the isomerization mixture was neutralized with 6*N* hydrochloric acid and was evaporated to dryness on the steam bath. The solid mass was extracted with anhydrous acetone. The acetone was evaporated and the residue was distilled to give 4.2 g (56%) of crude II, b.p. 157–161°/0.1 mm., which showed a positive ceric ammonium nitrate test. No depression was found in a mixed melting point determination with an authentic sample of II.

BLACKSBURG, VA.

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

4-Benzylidine-2,3-dioxopyrrolidines and 4-Benzyl-2,3-dioxopyrrolidines. Synthesis and Experiments on Reduction and Alkylation[1]

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The acid-catalyzed condensation of benzaldehyde with 1-substituted 2,3-dioxopyrrolidines (I) yielded 1-substituted 4-benzylidene-2,3-dioxopyrrolidines (III). A convenient preparative procedure is described in which 1-substituted 2,3-dioxopyrrolidines (I) are formed by acid hydrolysis and decarboxylation of the readily available 1-substituted 4-carbethoxy-2,3-dioxopyrrolidines (II) and condensed with benzaldehyde in a single operation. Sodium borohydride reduced both the conjugated olefinic bond and the ketonic carbonyl group of the 4-benzylidene derivatives (III) to yield 1-substituted 4-benzyl-3-hydroxy-2-oxopyrrolidines (XI). The latter compounds were reduced with lithium aluminum hydride to 1-substituted 4-benzyl-3-hydroxypyrrolidines (XII). Catalytic hydrogenation of the 4-benzylidene derivatives (III) yielded the 1-substituted 4-benzyl-2,3-dioxopyrrolidines (VIII). These highly enolized compounds [actually 1-substituted 4-benzyl-3-hydroxy-2-oxo-3-pyrrolines (IX)] resemble phenols in displaying appreciable acidity, forming deeply colored ferric chloride complexes and yielding ambident anions which undergo both C and O alkylation. Ketonic behavior was evident, however, in the formation of aniline derivatives (XV).

Simple 2,3-dioxopyrrolidines (I) with substituents only at the 1-position can be obtained conveniently by acid hydrolysis and decarboxylation of the readily available 1-substituted 4-carbethoxy-2,3-dioxopyrrolidines (II).[3] The dioxopyrrolidines (I) are promising starting materials for the synthesis of a variety of structures containing the pyrrolidine ring and have, for example, already been utilized for the synthesis of compounds related to the alkaloid vasicine.[4] The present investigation is concerned with the possibility of utilizing the 2,3-dioxopyrrolidines as the active methylene components in aldol condensations, in order to obtain additional types of pyrrolidine derivatives.

A pronounced tendency to undergo condensation reactions involving the methylene group at the 4-position was evident from earlier observations of the behavior of 2,3-dioxopyrrolidines; certain of these compounds had been found to undergo self-condensation in the aldol manner with remarkable speed under basic or even essentially neutral reaction conditions.[3a,5,6] However, the objective of the present investigation was to avert the self-condensations and permit the 2,3-dioxopyrrolidines to condense with the carbonyl function of other compounds. The objective has been achieved with benzaldehyde as the other carbonyl compound, and the resulting 4-benzylidene-2,3-dioxopyrrolidines (III) have been converted into a number of other types of substituted pyrrolidines, as discussed below.

The condensation of benzaldehyde with 2,3-dioxopyrrolidines was not achieved with a basic catalyst (pyridine); self-condensation of the 2,3-dioxopyrrolidine to the aldol condensation product (VII) occurred instead.[3a] The suppression of the self-condensation in favor of reaction with benzaldehyde was accomplished very successfully under acidic conditions, however. Evidently the enol form (IV) of the 2,3-dioxopyrrolidine is attacked more rapidly by protonated benzaldehyde (V) than by protonated 2,3-dioxopyrrolidine (VI), but it is uncertain whether the outcome reflects a higher intrinsic reactivity of V than of VI, or merely a lower concentration of VI. Actually, self condensation of the 2,3-pyrrolidinediones (I) does occur in acid solution, but only to a limited extent.[7] The enols IV, unlike many related compounds which have a substituent in the 4- position (*vide infra*), have not been isolated.

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(2) This paper is based on a thesis submitted by Eugene F. Barnas in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology, May 1960.

(3) (a) P. L. Southwick, E. P. Previc, Joseph Casanova, Jr., and E. Herbert Carlson, *J. Org. Chem.*, **21**, 1087 (1956); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953); (c) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949).

(4) (a) P. L. Southwick and J. Casanova, Jr., *J. Am. Chem. Soc.*, **80**, 1168 (1958); (b) P. L. Southwick and S. E. Cremer, *J. Org. Chem.*, **24**, 753 (1959); (c) F. Kuffner, G. Lenneis, and H. Bauer, *Monatsh. Chem.*, **91**, 1152 (1960).

(5) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1554, 1560 (1957).

(6) W. R. Vaughan and I. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958).

