The Synthesis of 3-Isopropylidene-2,5-piperazinediones[1]

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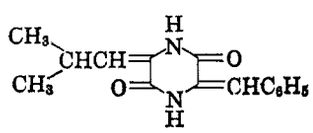
Synthetic routes to 3-alkylidene-2,5-piperazinedione have been studied. An enamine carboxylate, methyl 2-amino-3-methyl-2-butenoate, was treated with phthaloylglycyl chloride to give methyl 3-methyl-2-phthaloylglycylamino-2-butenoate, which, after removal of phthaloyl group, was cyclized to yield 3-isopropylidene-2,5-piperazinedione. The condensation reaction of the piperazinedione with aromatic aldehydes was also studied, and a homolog of albonoursin, 3-isopropylidene-6-benzylidene-2,5-piperazinedione, and some other 3-isopropylidene-6-arylidene-2,5-piperazinediones were synthesized.

Albonoursin, isolated from the culture filtrates of *Streptomyces noursei* and *Streptomyces albus var. fungatus*, has been assigned the 3-isobutylidene-6-benzylidene-2,5-piperazinedione structure (**1**) by



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Khokhlov and Lokshin,[2a] Vondráček and Vaněk,[2b] and Brown, *et al.*[2c] Although 3-mono- or 3,6-diarylidene-2,5-piperazinediones are known, no alkylidene derivative of 2,5-piperazinedione has been recorded in literatures except 3-methylene-2,5-piperazinedione, which was prepared by treatment of glycylserine with thionyl chloride and then with ammonia.[3]

In connection with a program directed to a synthesis of **1**, some attempts to synthesize alkylidene 2,5-piperazinediones have been made, and the present paper deals with a synthesis of 3-isopropylidene-2,5-piperazinedione (**2**) and a lower homolog of albonoursin, 3-isopropylidene-6-benzylidene-2,5-piperazinedione (**3**).

Methyl 2-amino-3-methyl-2-butenoate (**6a**) has been briefly described by Tatsuoka, *et al.*, who obtained it by reduction of methyl 3-methyl-2-nitro-2-butenoate (**4a**) with aluminum amalgam.[4] The reduction of the α-nitro olefin (**4a**) with aluminum amalgam was reinvestigated under various experimental conditions, and **6a** was obtained in 62% yield. The reduction with aluminum amalgam was attempted on other nitro olefins, because the enamine formation from nitro olefins is an interesting and novel case.[5] However, when ethyl 2-nitro-2-pentenoate (**4b**) was treated with aluminum amalgam under analogous experimental conditions, methyl 4-methyl-2-oximinovalerate (**5b**) was obtained as the sole isolated product in 42% yield. Reduction of analogous nitro olefins (**4c** and **4d**) afforded 2-oximino carboxylic esters (**5c** and **5d**); the results are summarized in Table I.

TABLE I

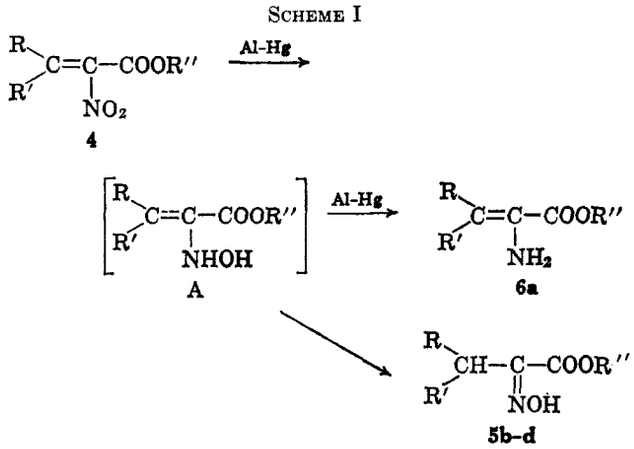
REDUCTION OF NITRO OLEFINS WITH ALUMINUM AMALGAM

Nitro olefin	Product	Bp (mm) or mp, °C	Yield, %
4a	Enamine (**6a**)[a]	61–67 (9)	62
4b	Ketoxime (**5b**)[b]	95–98 (5)	42
4c	Ketoxime (**5c**)[b]	96–97 (3)	49
4d	Ketoxime (**5d**)[a]	120–125 (20) 68–69	44

[a] See the Experimental Section. [b] Elemental analytical data in accord with theory were obtained for this compound, and the infrared spectrum was superimposable on that of an authentic sample, which was prepared by esterification of the corresponding acid [see R. H. Barry and W. H. Hartury, *J. Org. Chem.*, **12**, 460 (1949), and references cited therein].

