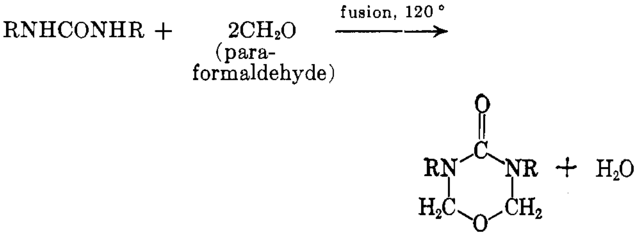
resistance to cotton fabrics without causing yellowing in the presence of chlorine bleaches.[1] Kadowaki[2] obtained tetrahydro-3,5-dimethyl-4H-oxadiazin-4-one (I) in 27% yield by the action of aqueous formaldehyde on 1,3-dimethylurea followed by treatment with methanol and hydrochloric acid. When he substituted urea for 1,3-dimethylurea, he obtained tetrahydro-3,5-bis(methoxymethyl)-4H-1,3,5-oxadiazin-4-one (II). Beachem, *et al.*,[3] repeated Kadowaki's procedure but were unable to reproduce his results. Pure II could be isolated only by vapor phase chromatography of the mixture, and I was obtained by hydrogenolysis of II.

Zigeuner[4] prepared various tetrahydro-3,5-dibenzyl-4H-1,3,5-oxadiazin-4-ones using a modification of Kadowaki's method, but yields were largely unreported.

A practical method of preparing these compounds is now reported. In this laboratory, fusion of 1,3-disubstituted ureas with paraformaldehyde at 120° gave high yields of the corresponding tetrahydro-4H-1,3,5-oxadiazin-4-ones and also made possible the preparation of these compounds with acid-susceptible groups.



When the substituent was an alkyl group the reaction proceeded in almost quantitative yield. For ureas substituted by electronegative groups the use of boric acid catalyst proved necessary. Thus, ring closure of 1,3-bis(carbethoxymethyl)urea to tetrahydro-3,5-bis-(carbethoxymethyl)-4H-1,3,5-oxadiazin-4-one failed in the absence of boric acid, but, when boric acid catalyst was used, yields up to 82% were obtained, the yields varying directly with catalyst concentration.

Starting materials for the synthesis of tetrahydro-4H-1,3,5-oxadiazin-4-ones, *viz.*, 1,3-bis(ω-alkoxyalkyl)-ureas, were prepared from 2:1 mole ratio of amino acid ester hydrochlorides and phosgene by a modification of the Emil Fischer method,[5] in which potassium carbonate was used to absorb hydrogen chloride formed in the reaction.

Experimental

1,3-Bis(ω-carboalkoxyalkyl)ureas.—Phosgene (49 g., 0.5 mole) in benzene (500 g.), was added dropwise over a period of 1 hr. to a stirred mixture of amino acid ester hydrochloride (2 moles), benzene (440 g.), and KOH (112 g., 2 moles), in water (300 g.). Temperature was maintained at 5–10°. A solution of K_2CO_3 (139 g., 1 mole) and $KHCO_3$ (50 g. 0.5 mole) in water (300 g.) was added. Additional phosgene (49 g. 0.5 mole), in benzene, (350 g.), was added dropwise over a period of 1 hr. The mixture was stirred for another 1.5 hr. and allowed to warm to room temperature. Solids were isolated by filtration, washed with water (1000 g.), and recrystallized from appropriate solvents.

1,3-Bis(carbethoxymethyl)urea was prepared in 71% yield, m.p. 147–148°, lit. m.p. 144°, recrystallized from water.

Anal. Calcd. for $C_9H_{16}N_2O_5$: C, 46.55; H, 6.94; N, 12.07. Found: C, 46.02; H, 7.05; N, 11.76.

1,3-Bis(carbomethoxypentyl)urea was prepared in 46% yield, m.p. 100°, lit.[6] m.p. 101°, recrystallized from aqueous methanol.

Anal. Calcd. for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.78; H, 8.86; N, 9.07.