CHART I

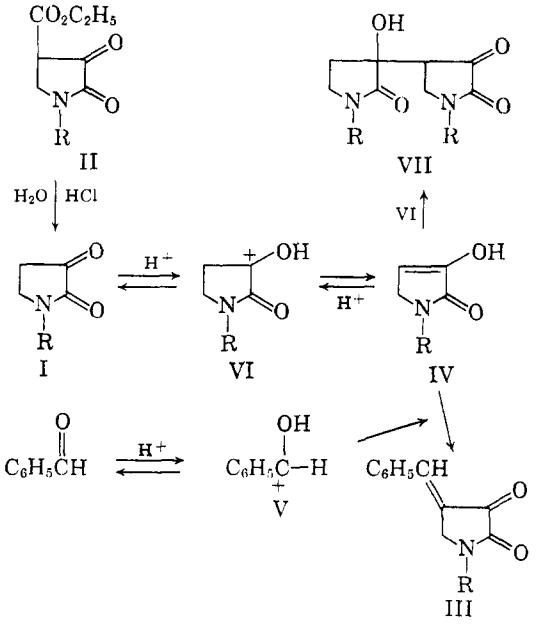
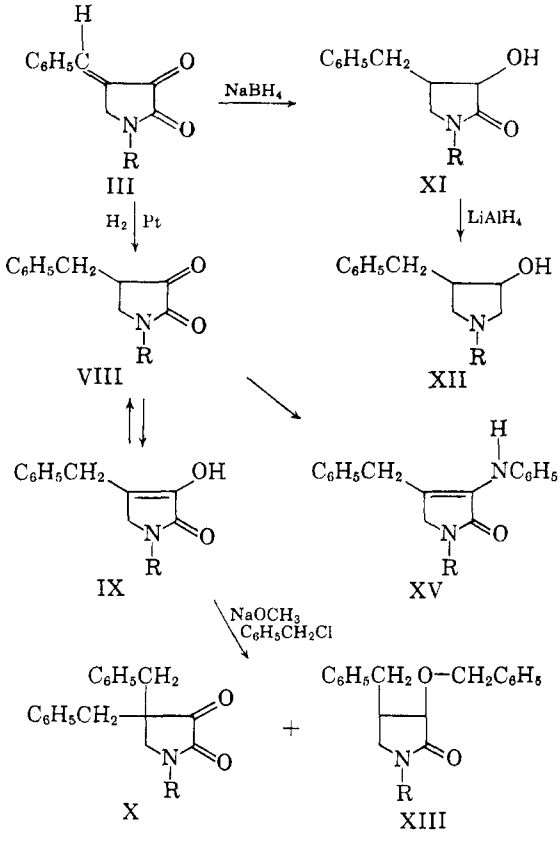


CHART II



Two different procedures were developed for conducting condensations between benzaldehyde and 2,3-dioxopyrrolidines. In the first (procedure A) the 2,3-dioxopyrrolidine was dissolved in approximately two equivalents of benzaldehyde, and dry hydrogen chloride was introduced until formation of the product caused the mixture to solidify. In the second method (procedure B) 2,3-dioxopyrrolidines were obtained from 4-carbethoxy-2,3-dioxopyrrolidines and condensed with benzaldehyde in a single combined operation. By introducing benzaldehyde into reaction mixture in which hydrolysis and decarboxylation of 4-carbethoxy-2,3-dioxopyrrolidines was being carried out by the action of hydrochloric acid, the 4-benzylidene-2,3-dioxopyrrolidines were obtained directly. Procedure B was generally preferred because of its convenience. In some instances procedure B enjoyed another advantage in addition to convenience; it permitted preparation of 4-benzylidene derivatives of 2,3-dioxopyrrolidines such as the 1-methyl and 1-isopropyl compounds which have thus far not been isolated as such in the pure condition.[3a] The yields (see Table I) produced by these procedures were generally fair to good.

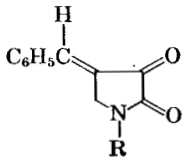
All of the 4-benzylidene-2,3-dioxopyrrolidines (III) were bright yellow crystalline compounds. The infrared spectra (determined in chloroform solution) showed bands which could be assigned to the ketonic carbonyl group (5.79 μ), the lactam (pyrrolidone) carbonyl group (5.88 μ), and the conjugated olefinic double bond (6.13 μ). The ultraviolet absorption was also in accord with expectation; the conjugated system gave rise to a broad maximum at 327.5 mμ, ϵ 24,600 (measured in ethanol solution on the *N*-benzyl and *N*-cyclohexyl compounds).

Chart II illustrates reactions by which the 4-benzylidene-2,3-dioxopyrrolidines (III) have been transformed into other types of pyrrolidine derivatives. The first reactions to be studied were reductions. Sodium borohydride reduced both the ketonic carbonyl group and the conjugated olefinic bond to yield 4-benzyl-3-hydroxyl-2-oxopyrrolidines (XI). The yields of the reaction products were quite good (see Table II), but, except in the case of the 1-cyclohexyl derivative, the initial melting points of these products were broad, suggesting the presence of both of the diastereoisomeric racemates possible for structure XI. In the case of the 1-methyl and 1-benzyl compounds, attempted fractional crystallization failed to yield more than one compound, but in the case of the 1-β-phenylethyl compound a separation of diastereoisomers may have been achieved. However, the presumed low-melting isomer did not yield completely satisfactory analytical data, and its melting point was not depressed by admixture with the easily purified, high-melting form, so the success of the separation effort is not completely established. With the relatively bulky cyclohexyl group at the 1-position, a higher degree of configuration control was evident in the reduction; only one easily purified compound seemed to be formed in significant amount.

