VII, which was acetylated with acetic anhydride, 2.5 ml in 20 ml of pyridine, at room temperature for 16 hr. Usual work-up afforded 1.73 g of crystalline VIII (from acetone–hexane), mp 189–193°. The analyzed sample melted at 193–196°, $[\alpha]^{28}_{\mathrm{D}}$ +4.3° ($CHCl_3$). *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.48; H, 8.07.

19,21-Dihydroxy-4-pregnen-3,20-dione 21-Acetate (IX).—The oxide VIII, 0.675 g in 20 ml of acetic acid, was treated with 16.9 g of zinc powder prewashed with diluted acetic acid, with stirring on a steam bath for 10 min. The metal was filtered and washed with acetic acid; the filtrate taken to dryness *in vacuo* and the residue was dissolved in methylene dichloride and washed to neutrality with sodium bicarbonate and water. Evaporation of the solvent gave 0.578 g of amorphous IX, which crystallized from acetone: mp 196–198°, $[\alpha]^{23}_{\mathrm{D}}$ +176.5° ($CHCl_3$); lit.[12] mp 197–199°, $[\alpha]^{24}_{\mathrm{D}}$ +178°.

19,21-Dihydroxy-4-pregnene-3,20-dione (19-Hydroxydeoxycorticosterone).—Alkaline hydrolysis of the monoacetate IX according to the procedure described by Barber and Ehrenstein[12] gave the title compound: mp 160–162° (from acetone–ether), $[\alpha]^{23}_{\mathrm{D}}$ +179° ($CHCl_3$); lit.[12] mp 163–165°, $[\alpha]^{25}_{\mathrm{D}}$ +180°.

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Carboxamidation of β-Dicarbonyl Compounds

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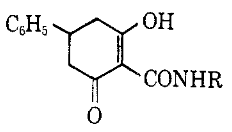
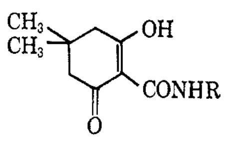
At the beginning of our work on the total synthesis of tetracycline antibiotics we were faced with the problem of constructing a 2-carboxamido 1,3-diketone moiety.[1] Although in the meantime the general synthetic approach has been changed[2] this Note describes some model experiments carried out previously in connection with this problem.

It has been known for a long time that organic isocyanates react with β-dicarbonyl compounds in the presence of catalytic amounts of base to yield N-substituted 2-carboxamido-1,3-dicarbonyl compounds. For instance, the reaction between 5-phenylcyclohexane-1,3-dione and phenyl isocyanate gave I.[3] Under the same conditions dimedon gave II.[3] Furthermore, dimedon reacts with acetyl isocyanate or carbomethoxy isocyanate to yield III and IV, respectively, which can be hydrolyzed with ammonia to V.[4,5]



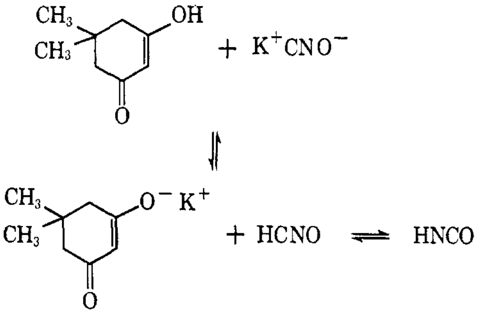
I, R = C_6H_5
VII, R = H



II, R = C_6H_5
III, R = $COCH_3$
IV, R = CO_2CH_3
V, R = H

At the outset of our work we tried to treat isocyanic acid with dimedon to form V. If dimedon was treated with isocyanic acid in chloroform–ether, a very slow reaction to V took place with most of the isocyanic acid polymerizing to cyamelide. However, if triethylamine was added to a chloroform–ether solution of dimedon and isocyanic acid, a faster reaction to V was observed. The fact that the polymerization of isocyanic acid is a main side reaction during these processes led to an attempt to find a system in which only a relatively low concentration of isocyanic acid would be available at a given time which might react in the wanted direction in preference to polymerization. Expecting that a solution of potassium cyanate and dimedon in water might establish the equilibrium outlined in Scheme I and that during and after establishment of this equilibrium V might be formed, dimedon and potassium cyanate were allowed to react in a mixture of dimethylformamide and water.[1b] The best results were obtained by dropping a water solution of potassium cyanate into a solution of dimedon in dimethylformamide. This way a 51% yield of V was obtained. If a greater amount of potassium cyanate was used or the reaction time was prolonged, the yields were lower. This may be due to the fact that potassium carbonate is formed by heating potassium cyanate in water and that potassium carbonate might degrade V. A control experiment showed that V is degraded by potassium carbonate in water.

