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SYNTHESIS OF 2-AMINO-1-ACETYL-5,5-DIMETHYL-3-CYANO-4,5,6,7-TETRAHYDROPYRROLO-[2,3-c]PYRAN AND ITS ACETYLATION

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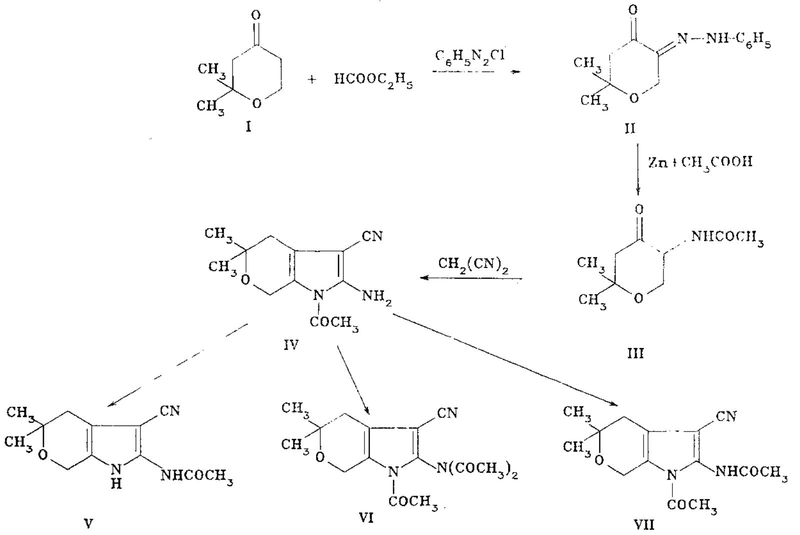
2,2-Dimethyltetrahydropyran-4-one was used to obtain 2-amino-1-acetyl-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran and its acetyl derivatives.

The condensed system of pyran and pyrrole may be considered as an analog of indole whose structure is the basis for many compounds with high biological activity.

There is only one example of the synthesis of pyranopyrroles. This system was obtained by Carr et al. [1] in the synthesis of porphyrins.

We have prepared this condensed system using 2,2-dimethyltetrahydropyran-4-one (I) [2]. The reaction of ketone I with ethyl formate and with phenyldiazonium chloride gave the 5-monophenylhydrazone of 2,2-dimethyltetrahydropyran-4,5-dione (II). This dione was reduced by zinc dust in acetic acid to give 5-acetamido-2,2-dimethyltetrahydropyran-4-one (III). The condensation of ketoamide III with malononitrile gave 2-aminol-1-acetyl-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (IV). Heating IV in acetic acid or pyridine gave 2-acetylamino-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (V). This transformation is apparently related to intramolecular migration of the acetyl group. The triacetyl derivative VI was obtained by heating aminonitrile IV with acetic anhydride at reflux. On the other hand, the acetylation of aminonitrile IV by acetic anhydride in benzene leads to the diacetyl derivative VII.



The PMR spectrum of aminonitrile IV shows a singlet at 2.35 ppm which is related to the protons in the spectrum of amidonitrile V are at higher field (2.25 ppm) than in the spectrum of aminonitrile IV. The signals for the acetyl group protons of triacetyl derivative VI are

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seen as a singlet at 2.70 ppm. The signals for the $NCOCH_3$ group protons in the PMR spectrum of diacetyl derivative VII are at 2.40 ppm while the $NHCOCH_3$ protons are at 1.50 ppm.

The IR spectrum of aminonitrile IV has a characteristic CO band at 1720 cm^{-1}. The CO band is shifted to 1680 cm^{-1} in the IR spectrum of amidonitrile V. The characteristic CO group bands in the IR spectra of the di- and triacetyl derivatives VI and VII are found as a broad band at 1720-1740 cm^{-1}.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in vaseline. The PMR spectra were taken on a Varian T-60 spectrometer. The mass spectra were taken on an MKh-1303 mass spectrometer with 70 eV ionizing voltage. The thin-layer chromatography was carried out on Silufol-254 plates using iodine vapor development.