The difference in the reduction course seems to be due to the presence or the absence of alkyl substituent (R = CH_3 or H) in the 3 position of **4**; the initial reduction of **4** would probably give a hydroxyamino olefin as an intermediate (A), which, in the case of **Ab**, **Ac**, and **Ad**, would readily transform into the ketoxime (**5**) by proton migration (Scheme I). On the other hand, the intermediate **Aa** would be further hydrogenated into the enamine (**6a**) prior to the tautomerization into the ketoxime form, owing to the stability of the fully substituted double bond.

SCHEME I



a, R = CH_3; R′ = CH_3; R″ = CH_3
b, R = H; R′ = C_2H_5; R″ = C_2H_5
c, R = H; R′ = *n*-C_3H_7; R″ = CH_3
d, R = H; R′ = *i*-C_3H_7; R″ = CH_3

When **6a** was treated with phthaloylglycyl chloride in aqueous solution in the presence of sodium hydrogen carbonate at room temperature, methyl 3-methyl-2-phthaloylglycylamino-2-butenoate (**7**) was obtained

(1) A part of this investigation was preliminarily communicated in *Bull. Chem. Soc. Japan*, **39**, 858 (1966).

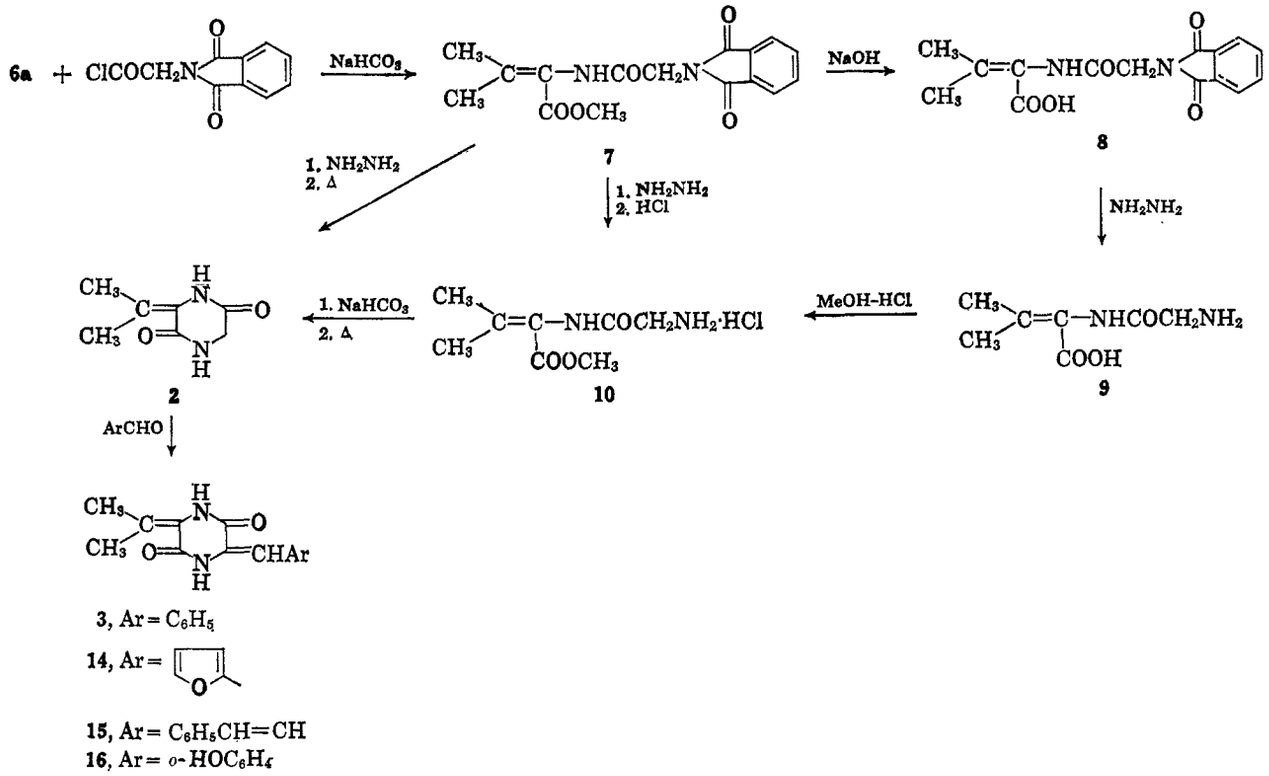
(2) (a) A. S. Khokhlov and G. B. Lokshin, *Tetrahedron Letters*, 1881 (1963); (b) M. Vondráček and Z. Vaněk, *Chem. Ind.* (London), 1686 (1964); (c) R. Brown, C. Kelley, and S. E. Wiberley, *J. Org. Chem.*, **30**, 277 (1965).

