[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

SYNTHESIS OF 5-PHENYL-4,6-DIMETHYL-2-PYRIMIDOL AND DERIVATIVES FROM THE CYCLIZATION OF UREA WITH 3-PHENYL-2,4-PENTANEDIONE

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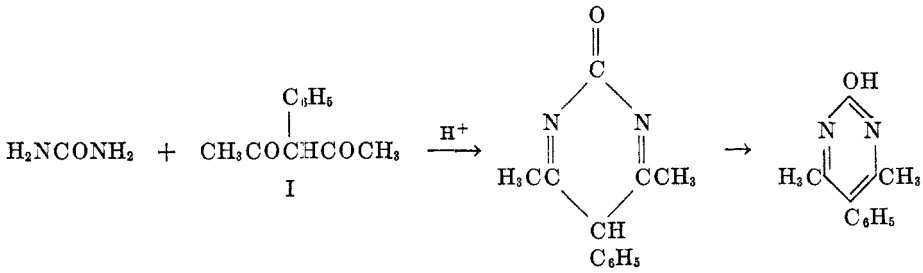
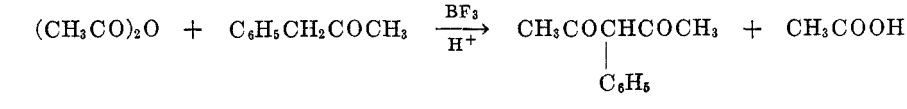
Earlier workers have effected the cyclization of urea with acetylacetone and other β-diketones to form 2-pyrimidols (1–6). In the present investigation this type of cyclization was carried out with 3-phenyl-2,4-pentanedione (I) to form the 5-phenyl derivative (II).



II

β-Diketone I was prepared by the acetylation of phenylacetone with acetic anhydride by means of boron trifluoride by a modification of the method described previously (7). The reported yield of 45% was raised to 56% by improving the purification procedure and to 63% by carrying out the reaction in the presence of a catalytic amount of *p*-toluenesulfonic acid.

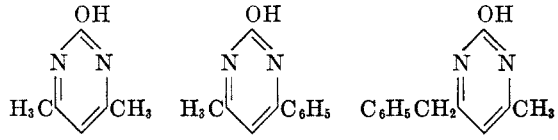


I

Pyrimidol II was obtained as its hydrochloride salt in 90% yields by refluxing (several hours) an ethanolic solution of β-diketone I and urea in the presence of only a slight excess of hydrochloric acid, followed by the addition of ether and filtration. Only low yields were obtained when ethanolic solutions of the reactants containing a considerable excess of acid were allowed to stand several days according to the procedure developed by Evans (1) for corresponding reactions with other β-diketones. Our more convenient procedure was also found satisfactory for the analogous cyclizations of urea with acetylacetone, benzoylacetone, and 1-phenyl-2,4-pentanedione. The pyrimidols III, IV, and V were obtained as the hydrochloride or free base in yields of 90%, 69%, and 52% respectively. Although Evans (1) effected the cyclization of urea with acetylacetone to

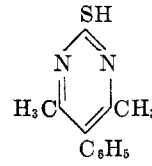
[1] Eli Lilly Fellow, 1950–1952.

form III in high yield he reported only poor yields for the corresponding reactions with benzoylacetone and 1-phenyl-2,4-pentanedione. Merkatz (8) also obtained only poor yields with benzoylacetone by the procedure of Evans but Ochiai and Tanai (6) reported a 51% yield with 1-phenyl-2,4-pentanedione by allowing the reaction mixture to evaporate over sulfuric acid.



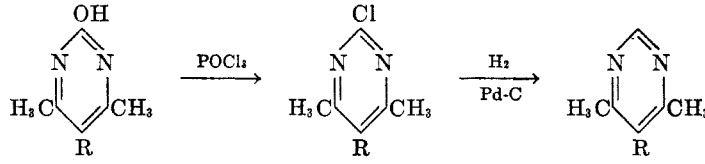
III IV V

β-Diketone I was condensed with thiourea to form thiol VI. The yield was only 24% when the reaction was carried out by the procedure developed for the synthesis of pyrimidol II but was increased to 33% when excess acid was employed and the reaction mixture allowed to stand according to the procedure of Evans (1). Attempts to cyclize guanidine with β-diketone I in the presence of either hydrochloric acid (1) or sodium methoxide were unsuccessful as was also direct fusion of the reactants (1, 9).