The 1-substituted 4-benzyl-3-hydroxy-2-oxopyrrolidines, (XI) were further reduced to 1-substi-

TABLE I

1-Substituted 4-Benzylidene-2,3-dioxopyrrolidines (III)

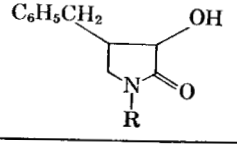


R	Form; M.P.	Yield, [a] %	Reaction Mixture: C_6H_5CHO	DOP,[b] g.	CDOP,[b] g.	95% Ethanol, ml.	HCl, ml.	Reaction Period, Hours	Formula	Calcd., %	Found, %	
CH_3—	Needles, 201.5–203	43 (B)	18 g.	—	25	100	500, 10%	.1	$C_{12}H_{11}O_2N$	C 71.62 H 5.51 N 6.96	69.85 6.12 7.20	69.84[c] 5.72 7.40
$(CH_3)_2CH$—	Plates, 183.5–185	54 (B)	3 g.	—	5	25	200, 10%	1.5	$C_{14}H_{15}O_2N$	C 73.34 H 6.59 N 6.11	73.59 6.38 6.35	
Cyclo-C_6H_{11}—[d]	Needles, 204–205.5	76 (B) 84 (A)	11 g. 2 ml.	— 2	20 —	150 —	500, 20% —	2 1	$C_{17}H_{19}O_2N$	C 75.81 H 7.11 N 5.20	75.65 7.03 5.18	
C_6H_5—	Needles, 181.5–183	32 (B)	10 g.	—	15	200	750, 20%	3	$C_{17}H_{13}O_2N$	C 77.55 H 4.98 N 5.32	77.28 5.04 5.26	
$C_6H_5CH_2$—	Needles, 188.5–190	67 (B) 76 (A)	14 g. 2 ml.	— 1.5	25 —	250 —	1000, 20% —	3 1	$C_{18}H_{15}O_2N$	C 77.96 H 5.45 N 5.05	77.87 5.34 5.12	
$C_6H_5CH_2CH_2$—	Plates, 157–158.5	53 (B)	11 g.	—	20	200	1000, 20%	3	$C_{19}H_{17}O_2N$	C 78.33 H 5.88 N 4.81	78.46 5.70 4.74	

[a] Letters (A or B) following yield figures identify the preparative procedure (Experimental section). [b] DOP = 1-substituted 2,3-dioxopyrrolidine; CDOP = 1-substituted 4-carbethoxy-2,3-dioxopyrrolidine. [c] No explanation of this unsatisfactory analytical result is apparent. Most derived compounds yielded satisfactory results. [d] Infrared spectrum (in chloroform): 3.43 m; 5.79 si; 5.88 i; 6.13 i; 6.25 m; 6.34 w; 6.71 w; 6.90 m; 7.02 w; 7.82 m; 8.65 i; 9.30 bw; 9.61 bw; 10.04 w; 10.66 bw; 11.19 w. (Figures are wave lengths in microns. Letters following figures describe bands as follows: i = intense—>60% absorption; m = medium—30–60% absorption; w = weak—<30% absorption; b = broad band; s = shoulder.) Ultraviolet spectrum (in 95% ethanol): λ_{max} 327.5 mμ, ε 24,600; λ_{min} 257.5 mμ, ε 1250.

TABLE II

1-SUBSTITUTED 4-BENZYL-3-HYDROXY-2-OXOPYRROLIDINES (XI)



R	Separated Isomer(s), M.P.; Form; Yield	Crude Mixed Isomers, M.P.; Yield	Reaction Mixture: BDOP,[a] g.	Reaction Mixture: $NaBH_4$, g.	Cryst. Solv.	Formula	Calcd., %	Found, %
CH_3—[b]	109–110.5 Prisms Poor yield	95–99 7.1 g. (89%)	8.0	2.0	Ether; $CHCl_3$ + pet. ether (b.p. 65–110°)	$C_{12}H_{15}O_2N$	C 70.22 H 7.37 N 6.82	70.29 7.18 7.15
Cyclo-C_6H_{11}—	128–130 Needles 7.16 g. (71%)	111.5–118 9.9 g. (98%)	10.0	2.0	Heptane	$C_{17}H_{23}O_2N$	C 74.69 H 8.48 N 5.12	74.89 8.42 5.23
$C_6H_5CH_2$—	107–109 Needles Poor yield	95–99 7.6 g. (76%)	10.0	2.0	Ether	$C_{18}H_{19}O_2N$	C 76.84 H 6.81 N 4.98	77.28 6.60 4.78
$C_6H_5CH_2CH_2$—[c]	(1) 141–142.5 Needles 6.7 g. (45%) (2) 65.5–68 Rods 1.7 g. (12%)	(1) 129–137 7.9 g. (52%) (2) 61–67	15.0	3.0	(1) $CHCl_3$ + pet. ether (b.p. 65–110°) (2) Benzene + hexane	$C_{19}H_{21}O_2N$	C 77.26 H 7.17 N 4.74	(1) 77.05 (1) 7.14 (1) 4.47 (2) 77.85 (2) 7.19 (2) 4.69

[a] BDOP = 1-substituted 4-benzylidene-2,3-dioxopyrrolidine. [b] Infrared spectrum (in chloroform): 2.83 sw; 3.04 bw; 3.52 bw; 5.94 i; 6.24 w; 6.70 w; 6.92 bw; 7.12 w; 7.89 bm; 8.76 bw; 9.28 m; 9.39 m (same notation as in Table I). [c] Data for two apparently different diastereoisomers are given separately as indicated by (1) and (2) designating high- and low-melting forms, respectively.

