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DAKIN – WEST REACTION WITH CYSTEINE, CYSTINE, AND SERINE

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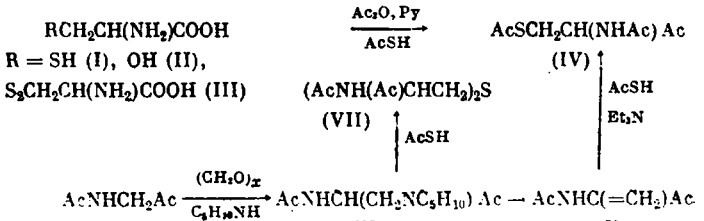
The C-acylation of cysteine (I) and serine (II) (Dakin–West reaction) lies at the base of some metabolic processes [1-3].

In order to create chemical models of these biochemical transformations we studied in the present paper the Dakin–West reaction of (I), (II), and cystine (III) with Ac_2O and either pyridine (Py) or γ-picoline:



When (I) was reacted with Ac_2O and Py we obtained, as the result of the C-, N-, and S-acetylation and decarboxylation of (I), 3-acetamido-4-acetylmercapto-2-butanone (IV) in 46% yield, whose structure was proved by the elemental analysis, IR and NMR spectra (see Experimental Part), and also by counter synthesis from 3-acetamido-2-butenone (V). The latter added AcSH under the influence of catalytic amounts of Et_3N to give (IV) in 20% yield. The reaction of 3-acetamido-4-piperidino-2-butanone (VI) with AsSH led to di(β-acetamido-γ-ketobutyl) sulfide (VII), whose structure was confirmed by the IR and NMR spectra. The same Dakin–West reaction product (IV) was formed by reacting Ac_2O and Py or γ-picoline with either (II) or (III) in the presence of AcSH.

The conversion of (II) and (III) to (IV) includes, together with the processes of decarboxylation and C- and N-acetylation, replacement of the β-substituents of (II) and (III) by the acetylmercapto group and the liberation of water and respectively sulfur and hydrogen sulfide.

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EXPERIMENTAL

The IR spectra were taken as KBr pellets on a UR-10 instrument, while the NMR spectra were taken on a a DA-60-IL instrument (internal standard = HMDS).

Reaction of (I) with Ac_2O and Py. With stirring, to 1 g of (I) as the hydrochloride monohydrate was gradually added 6 ml of Ac_2O, and then 4 ml of Py, after which the mixture was stirred for another 30 min at ~20°C, let stand at ~20° for 48 h, poured into excess Na_2CO_3 solution, and extracted with ethyl acetate (EA). The extract was dried over $MgSO_4$, evaporated in vacuo, and the residue was chromatographed on a column filled with SiO_2 (160 mesh), followed by elution with benzene and EA. From the EA eluate we isolated 0.53 g (46%) of (IV), mp 80-81° (from cyclohexane), R_f 0.44 (TLC, Silufol UV-254, 1 : benzene – EA mixture, detection of spots with I_2 vapors and in UV light). Infrared spectrum (ν, cm^{-1}): 1660 (CON), 1690 (AcS), 1725 (C=O). NMR spectrum ($CDCl_3$, δ, ppm): 2.00 s and 2.27 s (CH_3CON and CH_3COS); 2.34 s (CH_3CO); 3.39 m (CH_2); 4.76 m (CH); 6.57 m (NH). Found: C 47.27; H 6.47; N 6.94; S 15.58%. $C_8H_{13}NO_3S$. Calculated: C 47.27; H 6.40; N 6.89; S 15.76%. Similar results were obtained when (I) is reacted with Ac_2O and Py in the presence of AcSH.

Addition of AcSH to 3-Acetamido-2-butenone (V). With stirring, to 1 ml of AcSH + 2 drops of Et_3N was gradually added 0.9 g of (V) [4], after which the mixture was kept at 20° for 140 h. After the above described workup we isolated 0.29 g (20%) of (IV).

Reaction of 3-Acetamido-4-piperidino-2-butanone (VI) with AcSH. A mixture of 6 g of acetamidoacetone, 1.6 g of paraform, and 8 ml of piperidine in 24 ml of alcohol was kept for 6 days at 20°, after which it was evaporated in vacuo, to the residue with stirring was added 11 ml of AcSH, and the mixture was kept for another 7 days at 20°. After treating the reaction mixture with n-heptane the precipitate was filtered and washed with EA to give 3.01 g (40%) of di-(β-acetamido-γ-ketobutyl) sulfide (VII), mp 143-144° (from isoporpanol). Infrared spectrum (ν, cm^{-1}): 1640 (CON), 1618 (CO). NMR spectrum (CF_3COOH, δ, ppm): 1.90 s ($2CH_3CON$); 1.95 s ($2CH_3CO$); 2.72 t ($2CH_2$); 4.42 m (2CH); 8.14 m (2NH); Found: C 50.01; H 6.66; S 11.15%. $C_{12}H_{20}N_2SO_4$. Calculated: C 50.00; H 6.94; S 11.11%.

Reaction of Cystine (III) with Ac_2O and Py. With stirring, to 1 g of cystine (III) dihydrochloride were consecutively added 6 ml of Ac_2O, 1 ml of Py, and 1 ml of AcSH, after which the mixture was kept at 20° for 48 h and then treated with excess Na_2CO_3 solution. The product was isolated as described above. We obtained 0.61 g (47%) of (IV). The yield of (IV) was 39% when (II) was reacted with Ac_2O and AcSH in either Py or γ-picoline under analogous conditions (9 days, 20°).

CONCLUSIONS

3-Acetamido-4-acetylmercapto-2-butanone is formed when cysteine, cystine or serine is reacted with Ac_2O and either pyridine or γ-picoline in the presence of thioacetic acid.

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