Tetrahydro-3,5-dibutyl-4H-1,3,5-oxadiazin-4-one.—Paraformaldehyde, 21.0 g. (0.682 mole of CH_2O), and 1,3-dibutylurea, 42.1 g. (0.244 mole), were thoroughly mixed and heated slowly until the temperature of the mixture reached 124°. Water and formaldehyde distilled during the heating step and the mixture became a clear melt. The product, a colorless liquid, was purified by distillation under reduced pressure, yielding 49.3 g. (94.4%), b.p. 100° (0.1 mm.), $n^{27}\text{D}$ 1.4678.

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.34; N, 13.07. Found: C, 61.89; H, 10.50; N, 12.88.

Tetrahydro-3,5-bis(carboalkoxyalkyl)-4H-1,3,5-oxadiazin-4-ones from 1,3-Disubstituted Urea. Paraformaldehyde, 45.0 g. (1.46 moles of CH_2O), 1,3-bis(carboalkoxyalkyl)urea (0.50 mole), and boric acid (10.0 g., 0.16 mole) were mixed and heated slowly until the reaction mixture reached a temperature of 120–124°. Water and formaldehyde distilled during the heating step and the mixture finally became a clear melt which solidified on cooling. The crude product was slurried with 40 ml. of water.

Tetrahydro-3,5-bis(carbethoxymethyl)-4H-1,3,5-oxadiazin-4-one was prepared in 82% yield, m.p. 86–87°, recrystallized from water.

Anal. Calcd. for $C_{11}H_{18}N_2O_6$: C, 48.15; H, 6.62; N, 10.22. Found: C, 47.89; H, 6.68; N, 10.11.

Tetrahydro-3,5-bis(carbomethoxypentyl)-4H-1,3,5-oxadiazin-4-one, was prepared in 89% yield, m.p. 57–58°, recrystallized from aqueous methanol.

Anal. Calcd. for $C_{17}H_{30}N_2O_6$: C, 56.96; H, 8.44; N, 7.82. Found: C, 57.37; H, 8.63; N, 7.51.

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[1] R. L. Arceneaux and J. D. Reid, *Ind. Eng. Chem. Prod. Res. Develop.*, **1**, 181 (1962).

[2] H. Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936).

[3] M. T. Beachem, J. C. Oppelt, F. M. Cowen, P. D. Schickedantz, and D. V. Maier, *J. Org. Chem.*, **28**, 1876 (1963).

[4] G. Zigeuner and W. Hoselmann, *Monatsh. Chem.*, **86**, 425 (1955), **87**, 406 (1956); G. Zigeuner, R. Pitter, and K. Voglar, *ibid.*, **86**, 517 (1955).

[5] E. Fischer, *Chem. Ber.*, **34**, 440 (1901).

[6] A. F. McKay, E. J. Tarlton, S. I. Petri, P. R. Steyermark, and M. A Mosley, *J. Am. Chem. Soc.*, **80**, 1510 (1958).

Substituted γ-Lactones. XV.[1] Condensation between Phthalide and Benzaldehyde

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Recently it was reported[3] that phthalide underwent an aldol-type condensation with equimolar quantities of aromatic aldehydes to yield a mixture of diastereoisomeric *dl-erythro-* and *dl-threo-*3-(α-hydroxybenzyl)-phthalides. If 2 equiv. of benzaldehyde are used in this condensation, a different compound, I, is obtained.[4] I also resulted, although at a slower rate, from the reaction of benzaldehyde with *dl-erythro-* and *dl-threo-*3-(α-hydroxybenzyl)phthalide. Physical and chemical evidence (Scheme I) reported in this Note establishes the structure of I as spiro-1-keto-1,3-dihydrobenzo(*c*)furan-3,5′,2′,4′,6′-triphenyl-1′-3′-dioxane.