tuted 4-benzyl-3-hydroxypyrrolidines (XII) by treatment with lithium aluminum hydride. Results of these experiments are recorded in Table IV. Except for the 1-cyclohexyl derivative (m.p. 94°) the latter compounds were obtained as thick oils or glasses which were characterized as salts prepared with *p*-toluenesulfonic acid. When the reactions were performed on the separated racemic forms of the hydroxypyrrolidones (XI), the hydroxypyrrolidines (XII) were obtained in good yield, and there was no evidence that the product contained more than one racemate; evidently the established configurations at the asymmetric centers were not disturbed during reduction of the lactam carbonyl group.

Lithium aluminum hydride reductions were also performed on the unseparated mixtures of diastereoisomeric 1-substituted 4-benzyl-3-hydroxy-2-oxopyrrolidines (XI) produced by sodium borohydride reduction of the 4-benzylidene derivatives (III). The resulting mixtures of diastereoisomeric 1-substituted 4-benzyl-3-hydroxypyrrolidines (XII) were converted into *p*-toluenesulfonates, and these salts were subjected to fractional crystallization. With the 1-β-phenylethyl compounds this procedure resulted in the separation of two racemates, but in the other cases only one racemate could be purified. The 3-hydroxypyrrolidines were of interest from the standpoint of possible physiological activity; the results of tests now in progress will be reported elsewhere.

Catalytic hydrogenation of the 4-benzylidene-2,3-dioxopyrrolidines (III) over a platinum (Adams') catalyst reduced only the olefinic bond and permitted the preparation of 1-substituted 4-benzyl-2,3-dioxopyrrolidines (VIII) (see Table III). The latter compounds were enolized to a large extent and, hence, can best be represented by a 3-hydroxy-2-oxo-3-pyrroline structure IX. The evidence for enolization included infrared spectroscopic data, solubility in aqueous alkali, and positive tests (strong purple colors) with ferric chloride. The infrared spectra (measured in chloroform) contained *no* bands at the proper position for a ketonic carbonyl (*ca.* 5.67 μ in these five-membered rings).[3a] Strong absorption due to the lactam carbonyl groups gave rise in each case to a pair of overlapping bands in the 5.91- to 6.02-μ range. The hydroxyl absorption consisted of well defined bands at 2.86–2.88 μ overlapping broad maxima at 3.18–3.20 μ. The splitting of both the hydroxyl and lactam carbonyl absorptions suggested that these functional groups were participating to a considerable extent in hydrogen bonding, but were also present in the unassociated condition in the chloroform solutions used for the measurements.

It may be recalled that 2,3-dioxopyrrolidines substituted only at the 1- position[3a,b] or at the 1- and 5- positions[5] are obtained in unenolized form. On the other hand, all of the compounds carrying one substituent at the 4 position which have been examined in this regard have been found to be enolized to a large extent.[3,6,7] The enolizing effect is exerted by a diverse group of 4-substituents (carbalkoxy,[3] 1-alkyl-2-oxo-3-hydroxy-3-pyrrolidyl (as in VII),[3a] methyl,[6,7] ethyl,[6] benzyl,[6] phenyl,[6] bromo,[7] benzoyl,[7] cyano[7]) regardless of whether they would be expected to have an electron-donating or electron-withdrawing influence. Vaughan and Covey[6] have for this reason concluded that the enolizing effect of the 4-substituent cannot be electronic in origin. They have advanced the plausible suggestion that enolization is favored in the 4-substituted compounds because it would remove steric interactions which would be present between substituents at the 1- and the 4- positions in the keto forms of these compounds. It was anticipated that the series of compounds described here, in which the 1-substituent ranges in size from methyl to cyclohexyl, might display a variation in the presence or extent of enolization which would lend support to that hypothesis. However, the infrared spectra indicate that the 4-benzyl substituent is fully effective in promoting enolization even when the 1-substituent is as small as methyl. Ketonic reactivity was evident, nevertheless, in the formation of aniline derivatives (XV) (see Table III).

It was of interest to determine whether sodium enolates obtained from the 4-benzyl-2,3-dioxopyrrolidines (VIII or IX) would be alkylated preferentially on carbon in the manner of enolates derived from β-keto esters, or whether, like sodium phenoxides,[8] they might show a tendency toward oxygen alkylation. The results of our experiments showed that the latter possibility holds true; these 2,3-dioxopyrrolidines yield ambident enolate anions[9b] which behave much like phenoxide ions.[9] Thus, when a sodium enolate prepared from one of these compounds (VIII or IX, R = benzyl) was treated with benzyl chloride in refluxing toluene only a 19% yield of the C-alkylation product, the crystalline 2,3-dioxopyrrolidine (X, R = benzyl), was obtained. The infrared spectrum of this compound contained the expected strong bands at 5.67 μ (ketonic carbonyl) and 5.84 μ (lactam carbonyl). Most of the product mixture consisted of a yellow oil, the infrared spectrum of which dis-

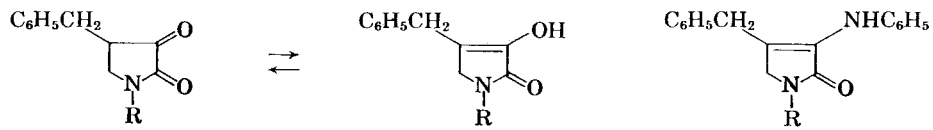
(7) Unpublished results from the Ph.D. thesis of Julius A. Vida, Carnegie Institute of Technology, January 1961.