VI

Pyrimidols II and III were converted in good yields (82–85%) to corresponding chloro derivatives (VII) by phosphorus oxychloride, and the chloro derivatives then were dechlorinated to form VIII by catalytic hydrogenation over palladium on charcoal. The dechlorination was realized in 93% yield with the 5-phenyl derivative but the yield was considerably lower (35%), perhaps because of ring reduction, when R in VII was hydrogen.

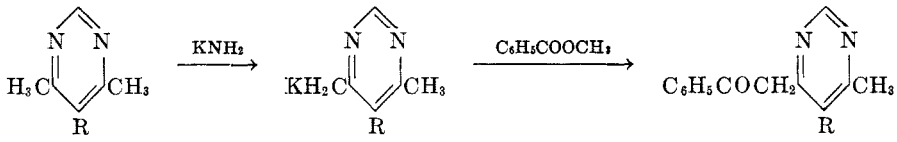


II. R = C_6H_5
III. R = H

VII VIII

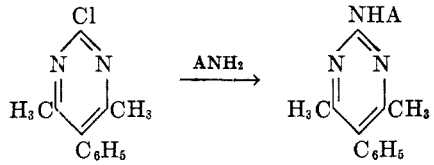
The dechlorinated pyrimidines (VIII) were condensed at one of the methyl groups with methyl benzoate by means of potassium amide to form the corresponding phenacyl pyrimidines (IX) in yields of 35–41%. These benzoylations appear to be the first examples of the Claisen type of acylation of pyrimidines,

although the analogous acylations of α-picoline and quinaldine have been described (10).



VIII IX

Chloro derivative VII (R = C_6H_5) was coupled in good yield with ammonia, 1-methyl-4-diethylaminobutylamine (Noval diamine), and N^4-acetylsulfanilamide to form derivatives X, XI, and XII, respectively. In the last reaction, the acetyl group was hydrolysed by alkali before isolation of the product.



X. A = —H (90%)
XI. A = —$CH(CH_2)_3N(C_2H_5)_2$ (44%)
XII. A = —$SO_2C_6H_5NH_2$—*p* (49%)

EXPERIMENTAL[2]

3-Phenyl-2,4-pentanedione (I). A mixture of 53.6 g. (0.4 mole) of phenylacetone (preferably purified through its bisulfite addition product), 81.6 g. (0.8 mole) of acetic anhydride, and 22.8 g. (0.12 mole) of *p*-toluenesulfonic acid was stirred for five minutes and then saturated at 0–10° with boron trifluoride during three to four hours. Toward the end of this time, the reaction mixture became quite viscous and the rate of addition of the reagent had to be decreased to keep the temperature below 10°. After saturation, the flow of boron trifluoride was continued for 15 minutes and then the reaction mixture was allowed to come to room temperature over a three-hour period. The reaction mixture was decomposed by refluxing one hour with 220 g. (1.5 moles) of sodium acetate trihydrate in 500 ml. of water, then cooled to room temperature and extracted several times with ligroin (b.p. 60–90°). The combined ligroin extracts were washed free of acid with saturated sodium bicarbonate solution, dried over Drierite, and the solvent distilled. The residue was distilled to give 54.5 g. of material, b.p. 116–118° at 20 mm., m.p. 55–59°. Recrystallization from ligroin (b.p. 60–90°) gave on cooling, in Dry Ice-acetone, 44.6 g. (63%) of 3-phenyl-2,4-pentanedione, m.p. 58.5–59.5°.

Other β-diketones. The acetylacetone[3] and benzoylacetone used were commercial products.

1-Phenyl-2,4-pentanedione was prepared by the acylation of acetone (0.22 mole) with ethyl phenylacetate (0.1 mole) by the sodium amide method (method B) described pre-

[2] Melting points and boiling points are uncorrected. Microanalyses by Clarke Microanalytical Laboratory, Urbana, Ill.