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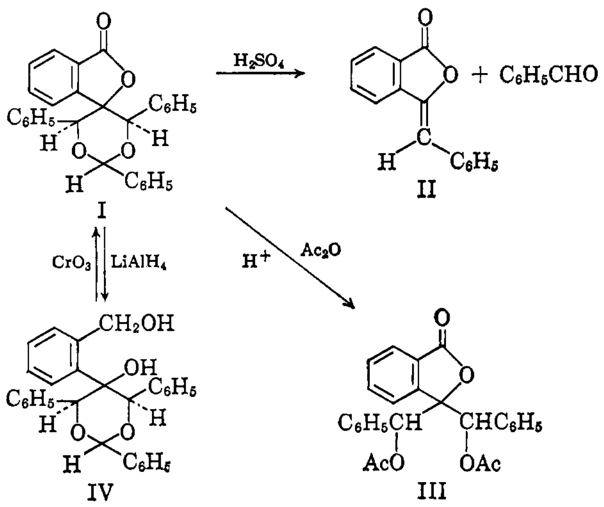
[1] Part XIV of this series: *J. prakt. Chem.*, in press.

[2] Taken in part from the Ph.D. Thesis of R. D. Barry, University of Cincinnati, 1960; Chattanooga Medicine Co. Fellow, 1957-1959; Ethyl Corp. Fellow, 1959-1960.

[3] H. Zimmer and R. D. Barry, *J. Org. Chem.*, **27**, 1602 (1962).

[4] The formation of I requires 3 moles of benzaldehyde. When the reaction was tried with a 3-mole amount, however, less than 10% of pure I was obtained. There was a large amount of oil, indicating that several side reactions occurred.

SCHEME I



Elemental analysis and molecular weight determination established the molecular formula of I as $C_{29}H_{22}O_4$. Its infrared spectrum showed characteristic absorptions, at 1765 (phthalide lactone carbonyl), and at 1124 cm.$^{-1}$ (assigned to a cyclic ether). The ultraviolet spectrum was found to be similar to that of phthalide and 3-(α-hydroxybenzyl)phthalide (Table I).

TABLE I

COMPARISON OF ULTRAVIOLET SPECTRA OF I, PHTHALIDE, AND 3-(α-HYDROXYBENZYL)PHTHALIDE

Compound	mμ[a]	$\epsilon \times 10^{-3}$
Phthalide	280	1.66
	273	1.72
3-(α-Hydroxybenzyl)phthalide	283	1.97
	275	1.97
	269	1.45 (sh)
	264	1.15 (sh)
	259	0.85 (sh)
	252	0.66 (sh)
	228	1.08
I	286	1.44
	278	1.44
	267	0.99
	263	0.99
	261	1.08 (sh)
	257	1.00
	250	0.91 (sh)

[a] Solvent, 95% aqueous ethanol.

The n.m.r. spectrum revealed a complex pattern between τ 2.00 and 3.27 (aromatic protons) and sharp singlets at 3.80 and 4.47. The ratio of the areas of these peaks was 19:1:2. The observed chemical shifts of the benzyl protons in I are similar to those reported for protons in similar environments.[5] A sharp singlet at τ 4.47 rather than two separate peaks indicates the presence of two equivalent protons and necessitates the *cis*-4′,6′-diphenyl stereochemistry for I. Magnetic nonequivalence of *trans*-4′,6′ protons is not eliminated upon rapid interconversion of chair conformations and a rapid equilibrium of the *cis*-4′,6′-diphenyl compound with two *trans*-4′,6′ isomers in deuteriochloroform is highly improbable.

Chemical investigation of I revealed the following facts. Neither chromium trioxide in glacial acetic acid nor potassium permanganate oxidized it. Pyrolysis gave a complex mixture of compounds from which benzaldehyde was identified. Treatment of I with concentrated sulfuric acid for a short period of time at room temperature, followed by dilution of the red solution with water, gave 3-benzylidenephthalide (II) in 80% yield. The formation of benzaldehyde was also shown by isolation as its 2,4-dinitrophenylhydrazone. Concentrated sulfuric acid for prolonged periods converted I to benzaldehyde and a water-soluble yellow amorphous product which had an infrared spectrum similar to that obtained from the product resulting from treatment of 3-benzylidenephthalide with sulfuric acid (sulfonation has probably occurred). Anhydrous aluminum chloride in benzene furnished a quantitative yield of 3-benzylidenephthalide as well as a moderate yield of benzaldehyde. Heating I for a short time with acetic anhydride and a catalytic amount of sulfuric acid yielded a compound having an elemental analysis and infrared spectrum in agreement with III. Excess lithium aluminum hydroxide in ether reduced I to a diol, IV, which could be converted back to I by chromium trioxide oxidation in acetic acid, a sequence characteristic of the phthalide grouping.[6] These findings confirm I as spiro-1-keto-1,3-dihydrobenzo(*c*)-furan-3,5′,2′,4′,6′-triphenyl-1′,3′-dioxane.