(8) The resemblance of many of the 4-substituted 2,3-dioxopyrrolidines to phenols is particularly striking with respect to ferric chloride colors, which are deeper and more varied in hue (violet, blue, blue-black or green, as well as red-brown) than those ordinarily observed with "active methylene" compounds. Vaughan and Covey (ref. 6) have referred to the "phenolic" characteristics of these compounds.

(9) Recent studies of the alkylation of phenoxides have been reported by (a) D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958) and (b) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959). These papers review and discuss earlier work on this subject.

TABLE III

1-SUBSTITUTED 4-BENZYL-2,3-DIOXOPYRROLIDINES (VIII) [OR 1-SUBSTITUTED 4-BENZYL-3-HYDROXY-2-OXO-3-PYRROLINES (IX)] AND DERIVED ANILS (XV)[a]



VIII IX XV

R	Form; M.P. Dec.	Wt. of Starting Material; Yield	Formula	Calcd., %	Found, %	Anils Yield; M.P. Dec.	Anil Formula	Calcd., %	Found, %
CH_3—	Needles 170–171	10 g.; 6.7 g. (67%)	$C_{12}H_{13}O_2N$[b]	C 70.91 H 6.45 N 6.89	70.72 6.63 6.69	93% 137–138	$C_{18}H_{18}ON_2$[c]	C 77.67 H 6.52 N 10.07	77.52 6.58 9.97
Cyclo-C_6H_{11}—	Needles 196–197	6.8 g.; 4.1 g. (61%)	$C_{17}H_{21}O_2N$	C 75.24 H 7.80 N 5.16	74.70 7.85 5.00	—	—	—	—
$C_6H_5CH_2$—	Needles 160–161	10 g.; 6.3 g. (63%)	$C_{18}H_{17}O_2N$[d]	C 77.39 H 6.13 N 5.01	77.52 6.16 4.69	87% 137.5	$C_{24}H_{22}ON_2$	C 81.32 H 6.62 N 7.90	80.98 6.12 7.90
$C_6H_5CH_2CH_2$—	Rods 161–162	10 g.; 6.3 g. (63%)	$C_{19}H_{19}O_2N$	C 77.79 H 6.53 N 4.77	77.56 6.45 4.85	96% 138.5–139	$C_{25}H_{24}ON_2$	C 81.49 H 6.57 N 7.60	81.84 6.22 7.33

[a] Infrared spectra of the anils indicate, by the presence of an N—H band, the 3-anilino-2-oxo-3-pyrroline structure (XV) shown. *Cf.* ref. 3a and W. R. Vaughan, *J. Org. Chem.*, **20**, 1613 (1955). [b] Infrared spectrum (in chloroform): 2.86 w; 3.18 bm; 3.44 m; 5.92 si; 5.99 i; 6.24 w; 6.72 m; 6.89 m; 7.26 i; 7.84 m; 9.13 m (same notation as in Table I). [c] Infrared spectrum (in chloroform): 2.97 w; 3.36 bw; 5.91 si; 5.95 i; 6.24 i; 6.63 sm; 6.70 i; 6.89 m; 7.02 m; 7.12 m; 7.68 m. [d] Infrared spectrum (in chloroform): 2.86 w; 3.20 bm; 3.44 m; 5.95 si; 5.99 i; 6.23 w; 6.69 m; 6.88 m; 7.25 i; 7.88 m; 9.24 m; 9.30 m; 9.50 bw.

played no strong bands in the range 3.50–6.00 μ. The material therefore cannot have contained more than small amounts either of starting material or of the C-benzylation product (X, R = benzyl). The oil did show bands at 6.12 μ (conjugated lactam carbonyl), 6.21 μ (conjugated carbon-carbon double bond), 8.70 μ (C—O bond of an aromatic ether), and 9.15 μ (C—O bond of an aliphatic ether). Acid hydrolysis of the oil resulted in a 56% recovery of the original enol (IX, R = benzyl); it is evident that the oil is the *O*-alkylation product (XIII, R = benzyl). Thus, on the basis of yields of isolated products the ratio of *O*-alkylation to C-alkylation was judged to be about 3:1. Rather similar results have been obtained with phenols.[9]

The same alkylation reaction was carried out in excess benzyl chloride as the solvent, and in absolute ethanol. In these experiments the reaction mixture was not examined for the presence of the *O*-alkylation product, but conversion to the C-alkylation product X occurred only to the extent of 8 or 9%. No procedure for obtaining high yields of the C-alkylation product was found. However, in view of the results with sodium phenoxide recently reported by Kornblum, Berrigan, and Le Noble[10] the possibility that C-alkylation would be favored in aqueous solution should be investigated.

The use of 4-benzylidene-2,3-dioxopyrrolidines (III) and 4-benzyl-3-hydroxy-3-pyrrolin-2-ones (IX) in the synthesis of new fused ring heterocyclic systems will be the subject of future reports.