SCHEME I



In order to extent the potassium cyanate reaction to other systems, *trans*-decalin-1,3-dione[6] and 5-phenylcyclohexane-1,3-dione were used. In both cases the expected reaction took place and compounds VI and VII, respectively, were isolated. Furthermore, compound VIII, prepared during attempts to synthesize tetracycline antibiotics,[7] reacted with potassium cyanate to give IX.

In all the cases mentioned so far, carboxamidation also occurred with lead cyanate in acetonitrile, but no markedly better results were obtained.

The reaction products V–VII and IX could be isolated directly or *via* their crystalline, water-insoluble copper chelates. Compounds V–VII show, even in dilute solution, no infrared absorption maxima of carbonyl groups <6.2 μ and are therefore completely enolized and chelated. The same is true for IX,

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(1) (a) For a general discussion of this problem, see H. Muxfeldt, *Angew. Chem.*, **74**, 443 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 372 (1962).

(2) H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).

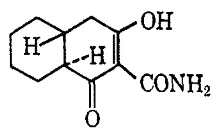
(3) W. Dieckmann, J. Hoppe, and R. Stein, *Ber.*, **37**, 4627 (1904).

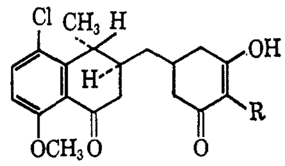
(4) M. M. Shemyakin, J. A. Arbuzow, M. N. Kolosov, G. A. Shatenshteyn, W. W. Onopienko, and J. V. Konnova, *Zh. Obshch. Khim.*, **30**, 542 (1960).

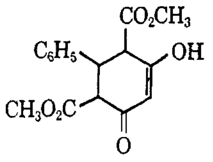
(5) Compound V was also prepared by fusing a mixture of dimedone and urea: H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).

(6) C.-K. Chuang and H.-L. Tien, *Ber.*, **69**, 25 (1936).

(7) H. Muxfeldt and W. Rogalski, *ibid.*, **95**, 2581 (1962).


VI


VIII, R = H
IX, R = CONH$_2$


X

except that IX has an additional absorption band at 5.96 μ from its tetralone carbonyl.

β-Dicarbonyl compounds of different types, such as compound X,[8] methyl benzoyl acetate, or methyl acetyl acetate did not react in the described manner.

Experimental Section

Carboxamidodimedon (V). A. From Dimedon and Isocyanic Acid in the Presence of Triethylamine.—To a solution of 2 g of dimedon and 2 ml of triethylamine in 200 ml of chloroform, 100 ml of an ether solution of isocyanic acid (prepared by thermal decomposition of 5 g of anhydrous cyanuric acid) was added. The mixture was stirred at room temperature for 10 days.[9] After filtration (cyamelide) the filtrate was acidified with dilute hydrochloric acid and washed with water. The organic phase was dried with sodium sulphate and evaporated. The remaining yellow, crystalline residue was recrystallized from ether–petroleum ether (bp 60–80°). A total of 758 mg (33%) of V was obtained: mp 148–149°; $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-HCl}}$ 258 mμ (ϵ 17,700); $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-NaOH}}$ 267–270 mμ (ϵ 18,600); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.9, 3.1, 3.4, 6.2 μ.

Anal. Calcd for $C_{19}H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.95; H, 7.16; N, 7.62.

B. From Potassium Cyanate and Dimedon.—A solution of 50 g of potassium cyanate in 150 ml of water was added dropwise during a period of 30 min with stirring to a solution of 50 g of dimedon in 500 ml of dimethylformamide at 100°. The mixture was heated for another 30 min at 100° and was then acidified with dilute hydrochloric acid and diluted with 300 ml of water. The mixture was cooled in an ice bath for 2 hr and the crystalline V was filtered off, washed with water, and dried in a desiccator. The dry V was recrystallized once from ether–petroleum ether. A total of 33.4 g (51%) of V was obtained, mp 148–149°.