(3) M. Bergmann, A. Miekeley, and E. Kann, *Ann.*, **445**, 17 (1925).

(4) S. Tatsuoka, M. Murakami, and T. Tamura, *J. Pharm. Soc. Japan*, **70**, 230 (1950).

(5) Reductions of nitro olefins with various metals and acids are known to give saturated ketoxime [O. Wallach, *Ann.*, **332**, 305 (1904); D. Nightingale and J. R. Janes, *J. Am. Chem. Soc.*, **66**, 352 (1944); H. B. Hass, A. G. Susie, and L. Heider, *J. Org. Chem.*, **15**, 8 (1950); A. Dornow and A. Müller, *Ber.*, **93**, 32 (1960)], and reduction with complex metal hydride was reported to yield saturated nitroalkanes [H. Shechter, D. E. Ley, and E. B. Roberson, *J. Am. Chem. Soc.*, **78**, 4984 (1956)].

SCHEME II



in 83% yield.[6] The hydrolysis of **7** with 1 *N* sodium hydroxide afforded 3-methyl-2-phthaloylglycylamino-2-butenoic acid (**8**) in 32% yield. Treatment of **8** with hydrazine hydrate in boiling methanol resulted the cleavage of the phthaloyl group to yield 2-glycylamino-3-methyl-2-butenoic acid (**9**), which was transformed by treatment in methanol with hydrogen chloride to the corresponding methyl ester hydrochloride (**10**). When **10** was heated in aqueous solution containing 1 equiv of sodium bicarbonate, cyclization occurred and 3-isopropylidene-2,5-piperazinedione (**2**) was obtained in 70% yield. Compound **2** was also derived from **7** *via* the various routes illustrated in Scheme II. Additionally, 6-methyl- and 6-isobutyl-3-isopropylidene-2,5-piperazinedione (**11** and **12**) were synthesized by using phthaloyl-DL-alanyl chloride or phthaloyl-L-leucyl chloride in place of phthaloylglycyl chloride.

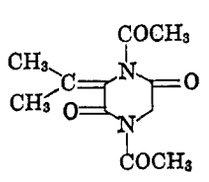
2,5-Piperazinedione is known to condense with aromatic aldehyde in the presence of acetic anhydride and sodium acetate to yield 3-mono- or 3,6-diarylidene derivative.[7] The condensation of **2** with benzaldehyde was carried out by using the analogous technique, and the expected **3** was obtained as colorless needles in 77% yield. The structure of **3** was confirmed by elemental analysis as well as infrared and ultraviolet spectra, which are very similar to those of albonoursin.[2c] The condensation reaction of **2** with furfural and cinnamaldehyde were also attempted, and 6-furfurylidene- and 6-cinnamylidene-3-isopropylidene-2,5-piperazinedione (**14** and **15**) were obtained in good yields. (See data given in Table II.)

(6) The benzoylation of **6a** has been reported to give the N-benzoyl derivative,[4] whose structure was supported by the presence of infrared absorption bands at 3250, 1720, 1640, and 1520 cm^{-1}. Treatment with benzenesulfonyl chloride also gave only N-acylated product (see the Experimental Section).