Experimental

Melting points are uncorrected. Microanalyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, Max-Planck Institut, Mülheim, Ruhr, Germany. The infrared spectra were determined on a Baird double beam or a Perkin-Elmer Model 21 infrared spectrophotometer in mineral oil as a medium. Ultraviolet spectra were determined on a Cary Model 12 ultraviolet spectrophotometer. The n.m.r. spectrum was obtained on a Varian Associates Model A-60 spectrometer in deuteriochloroform.

Preparation of I.—A solution of 1.0 mole of sodium methoxide in 500 ml. of dry methanol [prepared by adding 1.0 g.-atom of sodium (23 g.) to the methanol] was warmed to dissolve 134 g. (1.0 mole) of phthalide (recrystallized from aqueous ethanol and dried over phosphorus pentoxide *in vacuo* overnight). The solution was cooled to room temperature and treated with 200 ml. (2 moles) of benzaldehyde (freshly distilled in a nitrogen atmosphere). The mixture became warm and an orange color developed (this orange color is due to formation of some 2-phenylindane-1,3-dione). After 24 hr. at room temperature the orange solution was acidified with 100 ml. of concentrated sulfuric acid in 250 ml. of water, and the methanol was permitted to evaporate in a hood overnight. The resulting mixture consisted of a clear aqueous layer and an orange oil containing some unreacted benzaldehyde. Upon addition of 200 ml. of ether, white crystals of I (75 g., m.p. 237–239°) separated from the oil and were collected. Dilution of the mother liquor with additional ether to give a final volume of 1 l. furnished an additional 53 g. of I, m.p. 237–239°. The total yield of I was 128 g. (39% of theory based on 1.0 mole of phthalide).

Anal. Calcd. for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10; mol. wt., 434.47. Found: C, 80.51; H, 5.11; mol. wt., 412 (Rast), 431 (osmometer).

Preparation of I from *dl-erythro-* and *dl-threo-*3-(α-Hydroxybenzyl)phthalide.—A solution of 0.01 mole of sodium methoxide in 10 ml. of methanol (prepared by addition of 0.01 g.-atom of sodium to 10 ml. of methanol) was treated with 2.40 g. (0.01 mole) *dl-erythro*-3-(α-hydroxybenzyl)phthalide and 1.0 ml. (0.01 mole) of freshly distilled benzaldehyde. The solid dissolved slowly during 5 hr. at room temperature, and the characteristic orange color of 2-phenylindane-1,3-dione developed. After 24

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[5] N. Baggett, K. Buck, A. Foster, M. Randall, and J. Webber, *Proc. Chem. Soc.*, 118 (1964). The use of a dioxane instead of deuteriochloroform as solvent accounts for the small difference in chemical shifts.

[6] R. F. Bird and E. E. Turner, *J. Chem. Soc.*, 5050 (1952).

hr., the mixture was acidified with 10 ml. of 20% sulfuric acid, and the methanol was removed *in vacuo*. The residue, consisting of an orange oil and a clear aqueous layer, was shaken with 50 ml. of ether. The combined ethereal extracts were washed with 3-5-ml. portions of 10% sodium carbonate solution to remove 2-phenylindane-1,3-dione, and 3-5-ml. portions of 10% sodium bisulfite solution to remove unreacted benzaldehyde. Acidification of the sodium carbonate extracts furnished 0.11 g. of 2-phenylindane-1,3-dione. The yellow ethereal solution was dried and evaporated yielding a yellow oil. Benzene (120 ml.) was added to dissolve the oil, and crystals of I (0.39 g., m.p. 231–234°) separated. The mother liquor was chromatographed through a 3.5 × 12.5 cm. column of neutral alumina. Elution consecutively with benzene (1200 ml.), 10% chloroform in benzene (150 ml.), 30% chloroform in benzene (300 ml.), 50% chloroform in benzene (300 ml.), and chloroform yielded an additional 0.22 g. of I (m.p. 239–241°). The total yield of I was 0.61 g. (14% of theory).