EXPERIMENTAL[11]

1-Substituted-4-benzilidene-2,3-dioxopyrrolidines (III). *Procedure A.* The 1-substituted 2,3-dioxopyrrolidine[3] was dissolved in excess benzaldehyde and dry hydrogen chloride was passed into the solution for 30 min., by which time the reaction mixture had solidified. The mixture was allowed to stand for another 0.5 hr. and was then diluted with petroleum ether (b.p. 65–110°) and filtered to collect the product, which was recrystallized several times from 95% ethanol. Yields (and melting points) quoted in Table I are for fully purified products. All the compounds had a bright yellow color.

Procedure B. In general, approximately 0.1 mole of the 1-substituted 4-carbethoxy-2,3-dioxopyrrolidine[3] and slightly more than the equivalent amount of freshly distilled benzaldehyde were added to 500–1000 ml. of a dilute hydrochloric acid solution containing some ethanol, and the mixture was refluxed with stirring for several hours. The use of ethanol was necessary to insure solution of the starting materials before any precipitation of the product occurred. After being cooled for several hours in a refrigerator, the mixture was filtered to collect the product which had precipitated. The filtrate was extracted with several portions of chloroform, the chloroform was evaporated, and the residue was combined with the initial precipitate and recrystallized several times from 95% ethanol. In some cases the mother liquors of initial crystallizations were concentrated to recover more of the product. Results obtained and quantities of materials used in the preparation of individual compounds are recorded in Table I. Yields quoted are of fully purified products.

1-Substituted 4-benzyl-3-hydroxy-2-oxopyrrolidines (XI). In all cases 0.03 to 0.05-mole quantities of the 1-substituted 4-benzylidene-2,3-dioxopyrrolidines (III) were reduced by excess sodium borohydride (0.05 to 0.08 mole) dissolved in 150 ml. of 95% ethanol. The details of the procedure are illustrated by the experiment with the 1-β-phenylethyl derivative described below. Reduction of the other compounds were conducted in essentially identical fashion with analogous results except that, unlike the 1-β-phenylethyl compound, the others yielded no second crystalline fraction which could correspond to a second purified stereoisomer.

Fifteen grams (0.051 mole) of 1-β-phenylethyl-4-benzilidine-2,3-dioxopyrrolidine (III, R = β-phenylethyl) was added portion-wise over a period of about 10 min. to a solution of 3 g. (0.079 mole) of sodium borohydride in 150 ml. of 95% ethanol. After the addition was completed the reaction mixture was allowed to stand at room temperature for 1 hr. The excess borohydride was then destroyed by adding dilute hydrochloric acid until the evolution of hydrogen ceased. The solvent was evaporated under reduced pressure, leaving a white solid. This solid was washed several times with water. After being air-dried, it was dissolved in hot chloroform, and petroleum ether (b.p. 65–110°) was added until the solution became slightly cloudy. Crystals began to precipitate almost immediately. After allowing the solution to cool to room temperature and then leaving it in the refrigerator for several hours, the solution was filtered, yielding 7.9 g. of white needles, m.p. 129–137°. Recrystallization from a chloroform–petroleum ether solution gave 6.7 g. (45%) of white needles, m.p. 141–142.5° [form (1) in Table II]. Further recrystallization from chloroform–petroleum ether failed to raise the melting point of the compound.

The filtrate from the original recrystallization was evaporated to dryness, and the residue was recrystallized from a benzene-hexane solution, with enough ethyl ether added so that no oiling-out took place when the solution cooled to room temperature. The solution was left in the refrigerator overnight. Two precipitates formed, one consisting of small needles, m.p. 110–123°, along the bottom of the flask, the other of clusters of brown rods, m.p. 61–67°. The clusters were removed by hand and then recrystallized several times from a benzene-hexane solution, yielding 1.70 g. (12%) of slightly tan rods, m.p. 65.5–68° [form (2) in Table II]. A mixture of this substance and the 141–142.5° racemate melted at 74–84°.

Table II records data on the preparation and characterization of the compounds of type XI.

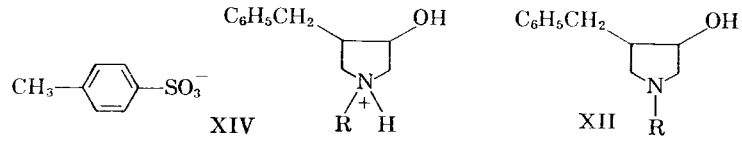
1-Substituted 4-benzyl-2,3-dioxopyrrolidines (VIII) *and their anils.* In a typical run, mixtures prepared from 10 g. of the 1-substituted-4-benzilidene-2,3-dioxopyrrolidine (III), 60 mg. of platinum oxide, and 125 ml. of glacial acetic acid were shaken in a Parr hydrogenation apparatus for 0.5 hr. at an initial hydrogen pressure of 60 p.s.i. The catalyst was removed by filtration, and all but about 15 ml. of the solvent was removed by distillation under reduced pressure. The mixture was then poured with stirring into 400 ml. of ice and water. The mixture was allowed to stand at room temperature for several hours, with periodic stirring to assist the solidification of the originally oily product. The mixture was then filtered, and the precipitate was recrystallized several times from 95% ethanol. Yields quoted are of fully purified products and include material obtained from concentration of the mother liquor of initial crystallization. The products all give a purple color with ferric chloride solution and dissolve in sodium hydroxide solution. In each of these reductions a small amount of very high-melting, white solid was

(10) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, 82, 1258 (1960).