[3] We are indebted to the Carbide and Carbon Chemicals Co., South Charleston, W. Va., for a generous sample of this material.

viously (11). The β-diketone, b.p. 150–155°, was obtained in 41% yield. Most of the product (36%) boiled at 150–153°.

4,6-Dimethyl-5-phenyl-2-pyrimidol (II). A solution of 1.77 g. (0.01 mole) of 3-phenyl-2,4-pentanedione, 0.96 g. (0.016 mole) of urea, and 1 ml. (0.012 mole) of concentrated hydrochloric acid in 80 ml. of ethanol was refluxed for 10 hours. The mixture was cooled, and ether was added slowly until crystals of the hydrochloride formed, and then more rapidly until no more crystals were precipitated. The *hydrochloride* was filtered, washed with ether, and air-dried. It decomposed about 245°; yield 89%. The reaction was carried out on 0.016- to 0.273-mole scales with both methanol and ethanol as solvent. The yields were 91% when the reflux times were 10 hours or more with ethanol and 17 hours or more with methanol.

Anal. Calc'd for $C_{12}H_{13}ClN_2O$: C, 60.88; H, 5.11; N, 11.83.

Found: C, 61.01; H, 5.20; N, 11.81.

The *free base* (II) was obtained by adding 1 *N* sodium hydroxide to an aqueous solution of the hydrochloride until no more precipitate formed. The product was filtered and crystallized from 95% ethanol; it melted at 241–242.5°, darkening at 237°.

Anal. Calc'd for $C_{12}H_{12}N_2O$: N, 13.99. Found: N, 13.82.

Pyrimidols III, IV, *and* V. These three compounds, having the properties reported previously (1, 6), were prepared by the cyclization of urea with the appropriate β-diketone essentially as described above for pyrimidol II. With acetylacetone (refluxing 2.5 hours in ethanol), the white crystalline hydrochloride of 4,6-dimethyl-2-pyrimidol (III) was obtained in 88% yield. With 4-benzoylacetone (refluxing 9 hours or longer in ethanol or 14 hours in methanol) 4-methyl-6-phenyl-2-pyrimidol (IV), m.p. 229–231° (reported 229°), was obtained in 69% yield after the impure hydrochloride was dissolved in water and neutralized with ammonia. With 1-phenyl-2,4-pentanedione (refluxing 18 hours in methanol), 4-benzyl-6-methyl-2-pyrimidol (V), m.p. 59–61° (reported m.p. 61–63°), was obtained in 52% yield.

4,6-Dimethyl-5-phenyl-2-pyrimidinethiol (VI). This compound was isolated as its hydrochloride, m.p. 241–242.5°, in 24% yield by the procedure described above for pyrimidol II. It was obtained in better yield by the following procedure. 3-Phenyl-2,4-pentanedione (1.77 g., 0.01 mole), thiourea (1.2 g., 0.015 mole), and 1 ml. of concentrated hydrochloric acid were mixed in 15 ml. of methanol and allowed to stand 20 hours when another 2.7 ml. of acid was added. After 4 days the crystals were filtered to give 0.9 g. of the yellow product.

Anal. Calc'd for $C_{12}H_{13}ClN_2S$: N, 11.09; S, 12.68.

Found: N, 10.86; S, 12.87.

The *free base*, prepared from the hydrochloride as described for pyrimidol II, melted at 225.5–226° (dec.) in a sealed tube.

Anal. Calc'd for $C_{12}H_{12}N_2S$: N, 12.84; S, 14.82.

Found: N, 12.99; S, 14.83.

2-Chloro-4,6-dimethyl-5-phenylpyrimidine (VII, R = C_6H_5). A mixture of 38.0 g. (0.16 mole) of the hydrochloride of II and 180 g. (1.2 moles) of phosphorus oxychloride was refluxed for 10 hours (4 hours after all solids were in solution). After the excess phosphorus oxychloride was removed by distillation, the viscous residue was poured on ice, and neutralized with sodium bicarbonate. The mixture was extracted with ether, and the solvent evaporated. The residue was recrystallized from acetic acid and water to give crystals melting at 121–123°, sintering at 119°; yield 85%. After four recrystallizations, the product melted at 122.5–124°.