5-Monophenylhydrazone of 2,2-dimethyltetrahydropyran-4,5-dione (II). A solution of sodium methylate in methanol prepared from 2.3 g (0.1 mole) sodium and 23 ml methanol was added with stirring to a mixture of 12.8 g (0.1 mole) ketone I [2] and 11.1 g (0.15 mole) ethyl formate cooled at −5°C. The precipitated sodium derivative of formyltetrahydropyranone was maintained for 20 h at 20-22°C. The precipitate was dissolved and 50 ml water was added to the reaction mixture at −5°C. The solution obtained was poured into aqueous phenyldiazonium chloride obtained by the usual method from 9.3 g (0.1 mole) aniline, 30 ml concentrated hydrochloric acid, and 6.9 g (0.1 mole) sodium nitrite and brought to pH 5.0-6.0 by the addition of sodium acetate; the phenyldiazonium chloride solution was maintained at 0°C. The crystalline precipitate was filtered off, washed with cold water, and dried to yield 19.0 g (81.9%) II with mp 67-68°C (from ethanol). R_f 0.60 (1:2 ethanol—petroleum ether). IR spectrum: 3260-3280 (NH), 1650 cm^{-1} (C=O). PMR spectrum (in CCl_4): 13.60 (1H, s, NH), 7.10-7.25 (5H, d, C_6H_5), 4.65 (2H, s, CH_2), 2.40 (2H, s, CH_2), 1.30 ppm (6H, s, $2CH_3$). Found: C, 67.2; H, 7.0; N, 12.1%. Calculated for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.9; N, 12.1%.

5-Acetamido-2,2-dimethyltetrahydropyran-4-one (III). A sample of 40.0 g zinc dust (0.6 mole) was added in small portions with vigorous stirring to a mixture of 46.4 g (0.2 mole) phenylhydrazone II, 20.5 g (0.24 mole) fused sodium acetate, 55.0 g (0.54 mole) acetic anhydride, and 200 ml glacial acetic acid heated to 40°C. The reaction mixture was stirred for 90 min at reflux. The slurry was filtered off and washed with hot acetic acid. The acetic acid solution was evaporated to dryness at reduced pressure. A sample of 200 ml water was added to the residue and the aqueous solution was evaporated in vacuum. A sample of 200 ml chloroform was added to the residue and the zinc acetate was filtered off. The chloroform was added to the residue and the zinc acetate was filtered off. The chloroform solvent was distilled off. The residue was distilled to give 27.1 g (73.3%) III with mp 113-114°C (1 mm), mp 43-44°C. IR spectrum: 3200-3400 (NH), 1680 and 1730 cm^{-1} (C=O). PMR spectrum (in CCl_4): 7.0 (1H, s, NH), 4.10-4.50 (2H, t, CH_2), 3.20-3.60 (1H, t, CH), 2.40-2.80 (2H, t, CH_2), 2.00 (3H, s, CH_3CO), 1.20 and 1.40 ppm (6H, s, $2CH_3$). M 185 (mass spectroscopy). Found: C, 58.3; H, 8.1; N, 7.6%. Calculated for $C_9H_{15}NO_3$: C, 58.4; H, 8.2; N, 7.6%.

2-Amino-1-acetyl-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (IV). A mixture of 18.5 g (0.1 mole) ketoamide III, 6.6 g (0.1 mole) malononitrile, 2 ml diethylamine, 1 ml acetic acid, and 100 ml absolute benzene was heated at reflux with a water trap for 1 h. The crystaloine precipitate was filtered off, washed with 30 ml benzene, and dried to yield 20 g (86.1%) IV with mp 180-181°C (from ethanol). R_f 0.55 (1:4 pyridine—ethyl acetate). IR spectrum: 3220, 3310, 3410 (NH_2), 2230 (C≡N), 1720 (N—C=O), 1640 cm^{-1} (NH def). PMR spectrum (in pyridine-d_5): 7.70 (2H, s, NH_2), 4.65 (2H, s, CH_2), 2.40 (2H, s, CH_2), 2.35 (3H, s, $NCOCH_3$), 1.30 ppm (6H, s, $2CH_3$). M 233 (mass spectroscopy). Found: C, 61.7; H, 6.5; N, 18.0%. Calculated for $C_{12}H_{13}N_3O_2$: C, 61.8; H, 6.5; N, 18.0%.