(11) Melting points are corrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Laboratories, Bardonia, N. Y. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer; ultraviolet spectra with a Cary recording spectrophotometer.

TABLE IV

1-SUBSTITUTED 4-BENZYL-3-HYDROXYPYRROLIDINES: *p*-TOLUENESULFONATES (XIV) OR FREE BASES (XII)



R	Exp.	Separated Isomer(s) Form; m.p.[a]	Separated Isomer(s) Yield, %	Crude Product M.p.[a]	Crude Product Yield, %	Starting Material	Formula	Calcd., %	Found, %
CH_3—	1	Needles 131.5–133 (T)	25	123–128 (T)	74	BDOP,[b] 6.8 g.	$C_{19}H_{21}O_4NS$	C 62.81 H 6.88	62.94 6.77
Cyclo-C_6H_{11}—	2	Needles 140–141 (T)	30	130–134 (T)	47	BDOP,[b] 8 g.	$C_{24}H_{27}O_4NS$	C 66.82 H 7.66 N 3.24	67.04 7.28 3.57
	3	Rods 93–94 (B)	—	90–91 (B)	46	BHOP[c] M.p. 116.5–118° 5.8 g.	$C_{17}H_{25}ON$	C 78.71 H 9.72	79.02 9.90
$C_6H_5CH_2$—	4	Needles 142.5–144 (T)	14	128–132 (T)	78	BDOP,[b] 12.3 g.	$C_{25}H_{29}O_4NS$	C 68.49 H 6.39 N 3.20	68.15 6.73 3.19
$C_6H_5CH_2CH_2$—	5	(1) Needles[d] 134–135.5 (T)	38	(1) 133–135 (T)	46	BDOP,[b] 10 g.	$C_{26}H_{31}O_4NS$	C 68.85 H 6.89 N 3.08	(1) 68.58 (1) 6.80 (1) 2.93
		(2) Needles 125–127 (T)	6	(2) 109–121 (T)	14				(2) 68.82 (2) 6.66 (2) 3.03
	6	(1) Needles 134–135.5 (T)[d]	—	(1) 133–134 (T)	68	BHOP[c] M.p. 141–142.5° 3 g.			

[a] Melting points followed by (T) are of *p*-toluenesulfonates (free bases were glasses or thick oils); melting points followed by (B) are for free base. [b] BDOP = 1-substituted 4-benzylidene-2,3-dioxopyrrolidines which were reduced successively with sodium borohydride and lithium aluminum hydride as in procedure A. [c] BHOP = 1-substituted 4-benzyl-3-hydroxy-2-oxopyrrolidines; products of the indicated melting point were reduced with lithium aluminum hydride by procedure B. [d] Higher melting form (1) from procedure A was identical with product from reduction of BHOP of m.p. 141–142.5° by procedure B. The lower melting form (2) was obtained only from procedure A. Data for two forms are designated by numbers (1) and (2) preceding figures in the table. A mixture of the two forms showed the m.p. 115–123°.

obtained. This material was not further investigated. Data on these experiments are recorded in Table III.

To prepare the anils, a mixture of 1 g. of the 1-substituted 4-benzyl-2,3-dioxopyrrolidine, an equivalent amount of freshly distilled aniline, 1 ml. of 1.76*M* acetic acid solution, and 20 ml. of 95% ethanol was refluxed for 1 hr. The solution was cooled for several hours in the refrigerator and was then filtered to collect the crystalline product. The filtrate was evaporated, and the residue was combined with the original precipitate. The combined product was recrystallized from 95% ethanol. Further recrystallization from 95% ethanol was used to prepare analytical samples of the anils. Data on individual compounds obtained are recorded in Table III.

1-Substituted 4-benzyl-3-hydroxypyrrolidines (XII) *and their p-toluenesulfonates* (XIV). *Procedure A.* Approximately 0.03 mole of the 1-substituted 4-benzylidene-2,3-dioxopyrrolidine (III) was added in portions to a solution of 2 g. (0.053 mole) of sodium borohydride in 150 ml. of 95% ethanol. The reaction mixture was allowed to stand for 1 hr.; then the reduction product was separated as in the procedure described above. The resulting crude 3-hydroxy-2-oxopyrrolidine (XI) was next added (the 1-β-phenylethyl and 1-cyclohexyl derivatives in solid form, the 1-benzyl and 1-methyl derivatives dissolved in anhydrous ether) to a slurry of 2 to 3 g. (0.053 to 0.08 mole) of lithium aluminum hydride in 250 ml. of anhydrous ether, and the mixture was refluxed for 24 hr.

The excess hydride was destroyed by dropwise addition of an aqueous sodium potassium tartrate solution until the evolution of hydrogen ceased. The solution was filtered to remove the aluminum salts. The precipitate was washed several times with ether, and the washings were added to the original filtrate. The filtrate was dried with anhydrous magnesium sulfate, and the solvent was then removed by evaporation under reduced pressure, leaving a colorless glass. This glass was dissolved in a minimum amount of absolute ethanol and mixed with an absolute ethanol solution containing an amount of *p*-toluenesulfonic acid monohydrate equivalent to the starting material used. Ethyl acetate was added, and the solution was left in the refrigerator overnight. The precipitate that formed was separated by filtration, the filtrate was evaporated to dryness, and the residue was recrystallized from an absolute ethanol–ethyl acetate solution. The combined crystalline fractions were recrystallized a number of times from absolute ethanol–ethyl acetate.