(7) (a) T. Sasaki, *Ber.*, **54**, 163 (1921); (b) T. Sasaki and T. Hashimoto, *ibid.*, **54**, 168 (1921).

In the condensation reaction of 2,5-piperazinedione with benzaldehyde, it has been postulated that 2,5-piperazinedione reacts initially with acetic anhydride to give 1,4-diacetyl-2,5-piperazinedione, the condensation of which with benzaldehyde followed by elimination of acetyl group yielded 3,6-dibenzylidene-2,5-piperazinedione.[7,8]

When **2** was heated with acetic anhydride at 130°, 1,4-diacetyl-3-isopropylidene-2,5-piperazinedione (**13**) was obtained in good yield. The diacetyl derivative (**13**) easily underwent alkaline hydrolysis to be transformed into **2**. On treatment of **13** with benzaldehyde in the presence of triethylamine at 120–130°, **3** was obtained in an excellent yield. It seems of interest that an analogous treatment of **13** with salicylaldehyde gave 3-isopropylidene-6-*o*-hydroxybenzylidene-2,5-piperazinedione (**16**), while the latter could not be obtained by the direct condensation of **2** with salicylaldehyde. However, condensation of **13** with aliphatic aldehydes did not occur. The trifluoroacetylation of **2** was then attempted, but the crude 1,4-di(trifluoroacetyl)-3-isopropylidene-2,5-piperazinedione (**17**)[9] also failed to be condensed with aliphatic aldehydes.



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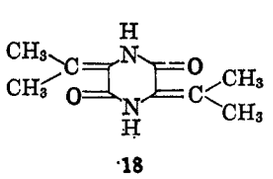

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When **6a** was heated in a sealed tube at 180–190°, 3,6-diisopropylidene-2,5-piperazinedione (**18**) was ob-

(8) E. Ueda, *J. Chem. Soc. Japan*, **50**, 502 (1929).

(9) This compound was very unstable and not characterized, but the formation was supported by the reaction of benzaldehyde to give **3** in good yield.

TABLE II

6-ARYLIDENE-3-ISOPROPYLIDENE-2,5-PIPERAZINEDIONES

Compd	Reacn time, hr	Yield %	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Spectrum: Infrared, cm^{-1}	Spectrum: Ultraviolet, mμ ($\epsilon \times 10^{-3}$)
3	8[b]	77	283–284[c]	$C_{14}H_{14}N_2O_2$	69.40	5.83	11.56	69.45	5.72	11.81	3250, 3050, 1680, 1635[d]	321 (21.6)[e]
	6[f]	68										
	3[g]	74										
14	8[b]	67	274–275[h]	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.26	5.18	11.90	3250, 3050, 1685, 1640[d]	264 (7.4)[i] 354 (32.0)
15	5[b]	89	322–324[j]	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44	71.33	5.99	10.65	3200, 3050, 1665, 1630[d]	365 (49.9)[e] 382 (38.3)
16	4[f]	66	279–282[k]	$C_{14}H_{14}N_2O_3$	65.10	5.97	10.85	64.87	5.97	10.82	3200, 3050, 1670, 1640[d]	334 (17.9)[e] 422 (1.6)

[a] Partial sublimation and decomposition. [b] Procedure A. [c] Colorless needles. [d] In KBr. [e] In dimethylformamide. [f] Procedure B. [g] Procedure C. [h] Yellow needles. [i] In glacial acetic acid. [j] Yellow powder. [k] Yellow prisms.

tained in 27% yield. This compound is the first example of a 3,6-dialkylidene-2,5-piperazinedione and the structure was confirmed by elemental analysis and the infrared spectrum.

Experimental Section

Methyl 2-Amino-3-methyl-2-butenoate (6a).—The procedure was modified from the method of Tatsuoka.[4] A solution of methyl 3-methyl-2-nitro-2-butenoate (**4a**, 22 g) in ether (150 ml) was added drop by drop to aluminum amalgam (from 13 g of aluminum) placed in ether (300 ml) with vigorous stirring at room temperature. After a few minutes, the ether began to reflux. During the addition of the above solution, a few drops of water was added at 7-min intervals to maintain refluxing. After addition of the solution was completed, the stirring was continued for 1 hr. The mixture was extracted thoroughly several times with ether. The combined ethereal extract was dried over anhydrous sodium sulfate and then evaporated. Distillation of the residual oil afforded a pale yellow oil (11.1 g, 62%), bp 61–67° (9 mm) [lit.[4] bp 63–68° (10 mm)].