Similarly, *dl-threo*-3-(α-hydroxybenzyl)phthalide gave I in 14% yield.

Action of Sulfuric Acid on I. A. Isolation of *trans*-3-Benzylidenephthalide.—A red solution of 0.1 g. (0.00023 mole) of I in 1 ml. of sulfuric acid (*d* 1.84) at room temperature was poured into 5 ml. of water after 45 sec. A strong odor of benzaldehyde was noted. The mixture was cooled 1 hr. and the precipitate collected. Recrystallization from methanol furnished pale yellow crystals of *trans*-3-benzylidenephthalide (0.04 g., 80%), m.p. 98–100°. Mixture melting point with authentic material was not depressed.

B. Isolation of Benzaldehyde.—A solution of 5 g. (0.012 mole) of I in 80 ml. of sulfuric acid (*d* 1.84) was left at room temperature for 5 min., then poured over a mixture of 100 g. of ice and 100 ml. of water. The aqueous mixture was extracted with three 100-ml. portions of ether, and the ethereal extracts were washed with three 125-ml. portions of 10% sodium bisulfite solution. The bisulfite extracts were acidified with hydrochloric acid (350 ml.) and re-extracted with two 150-ml. portions of ether. This ethereal solution was then treated with a solution of 6.0 g. of 2,4-dinitrophenylhydrazine in 5 ml. of sulfuric acid, 10 ml. of water, and 20 ml. of 95% alcohol. An orange precipitate of benzaldehyde 2,4-dinitrophenylhydrazone immediately separated and was collected and recrystallized from aqueous 2-methoxyethanol (Methyl Cellosolve) furnishing 1 g. (15% yield) of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 237° dec.

C. Prolonged Sulfuric Acid Treatment.—A red solution of 0.1 g. (0.00023 mole) of I in 10 ml. of sulfuric acid became brown after 30 min. at room temperature. The solution was poured into 100 ml. of cold water and a fine yellow precipitate separated. The precipitate was water soluble and slowly decomposed on heating. The product obtained from a similar treatment of *trans*-3-benzylidenephthalide with sulfuric acid also decomposed on heating without a sharp melting point. The infrared spectra of both products were identical.

Action of Aluminum Chloride on I. A. Isolation of *trans*-3-Benzylidenephthalide.—A mixture of 3.0 g. (0.023 mole) of anhydrous aluminum chloride, 100 ml. of dry benzene, and 1.0 g. (0.003 mole) of I was stirred at room temperature for 6 hr. After standing overnight, during which time the color changed from yellow to orange, 100 ml. of hydrochloric acid (36%) was added and the benzene layer was separated and dried. Benzene was removed *in vacuo* and the orange oily residue crystallized from 95% alcohol, furnishing 0.61 g. (91%) of *trans*-3-benzylidenephthalide, m.p. 95–105°. Mixture melting point with authentic material was not depressed.

B. Isolation of Benzaldehyde.—The above reaction was repeated and the oily orange residue was dissolved in 10 ml. of 95% alcohol. The alcohol solution was treated with a solution of 0.4 g. of 2,4-dinitrophenylhydrazine, 2 ml. of sulfuric acid, 10 ml. of 95% alcohol, and 3 ml. of water, and the resulting red-orange precipitate of benzaldehyde. 2,4-dinitrophenylhydrazone collected; the yield was 0.66 g. (74%), m.p. 238–239° dec.