In the case of the 1-β-phenylethyl compound careful fractional crystallization of the salt from this solvent mixture yielded two products, m.p. 135–135.5° and 125–127°. A mixture of these products melted at 115–123°. Analysis (Table IV) showed them to be isomers; presumably they represent the two possible racemic forms of the 4-benzyl-3-hydroxypyrrolidine.

Table IV records data on these experiments, and on those in which procedure B (below) was used to reduce separated forms of the 4-benzyl-3-hydroxy-2-oxopyrrolidines (XI).

Procedure B. An experiment in which the higher melting form of 1-β-phenylethyl-3-hydroxy-4-benzyl-2-pyrrolidone (XI, R = β-phenylethyl) (m.p. 141–142.5°) was reduced will illustrate procedure B. Three grams (0.01 mole) of the compound was added in portions to a slurry of 1 g. (0.03 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether, and the mixture was refluxed for 24 hr. The excess lithium aluminum hydride was then destroyed by the dropwise addition of an aqueous sodium potassium tartrate solution until the vigorous evolution of hydrogen ceased. The mixture was filtered to remove the precipitate of aluminum salts. This precipitate was washed with several portions of chloroform, and the chloroform washings were added to the ether filtrate. The chloroform and ether were dried over anhydrous magnesium sulfate for approximately 0.5 hr. The solvents were then removed by evaporation under reduced pressure, leaving a colorless glass. This glass could not be crystallized easily. Attempts to make a solid hydrochloride derivative also failed. The glass was then dissolved in a minimum amount of absolute ethanol, and a solution of 1.9 g. (0.01 mole) of *p*-toluenesulfonic acid monohydrate in absolute ethanol was added. The solution was placed in the refrigerator overnight. The product was removed by filtration, ethyl acetate was added to the filtrate, and the solution was again left in the refrigerator overnight. Filtration of this solution and combination of the precipitates yielded 3.1 g. (68%) of white needles, m.p. 133–134°. Further recrystallization from an absolute ethanol–ethyl acetate solution raised the melting point of the compound to 134–135.5°.

In a similar experiment 5.8 g. (0.021 mole) of the corresponding 1-cyclohexyl compound, m.p. 116.5–118°, was reduced with 1.5 g. (0.04 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. The crude product was first obtained as a glass but was crystallized from petroleum ether (b.p. 65–110°) to yield 2.7 g. (46%) of colorless rods, initial m.p. 90–91°; melting point after additional crystallizations from petroleum ether, 93–94°. This was the only compound of Type XII which crystallized well as the free base.

1,4,4-Tribenzyl-2,3-dioxopyrrolidine (X). Five grams (0.018 mole) of 1,4-dibenzyl-2,3-dioxopyrrolidine (VIII or IX, R = benzyl) was added to a solution of 0.47 g. (0.021 mole) of sodium ethoxide in 50 ml. of absolute ethanol, and the solution was refluxed under a nitrogen atmosphere for approximately 10 min. The ethanol was then replaced with anhydrous toluene by repeated addition of the toluene and subsequent distillation of the mixture. Benzyl chloride (2.8 ml.; 0.023 mole) was then added and the heterogeneous reaction mixture, now containing approximately 50 ml. of toluene, was refluxed under nitrogen for 20 hr., the mixture being continuously agitated with a Hershberg stirrer. The solution was allowed to cool to room temperature, whereupon a heavy precipitate formed. The solvent was removed by evaporation on a steam bath in the hood. The crude product was then triturated with ethyl ether, and the solid material was separated by filtration. The solid was washed several times with water. After being air dried, it weighed 1.25 g. (19% yield) and melted at 168.5–170°. Recrystallization from 95% ethanol raised the melting point of the compound to 170–170.5°.

Anal. Calcd. for $C_{25}H_{23}O_2N$: C, 81.26; H, 6.28; N, 3.79. Found: C, 81.20; H, 5.98; N, 3.92.

Infrared spectrum (chloroform). 3.42 bw; 5.67 i; 5.84 i; 6.24 w; 6.69 w; 6.84 bm; 7.38 w. (See explanation of notation used for spectral data in Table I.).

The portion of the crude product which dissolved in ether during the trituration was recovered by evaporation of the ether. A light yellow oil was obtained which showed no infrared bands between 3.50 and 6.00 μ, but had strong absorption at 6.12, 6.21, 6.54, 6.99, 7.47, 7.63, 7.90, 8.70, 9.18, and 10.88 μ. The oil was dissolved in a mixture prepared from 25 ml. of 95% ethanol and 100 ml. of a 3:1 mixture of concentrated hydrochloric acid and glacial acetic acid. The mixture was refluxed for 4 hr., then poured into *ca.* 600 ml. of ice and water. The resulting mixture was stirred occasionally during a period of 1 hr., then filtered to collect the product, which proved to be crude 1,4-dibenzyl-2,3-dioxopyrrolidine (VIII or IX, R = benzyl). After the material was washed with ether and air dried the yield was 2.8 g. (56% recovery); m.p. 154–156° dec. Recrystallization from 95% ethanol gave a product, m.p. 160–161° dec., identical with the original starting material (VIII or IX, R = benzyl).

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