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.78; H, 8.58; N, 10.85. Found: C, 55.48; H, 8.14; N, 10.42.

Reduction of Methyl 4-Methyl-2-nitro-2-pentenoate (4d) with Aluminum Amalgam.—In a manner analogous to the preparation of **6a**, a solution of **4d** (6 g) in ether (50 ml) was treated with aluminum amalgam (from 4 g of aluminum) placed in ether (100 ml). A pale yellow, oily product (2.5 g) crystallized on being allowed to stand overnight, and then was recrystallized from *n*-hexane. The product was identical in all respects with authentic methyl 2-oximinovalerate (**5d**), which was obtained by esterification of 4-methyl-2-oximinovaleric acid[10] with methanol in the presence of *p*-toluenesulfonic acid.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 53.30; H, 8.44; N, 9.18.

Methyl 2-Benzenesulfonylamino-3-methyl-2-butenoate.—Benzenesulfonyl chloride (0.7 g) was added portionwise, with vigorous stirring, to **6a** (0.5 g) suspended in a solution of sodium hydrogen carbonate (0.3 g) in water (10 ml) at room temperature. The resultant viscous syrup crystallized gradually. After 1 week, the crystals were collected, washed thoroughly with water, and recrystallized from acetone–petroleum ether (bp 30–60°) to afford colorless, prismatic needles (0.7 g, 67.4%): mp 113–114°; ν_{max}^{KBr} 3200, 1700, and 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.62; N, 5.28. Found: C, 53.48; H, 5.61; N, 5.46.

Methyl 3-Methyl-2-phthaloylglycylamino-2-butenoate (7).—Phthaloylglycyl chloride (30 g) was added portionwise, with vigorously stirring, to **6a** (17 g) suspended in a solution of sodium hydrogen carbonate (11 g) in water (150 ml) at room temperature. After stirring for 1 hr, the crystalline precipitate was collected and washed with water. Recrystallization from aqueous ethanol afforded colorless needles (38 g, 83%), mp 234–235°.

Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.50; H, 5.38; N, 8.95.

3-Methyl-2-phthaloylglycylamino-2-butenoic Acid (8).—A suspension of **7** (4 g) in 1 *N* sodium hydroxide (28 ml) and methanol (5 ml) was heated under reflux for 3 hr. The resultant solution was cooled to room temperature, neutralized with 2 *N* hydrochloric acid, and then concentrated under reduced pressure to separate the colorless precipitate gradually. The precipitate was collected and washed with water. Recrystallization from methanol afforded colorless, fibrous needles (1.2 g, 31.8%), mp 258–259° dec.

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.21; H, 4.82; N, 9.44. Found: C, 59.60; H, 4.67; N, 9.27.

2-Glycylamino-3-methyl-2-butenoic Acid (9).—To a solution of **8** (1.2 g) in methanol (10 ml) was added 80% hydrazine hydrate (0.2 g) and the solution was heated under reflux for 1 hr. The phthaloylhydrazine was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in water (10 ml) and the solution was acidified to pH 6 with glacial acetic acid and heated on a boiling water bath for 30 min. The mixture was diluted with water (20 ml) and cooled to room temperature. The insoluble substance was removed and the filtrate was treated with activated charcoal. Concentration of the clear solution afforded a colorless, viscous oil, which on treatment with acetone crystallized. Recrystallization from ethanol–water afforded colorless prisms (0.5 g, 74%), mp 232–233° dec.

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 49.05; H, 7.09; N, 16.31.

Methyl 2-Glycylamino-3-methyl-2-butenoate Hydrochloride (10). A. From 9.—A suspension of **9** (0.5 g) in methanol (15 ml) was refluxed for 3 hr, while dry hydrogen chloride was passed continuously through the mixture. The solution was concentrated under reduced pressure to give a colorless, viscous residue, which gradually crystallized. Recrystallization from *n*-butyl alcohol afforded colorless prisms (0.37 g, 58%), mp 129–132°.