Action of Acetic Anhydride on I.—A solution of 1.0 g. (0.003 mole) of I in 30 ml. of acetic anhydride and 2 drops of sulfuric acid (*d* 1.84) was refluxed for 15 min. The red-brown solution was cooled to room temperature and poured into 100 ml. of water. A red-brown oil separated and after 1 hr. the mixture was extracted with two 100-ml. portions of ether. The extracts were combined and dried, followed by removal of the ether *in vacuo* giving a red-brown oil which yielded crystals of III (0.57 g., 43%), m.p. 199–201° (from 95% alcohol).

Anal. Calcd. for $C_{26}H_{22}O_6$: C, 72.54; H, 5.15. Found: 72.80; H, 5.18.

Infrared absorption (Nujol) was observed at 1730–1800 (acetate and lactone carbonyl absorption region) and 1215–1245 cm.$^{-1}$ (acetate ethereal oxygen). Ultraviolet absorption (ethanol) follows: 283 mμ (log ε 3.16), 276 (3.16), 268 (3.11), 264 (3.10), 262 (3.05), 258 (3.07), and 228 (4.02).

Lithium Aluminum Hydride Reduction of I.—A mixture of 0.3 g. (0.0079 mole) of lithium aluminum hydride in 150 ml. of ether (distilled from lithium aluminum hydride) was treated with 1.0 g. (0.003 mole) of I and refluxed with stirring for 5 hr. Excess lithium aluminum hydride was decomposed by addition of methanol, and the mixture was poured into 50 ml. of 20% sulfuric acid. Evaporation of the ether layer left a white crystalline product which was recrystallized from benzene–heptane furnishing 0.88 g. of IV, m.p. 186–187°.

Anal. Calcd. for $C_{29}H_{26}O_4$: C, 79.43; H, 5.98. Found: C, 79.88; H, 6.15.

Infrared absorption (Nujol) was observed at 3200 and 3500 cm.$^{-1}$ (hydroxyl) and no absorption was found in the carbonyl region (1650–1800 cm.$^{-1}$). Ultraviolet spectrum (ethanol) follows: 267 mμ sh (log ε 2.56), 264 (2.78), 261 (2.74), 257 (2.85), and 250 (2.72).

Chromium Trioxide Oxidation of IV.—A solution of 0.1 g. of IV in 1 ml. of acetic acid was treated with 1 ml. of acetic acid containing 0.01 g. (0.0001 mole) of chromium trioxide. The mixture was boiled for 1 min. and the green solution cooled, yielding white needles of I, 0.04 g., m.p. 220–224°. Mixture melting point with authentic I was not depressed.

Unsaturated Lactams from Ketones and Acrylonitrile

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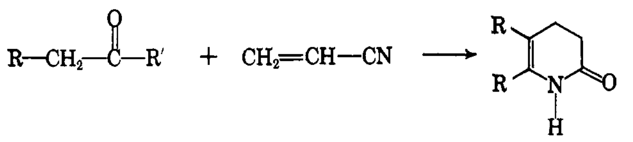
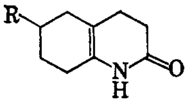
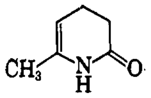
Ketones are known to react with acrylonitrile in the presence of an amine–acid catalyst to give good yields of α-monocyanoethyl ketones.[1] We wish to report a novel modification of this reaction whereby γ,δ-unsaturated lactams are formed in one step from a ketone and acrylonitrile when the reaction is carried out at elevated temperature in the presence of a trace amount of water.



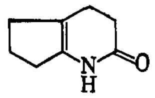
The following compounds have been prepared in this way: 1,2,3,4,5,6,7,8-octahydro-2-quinolone (Ia, 79% from cyclohexanone); 6-methyl-1,2,3,4,5,6,7,8-octahydro-2-quinolone (Ib, 55% from 4-methylcyclohexanone); 6-methyl-1,2,3,4-tetrahydro-2-pyridone (II, 15% from acetone); and 1,2,3,4,5,6,7-hexahydro-5H-1-pyrind-2-one (III, 18% from cyclopentanone). The



Ia, R = H
Ib, R = CH_3



II



III

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[1] H. Krimm, U. S. Patent 2,850,519 (1958).