Anal. Calc'd for $C_{12}H_{11}ClN_2$: Cl, 16.21. Found: Cl, 16.30.

2-Chloro-4,6-dimethylpyrimidine (VII, R = H) was prepared similarly from pyrimidol III except that the residue from the evaporation of the ether extracts was distilled as described by St. Angerstein (3) who reported that the product melted at 38° and boiled at 223° at 756 mm. Our product, b.p. 100–102.5° at 13 mm. (117–119 at 30 mm.), was obtained as a solid in 82% yield and was used as described below without further purification.

4,6-Dimethyl-5-phenylpyrimidine (VIII, R = C_6H_5). A mixture of 2.19 g. (0.01 mole)

of 2-chloro-4,6-dimethyl-5-phenylpyrimidine (VII, R = C_6H_5), 0.82 g. (0.01 mole) of sodium acetate, and 0.25 g. of 5% palladium on charcoal in 20 ml. of acetic acid was hydrogenated at 70° and 15 lbs. pressure. When hydrogen was no longer absorbed (3 hours) the reaction mixture was cooled and filtered. To the filtrate was added water, followed by sufficient solid sodium hydroxide to make the solution basic to litmus. The mixture was extracted with ether and, after drying over Drierite, the solvent was removed to give an oil which solidified, m.p. 56–62°, sintering at 52°; yield 93%. After distillation, b.p. 157–159° at 25 mm. (130–131° at 7.5 mm.) the product melted at 61–63.5°; yield 81%.

Anal. Calc'd for $C_{12}H_{12}N_2$: N, 15.21. Found: N, 15.24.

The *picrate*, recrystallized from 95% ethanol, melted at 152–153.5° with previous sintering.

Anal. Calc'd for $C_{18}H_{15}N_5O_7$: C, 52.28; H, 3.66; N, 16.98.
Found: C, 52.40; H, 3.52; N, 16.89.

4,6-Dimethylpyrimidine (VIII, R = H) was prepared similarly from 2-chloro-4,6-dimethylpyrimidine (VII, R = H) except that the basic solution resulting from neutralization of the reaction mixture was concentrated before extraction with ether. The product, b.p. 157–161° (recorded 159.5°) (3), was obtained in 45% yield.

4-Phenacyl-5-phenyl-6-methylpyrimidine (IX, R = C_6H_5). To the stirred potassium amide suspension, prepared from 4.3 g. (0.11 g.-atom) of potassium in liquid ammonia, was added an ethereal solution of 9.2 g. (0.05 mole) of 4,6-dimethyl-5-phenylpyrimidine (VIII, R = C_6H_5). After one hour, 8.16 g. (0.06 mole) of methyl benzoate was added and the stirring was continued for another hour. The reaction was then stopped by the addition of solid ammonium chloride and the ammonia was evaporated. Water was added followed by hydrochloric acid, and the precipitated hydrochloride was filtered. Only starting material (4.5 g.) was obtained from the aqueous acid solution. The hydrochloride (3.0 g., 36% yield based on recovered starting material), after crystallization from benzene and ethanol, melted at 180° with slight decomposition. The *picrate*, recrystallized from ethanol, melted at 197–198° dec.

Anal. Calc'd for $C_{25}H_{19}N_5O_8$: C, 58.04; H, 3.70; N, 13.54.
Found: C, 58.24; H, 3.86; N, 13.55.

4-Phenacyl-6-methylpyrimidine (IX, R = H). 4,6-Dimethylpyrimidine was benzoylated in the manner described for the preparation of IX, R = C_6H_5. The insoluble hydrochloride, which separated on working up the reaction mixture, was treated with a mixture of dilute sodium bicarbonate solution and ether. The ethereal solution of the free base was dried and distilled. The product boiled at 154–160° at 0.5 mm. (solidifying on cooling); yield 3.7 g. (35%). After recrystallization from ligroin (b.p. 60–90°) it melted at 69–69.5°, sintering at 68°.