Anal. Calcd for $C_8H_{14}N_2O_3 \cdot HCl$: N, 12.58. Found: N, 12.42.

B. From 7.—A mixture of **7** (2 g) and 80% hydrazine hydrate (0.4 g) in methanol (40 ml) was heated under reflux for 2 hr. The solvent was evaporated under reduced pressure and concentrated hydrochloric acid (0.5 ml) was added to the residue. The mixture was heated on a boiling water bath for 20 min and then diluted with water (20 ml). The insoluble substance was removed from the cooled mixture and the filtrate was concentrated to dryness under reduced pressure to give an oily residue. The residue was again dissolved in water (10 ml) and filtered from an insoluble substance and the solvent was evaporated under reduced pressure. The treatments were repeated three times, in order to remove a trace of phthaloylhydrazine. The third concentration of the filtrate afforded a colorless, viscous oil which soon crystallized. Recrystallization from *n*-butyl alcohol afforded colorless prisms (1 g, 72%), mp 130–132°, undepressed on admixture with the sample obtained by method A.

3-Isopropylidene-2,5-piperazinedione (2). A. From 10.—A solution of **10** (1 g) and sodium hydrogen carbonate (0.4 g) in water (10 ml) was heated on a boiling water bath for 30 min. Evaporation of water under reduced pressure afforded a viscous, pale yellow oil, which was treated in refluxing methanol for 10 min. After removal of sodium chloride, the filtrate was concentrated under reduced pressure. To the residue a small quantity of water was added and boiled for 30 min. Then the aqueous solution was again concentrated under reduced pressure;

(10) This compound was prepared according to the method of Barry and Hartury, footnote *b*, Table I.

the residual, viscous oil soon crystallized. Recrystallization from water afforded colorless prisms (0.5 g, 72%): mp 260–261° dec; ν_{max}^{KBr} 3200, 3050, 1680, 1665, and 1625 cm^{-1}; λ_{max}^{EtOH} 230 mμ (ε 22,800) and 240 (23,000).

B. From 7.—A solution of **7** (4 g) in methanol (20 ml) containing 80% hydrazine hydrate (0.8 g) was heated under reflux for 2 hr. After the precipitated phthaloylhydrazine had been removed, the solvent was evaporated under reduced pressure, and the residue was dissolved in water (20 ml). The solution was acidified to pH 6 with glacial acetic acid, then heated for 30 min and concentrated to dryness under reduced pressure. The residue was treated with water (20 ml) and the insoluble substance was filtered off. Concentration of the filtrate afforded a colorless, viscous oil, which crystallized upon being heated on a boiling water bath for 30 min. Recrystallization from water afforded colorless prisms (1.4 g, 70%), mp 260–261° dec. The infrared spectrum was superimposable on that of a sample prepared by method A.

Methyl 3-Methyl-2-phthaloyl-DL-alanylamino-2-butenoate.—In a manner analogous to the case of **7**, **6a** (0.5 g) was treated with phthaloyl-DL-alanyl chloride (1 g). Recrystallization from 50% aqueous ethanol gave colorless needles (1.1 g, 86%), mp 160–161°.

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.47; N, 8.48. Found: C, 62.19; H, 5.51; N, 8.39.

3-Isopropylidene-6-methyl-2,5-piperazinedione (11).—In a manner analogous to procedure B described for **2**, the above methyl ester was converted into **11**. Recrystallization from water afforded colorless needles (67%): mp 231–232° dec; ν_{max}^{KBr} 3200, 3050, 1680, 1660, and 1620 cm^{-1}; λ_{max}^{EtOH} 230 mμ (ε 11,300).

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.34; H, 6.84; N, 16.74.

3-Isopropylidene-6-isobutyl-2,5-piperazinedione (12).—In a manner analogous to the case of **7**, **6a** was treated with phthaloyl-L-leucyl chloride to give methyl 3-methyl-2-phthaloyl-L-leucylamino-2-butenoate as an oily product, which, without purification, was converted directly into **12** by using a technique described in procedure B for **2**. Recrystallization from water afforded colorless prisms (53%): mp 246–248° dec; ν_{max}^{KBr} 3200, 3050, 1680, 1670, and 1620 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: N, 13.32. Found: N, 13.45.

