4-Carbethoxy-4-ethyl-1,5-diphenyl-2,3-pyrrolidinedione (IVa).—An ethereal solution of 3.9 g. (0.018 mole) of ethyl ethoxalylbutyrate[23] and 3.3 g. (0.018 mole) of benzylideneaniline containing 2 drops of piperidine was refluxed for 6 hr. and then was allowed to stand for three days in the refrigerator. The crude precipitate was twice recrystallized from absolute ethanol to give 1.8 g. (28%) of IVa' as white needles, m.p. 108.5–109.5°.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.82; H, 6.04; N, 3.90 (S).

As for IIIa the mother liquors afforded a second product, 0.8 g. (12%) of IVa" as light yellow platelets, m.p. 114–115°, from absolute ethanol. Infrared spectra of chloro-

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[22] R. F. B. Cox and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 272.

[23] A. Brandstrom, *Acta Chem. Scand.*, **5**, 485 (1951).

form solutions of these two dimorphic products were identical.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.79; H, 5.90; N, 3.96 (S).

4-Carbethoxy-4-benzyl-1,5-diphenyl-2,3-pyrrolidinedione (Va).—An ethereal solution of 28.1 g. of crude ethyl ethoxalyldihydrocinnamate[24] and 15.0 g. (0.083 mole) of benzylideneaniline was treated as in the preceding experiments and thus afforded 10.1 g. (29.5%) of Va, m.p. 188.0–188.5°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.53; H, 5.39 (G); N, 3.32 (S).

4-Substituted-1,5-diphenyl-2,3-pyrrolidinediones (4-Substituted-1,5-diphenyl-3-hydroxy-Δ^3-2-pyrrolinones) (III–VI).—Two methods of preparation were used: A. Borsche's procedure[11] in which the appropriate α-ketoacid was warmed with benzylideneaniline in ethanol for a few minutes on the steam-bath. B. Refluxing the corresponding 4-carbethoxy-4-substituted intermediate (IIIa–Va) in methanol containing one equivalent of potassium hydroxide for six hours. Subsequent acidification of the cooled solution afforded the desired product, either as an immediate precipitate or upon evaporation under an air jet.

Acetates were prepared by means of acetic anhydride and sodium acetate,[11] usually being precipitated by dilution with water.

The "anils" (phenylamino derivatives) were prepared by refluxing the compounds with two equivalents of aniline for 2–10 min. After cooling the mixtures were diluted with absolute ethanol, whereupon the derivatives crystallized. Pertinent data are assembled in Table I.

β-Benzylidene-α-ketobutyric Acid.—A procedure described for another substance[25] was adapted for this preparation. By adding 4.6 g. (0.083 mole) of potassium hydroxide in 10 ml. of absolute methanol to 5.6 g. (0.055 mole) of α-ketobutyric acid (*cf.* footnote *b*, Table I for alternative preparations for this substance) and 5.83 g. (0.055 mole) of benzaldehyde dissolved in 10 ml. of absolute methanol, there was obtained 6.9 g. (13%) of the potassium salt of the acid. When a saturated aqueous solution of this salt was acidified with 1.6 *N* hydrochloric acid, an oil separated. It was taken up in ether, dried over magnesium sulfate and recovered as a solid upon filtration and evaporation. Recrystallization from benzene–petroleum ether (90–100°) afforded pure material, m.p. 107.5–108.5°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.42; H, 5.19 (G).

When run on a larger scale this procedure yielded less tractable material, as did decreasing the relative quantities of methanol. No extensive attempts were made to improve it, however.

Thermal Decomposition of 1,4,5-Triphenyl-2,3-pyrrolidinedione.—This substance was placed in a 50-ml. ₮ flask connected to a gas buret, as for a Dumas nitrogen determination.[8] The air was displaced by carbon dioxide, and the flask was heated with a flame in such a manner that the gas evolution was moderate and constant. When gas evolution ceased, the apparatus was swept out with carbon dioxide, all gases being collected over 50% potassium hydroxide solution. The residual gas from 1.0 g. of solid was 65.4 ml. (739.4 mm., 25.5°) (85%) and was identified by mass spectrometric analysis as carbon monoxide.[26] The residue in the flask was purified by recrystallization from acetonitrile to give a product, m.p. 333–334°; Borsche[11] had reported 338° (see text). An authentic sample of 2,3-diphenyl-4-hydroxyquinoline[14] melted at the same temperature and showed no depression in melting point upon admixture with the product of this reaction. The infrared spectra were identical.

An acetate was prepared by means of acetic anhydride and sodium acetate. After recrystallization from ethanol–water it melted at 149.5–150.5°.

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.46; H, 4.97 (G); N, 4.13 (S).

Thermal Decomposition of 4-Benzyl-1,5-diphenyl-2,3-pyrrolidinedione.—A 0.5-g. sample was treated as in the preceding experiment. Less extensive decomposition was achieved, but carbon monoxide was again shown to be evolved. The decomposition product was purified by recrystallization from acetone–water, m.p. 262.0–262.5°. The infrared spectrum of this sample is almost identical with that of 2,3-diphenyl-4-hydroxyquinoline.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 85.02; H, 5.86; N, 4.52 (S).

Compounds III and IV did not decompose when subjected to similar treatment.

ANN ARBOR, MICH.

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[26] Very kindly performed by Professor Richard B. Bernstein of this department.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Investigations in Heterocycles. IV.[1] Substituted Cycloalkeno[d]thiazolin-2-ones

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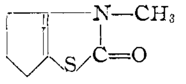
The condensation of substituted α-halocycloalkanones with ethyl xanthamidate or ethyl N-methylxanthamidate has resulted in the formation of several new thiazolin-2-ones possessing significant analgetic properties when tested in laboratory animals. These compounds, all cycloalkeno[d]thiazolin-2-ones, are substituted in the 4- or 5-position of the alicyclic ring with a tertiary amino moiety either directly or through a methylene group. The chemistry of the intermediary compounds and the final products is discussed.

In our general program of synthesizing compounds of the thiazolin-2-one class for testing as analgetics, it was found that 2,3,5,6-tetrahydro-3-methyl-4-cyclopentathiazolin-2-one (I) and its six carbon analog, 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one[2,3] (II) raised noticeably the threshold of pain in experimental animals suggesting analgesia.



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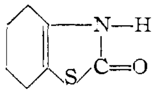

II

Substitutions on the hetero ring nitrogen other than methyl led to a diminution in activity concurrent with an alteration of the toxicity factor. It was thus felt that a more favorable activity–toxicity ratio might be obtained if alterations in structure

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