2-Acetylamino-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (V). A. A mixture of 2.3 g (0.01 mole) aminonitrile IV and 10 ml glacial acetic acid was heated at reflux for 2 h, cooled, and the precipitate was filtered off, washed with methanol and ether, and dried to yield 1.2 g (52.5%) V with mp 303-304°C (from methanol). R_f 0.66 (1:6 ethanol—ether). IR spectrum: 1680 (C=O), 2230 (C≡N), 3100, 3180, 3240, 3320 cm^{-1} (NH). PMR spectrum (pyridine-d_5): 7.60 (1H, s, NH), 7.25 (1H, s, NH), 4.70 (2H, s, CH_2), 2.65 (2H, s, CH_2), 2.25 (3H, s, $NHCOCH_3$), 1.40 ppm (6H, s, $2CH_3$). M 233 (mass spectroscopy). Found: C, 61.7; H, 6.6; N, 17.0%. Calculated for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.5; N, 18.0%.

B. A mixture of 1.15 g (5 mmoles) aminonitrile IV and 4 ml pyridine was heated at reflux for 2 h, cooled, the precipitate was filtered off, washed with methanol and ether and dried to yield 1.0 g (86.9%) V with mp 303-304°C.

1-Acetyl-2-diacetylamin-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (VI). A mixture of 1.15 g (5 mmoles) aminonitrile IV and 8 ml (0.08 mole) acetic anhydride was heated at reflux for 1 h, cooled and 30 ml ethanol was added. The precipitate was filtered off, washed with ethanol and dried to yield 1.1 g (72.3%) VI with mp 117-118°C (from ethanol). R_f 0.62 (4:1:1 ethanol—chloroform—ether). IR spectrum 2250 (C≡N), 1720-1740 cm^{-1} (C=O). PMR spectrum (in pyridine-d_5): 4.85 (2H, s, CH_2), 2.70 (11H, s, CH_2, $3CH_3$), 1.35 ppm (6H, s, $2CH_3$). M 317 (mass spectroscopy). Found: C, 60.5; H, 6.1; N, 13.8%. Calculated from $C_{16}H_{19}N_3O_4$: C, 60.6; H, 6.0; N, 13.2%.

1-Acetyl-2-acetylamin-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (VII). A mixture of 1.15 g (5 mmoles) aminonitrile IV, 75 ml absolute benzene, and 0.5 ml (5 mmoles) acetic anhdride was heated at reflux for 3 h and cooled. The precipitate was filtered off, washed with methanol and ether, and dried to yield 1.0 g (75.6%) VII with mp 152-153°C (from methanol), R_f 0.70 (2:1:2 ethanol—chloroform—petroleum ether). IR spectrum: 3120, 3230, 3310 (NH 2230 (C≡N), 1720-1740 cm^{-1} (C=O). PMR spectrum (in pyridine-d_5): 7.90 (1H, s, NH), 4.70 (2H, s, CH_2), 2.40 (5H, s, CH_2 and $NCOCH_3$), 1.50 (3H, s, $NHCOCH_3$), 1.20 (6H, s, $2CH_3$). Found: C, 61.2; H, 6.3; N, 15.3%. Calculated for $C_{14}H_{17}N_2O_3$: C, 61.1; H, 6.2; N, 15.3%.

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ARYLATION OF HETEROCYCLES IN THE REACTION OF HETEROCYCLIC MERCURY DERIVATIVES IN THE PRESENCE OF PALLADIUM COMPLEXES

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A convenient method is proposed for the synthesis of aryl derivatives of heterocyclic compounds by the coupling reaction of heterocyclic mercury derivatives and tin derivatives with aryl and heteryl iodides in the presence of palladium complexes. In the case of organotin compounds, the reaction proceeds without the formation of side-products although mercury derivatives are usually more available.

The Gomberg—Bachmann—Hey reaction [1] is most often used to prepare aryl derivatives of heterocyclic compounds. However, this reaction requires the use of a large excess of one of the reagents. A mixture of isomers formed and the yield of the desired product is usually low. These disadvantages have recently been eliminated by the discovery of the coupling reaction of organic halides with organometallic compounds catalyzed by transition metal complexes [2-6]. We have previously shown that the introduction of organic mercury and tin derivatives instead of Grignard reagents permits expansion of the synthetic scope of the reaction and the use of organic halides containing various functional groups [7, 8]. In the present work, this reaction is used for the preparation of arylated hyterocycles.

We have found that organomercury and organotin derivatives of thiophene and furan react under mild conditions with aryl iodides in the presence of 1% palladium complex to give high yields of the corresponding derivatives of these heterocycles (see Table 1). The reactions of the organomercury compounds were carried out in the presence of two or three equivalents of iodide ion (Bu_4NI in HMPTA and THF and NaI in acetone), which acts as a nucleophilic catalyst accelerating the exchange of the organomercury compounds with palladium complex, which

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