Anal. Calc'd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20.
Found: C, 73.66; H, 5.58; N, 13.06.

The *picrate*, crystallized from 95% ethanol, melted at 183–183.5° dec.

Anal. Calc'd for $C_{19}H_{15}N_5O_8$: N, 15.87. Found: N, 16.05.

2-Amino-4,6-dimethyl-5-phenylpyrimidine (X). To 40 ml. of methanol, saturated with ammonia at 0°, was added 3.27 g. (0.015 mole) of 2-chloro-4,6-dimethyl-5-phenylpyrimidine (VII, R = C_6H_5). The resulting mixture was heated at 150° in a sealed tube for 23 hours and then evaporated to give 2.7 g. (91%) of crystalline product, m.p. 177–180°. After crystallization from ethanol-water, it melted at 180–181°.

Anal. Calc'd for $C_{12}H_{13}N_3$: C, 72.35; H, 6.58; N, 21.10.
Found: C, 72.63; H, 6.36; N, 21.02.

The *picrate*, recrystallized from 95% ethanol, decomposed at 242°.

Anal. Calc'd for $C_{18}H_{16}N_6O_7$: C, 50.47; H, 3.76.
Found: C, 50.83; H, 3.46.

2-(4'-Diethylamino-1'-methylbutylamino)-4,6-dimethyl-5-phenylpyrimidine (XI). A mixture of 2.19 g. (0.01 mole) of VII (R = C_6H_5), 3.95 g. (0.025 mole) of Noval diamine, and 1 g. of phenol was slowly heated to 110° where a vigorous reaction took place with refluxing of the phenol. When the reaction abated the mixture was refluxed for 2 hours, cooled, and

taken up in ether. The ethereal solution was washed with 2.5 *N* sodium hydroxide, dried over Drierite, and the solvent distilled. The residue was distilled to give the amine (XI), b.p. 235–238° at 8 mm., in 44% yield.

Anal. Calc'd for $C_{21}H_{32}N_4$: N, 16.46. Found: N, 16.39.

The *dipicrate*, recrystallized from 95% ethanol, melted at 165.5–166.5°.

Anal. Calc'd for $C_{33}H_{38}N_{10}O_{14}$: C, 49.49; H, 5.03; N, 17.49.
Found: C, 49.87; H, 4.86; N, 17.16.

2-Sulfanilamido-4,6-dimethyl-5-phenylpyrimidine (XII). A mixture of 2.75 g. (0.0128 mole) of N^4-acetylsulfanilamide, 2.8 g. (0.013 mole) of VII (R = C_6H_5), and 2.7 g. (0.019 mole) of anhydrous potassium carbonate (after grinding in a mortar) was heated at 190° for one hour, and then refluxed with 10 g. of phenol for another hour. After refluxing with 20 ml. of 2 *N* sodium hydroxide (to hydrolize the acetyl derivative) the mixture was filtered and neutralized with dilute hydrochloric acid. The tan precipitate was filtered and washed with acetone to give 1.95 g. (49%) of product. After crystallization from tetrahydrofuran, it melted at 283–285° dec.

Anal. Calc'd for $C_{18}H_{18}N_4O_2S$: N, 15.81; S, 9.05.
Found: N, 15.70; S, 8.77.

SUMMARY

1. 3-Phenyl-2,4-pentanedione (I) has been cyclized with urea to form 5-phenyl-4,6-dimethyl-2-pyrimidol (II) and with thiourea to form the corresponding thiol (VI).

2. The procedure developed for the synthesis of II was found satisfactory for the cyclization of certain other β-diketones with urea to form pyrimidols.

3. The hydroxy group of certain pyrimidols was removed and one of the methyl groups of the resulting dimethylpyrimidines benzoylated with methyl benzoate by means of potassium amide to form phenacylpyrimidines (Claisen condensation).

4. 2-Chloro-4,6-dimethyl-5-phenylpyrimidine (VII), prepared from pyrimidol II, was coupled with certain nitrogen compounds.

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