C. From Dimedon and Lead Cyanate.—A suspension of 300 mg of dimedon and 900 mg of lead cyanate in 40 ml of acetonitrile was heated to reflux for 3 days. The mixture was diluted with 40 ml of water, acidified with dilute hydrochloric acid, and immediately filtered. The filtrate was further diluted with 100 ml of water and extracted three times with chloroform. The combined extracts were dried over sodium sulphate and evaporated to dryness. The crystalline residue was dissolved in methanol and an excess of a solution of copper acetate in water was added. The crystalline copper chelate of V was filtered off, washed with water–methanol (1:1), and then suspended in water. The suspension was acidified with dilute hydrochloric acid and extracted with chloroform. After drying the extracts and evaporating the solvent there remained 242 mg (63%) of crude V: mp 146–147°; after recrystallization from ether–petroleum ether, mp 148–149°.

D. From Dimedon and Silver Cyanate.—If 300 mg of dimedon was treated with 1 g of silver cyanate as described under C, 240 mg (63%) of V was obtained.

Carboxamidation of 5-Phenylcyclohexane-1,3-dione with Potassium Cyanate.—Within a period of 30 min a solution of 2.5 g of potassium cyanate in 40 ml of water was added with stirring to a solution of 4 g of 5-phenylcyclohexane-1,3-dione in 40 ml of dimethylformamide at 100°. The mixture was kept at this temperature for another 90 min and worked up as described above. The crude material was crystallized from chloroform and ether. A total of 1.4 g (35%) of VII was obtained: mp 162–164°; $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-HCl}}$ 257–258 mμ (ϵ 17,900); $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-NaOH}}$ 268–269 mμ (ϵ 19,000); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.9, 3.1, 3.4, 6.2 μ.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.41; H, 5.70.

Carboxamidation of *trans*-Decalin-1,3-dione with Potassium Cyanate.—A solution of 5 g of *trans*-decalin-1,3-dione in 50 ml of dimethylformamide was treated with a solution of 3.75 g of potassium cyanate in 50 ml of water as described above. The crude reaction product was recrystallized from ether. A total of 2.32 g (37%) of VI was obtained: mp 114–116°; $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-HCl}}$ 259 mμ (ϵ 16,700); $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-NaOH}}$ 267–269 mμ (ϵ 18,700); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.9, 3.1, 3.45, 6.2–6.4 μ.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 63.14; H, 7.26; N, 6.54. Found. C, 63.27; H, 7.25; N, 6.91.

Carboxamidation of VIII with Potassium Cyanate.—A solution of 250 mg of potassium cyanate in 2.5 ml of water was added with stirring during a period of 25 min to a solution of 720 mg of VIII in 3.5 ml of dimethylformamide at 100°. The mixture was kept at this temperature for another 3 hr, diluted with water, acidified with dilute hydrochloric acid, and extracted with chloroform. The combined extracts were washed with water and evaporated after drying over sodium sulphate. The crude amorphous residue (680 mg) was then dissolved in benzene–ether (1:1) and shaken with 10 ml of a 10% solution of copper acetate in water for 20 min. The crystalline copper chelate of IX was filtered off and suspended in 20 ml of a 1:1 mixture of methanol–2 *N* hydrochloric acid and extracted with chloroform. The combined chloroform extracts were dried over sodium sulphate and evaporated and the residue was crystallized from acetone and ether. A total of 280 mg (35%) of IX was obtained: mp 209–214° dec; $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-HCl}}$ 328 mμ (ϵ 4400), 258 (ϵ 23,200), 226 (ϵ 27,000); $\lambda_{\max}^{0.01\,N\ \mathrm{MeOH-NaOH}}$ 328 mμ (ϵ 4400), 262 (ϵ 22,600), 227 (ϵ 25,400); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.85, 3.05, 3.30, 3.40, 5.96, 6.33 μ.

Anal. Calcd for $C_{20}H_{22}ClNO_5$: C, 61.30; H, 5.66; Cl, 9.05; N, 3.57. Found: C, 61.41; H, 5.80; Cl, 9.15; N, 3.62.

Acknowledgment.—This work was supported by the National Science Foundation (Grants No. I9242 and 6P-3696.

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[8] H. Muxfeldt, G. Grethe, K. Uhlig, and H. Zeugner, *Ber.*, **96**, 2943 (1963).

[9] During preliminary experiments the reaction was run as described above and samples were taken at different times. It was found that after 10 days no increase of the yield of V could be detected.