1,4-Diacetyl-3-isopropylidene-2,5-piperazinedione (13).—A suspension of **2** (0.4 g) in acetic anhydride (2 ml) was heated at 130° for 30 min, and the resultant solution was allowed to stand at room temperature overnight. The solution was concentrated under reduced pressure to dryness giving a crystalline residue. Recrystallization from ethanol afforded colorless prisms (0.55 g, 90.7%): mp 131–132°; ν_{max}^{KBr} 1740, 1710, and 1650 cm^{-1}; λ_{max}^{EtOH} 227.5 mμ (ε 26,600), 280 (1400).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.39; H, 5.67; N, 11.91.

1,4-Diacetyl-3-isopropylidene-6-methyl-2,5-piperazinedione.—In a manner analogous to the case of **13**, **11** (0.2 g) was treated with acetic anhydride. Recrystallization from ethanol afforded colorless needles (0.22 g, 67%): mp 162–163°; ν_{max}^{KBr} 1730, 1710, 1695, and 1645 cm^{-1}; λ_{max}^{EtOH} 229 mμ (ε 16,100).

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.23; H, 6.63; N, 11.15.

Condensation of 2 with Aldehyde (Procedure A).—A mixture of **2** (6.5 mmoles), the appropriate aldehyde (16.2 mmoles), and anhydrous sodium acetate (2.6 g) in acetic anhydride (4 ml) was heated at 120–130° and then allowed to stand overnight at room temperature. The mixture was treated with a small quantity of water and ether and filtered. The crystalline product was washed successively with ether and ethanol. Recrystallization from glacial acetic acid afforded the expected condensation product.

Condensation of 13 with Aldehyde (Procedure B).—A mixture of **13** (2.4 mmoles) and the appropriate aldehyde (2.4 mmoles) was heated in the presence of triethylamine (0.12 g) at 120–130°. The resultant reddish solid mass was treated with ethanol and filtered. The collected crystals were recrystallized from glacial acetic acid to afford the expected condensation product.

1,4-Di(trifluoroacetyl)-3-isopropylidene-2,5-piperazinedione (17).—A suspension of **2** (0.2 g) in trifluoroacetic anhydride (2 ml) was heated at 100° for 1 hr, and the resultant solution was allowed to stand at room temperature for several hours. The solution was concentrated under reduced pressure to dryness yielding a brownish, solid mass. The crude product was 0.48 g.[9]

Condensation of 17 with Benzaldehyde (Procedure C).—A mixture of **17** (1.2 g) and benzaldehyde (0.4 g) was heated in the presence of triethylamine (0.5 g) at 120–130°. The resultant, reddish, solid mass was treated with ethanol and filtered. The collected crystals were recrystallized from glacial acetic acid to afford **3**.

3,6-Diisopropylidene-2,5-piperazinedione (18).—The reaction was carried out using the technique of Fischer for 3,6-dialkyl-2,5-piperazinediones.[11] Compound **6a** (0.5 g) was heated in a sealed tube at 180–190° for 48 hr. The reaction mixture was treated with a small quantity of ethanol. The crystalline product was collected and recrystallized from ethanol to afford colorless needles (0.1 g, 27%): mp 264–265° dec; ν_{max}^{KBr} 3200, 3050, and 1665 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: N, 14.42. Found: N, 14.43.

Registry No.—**2**, 6499-33-8; **3**, 6499-73-6; **5b**, 7463-34-5; **5c**, 10409-25-3; **5d**, 10409-26-4; **6a**, 10409-27-5; **7**, 6499-74-7; **8**, 6499-75-8; **9**, 6499-76-9; **10**, 6499-77-0; **11**, 10409-32-2; **12**, 10409-33-3; **13**, 10409-34-4; **14**, 10409-35-5; **15**, 10409-36-6; **16**, 10414-80-9; **18**, 6499-78-1; methyl 2-benzenesulfonylamino-3-methyl-2-butenoate, 10409-38-8; methyl 3-methyl-2-phthaloyl-DL-alanylaminol-2-butenoate, 10409-39-9; 1,4-diacetyl-1-isopropylidene-6-methyl-2,5-piperazinedione, 10409-40-2.

(11) E. Fischer, *Ber.*, **34**, 433 (1901).