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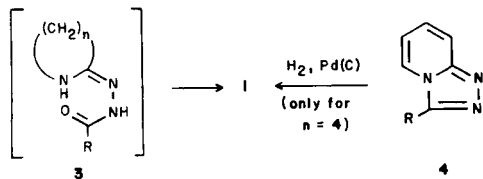
It is already known that ethyl ω -chloroalkylimidate hydrochlorides and aroyl hydrazides gave, when reacted together in boiling ethanol, 2-aryl-5- ω -haloalkyl-1,3,4-oxadiazoles. It has now been found that the reaction follows a different course in the presence of triethylamine. In particular, 2-aryl-5,6,7,8-tetrahydro-1,2,4-triazolo[5,1-*a*]pyridines were obtained from ethyl δ -chlorovalerimidate, whereas *N*-aroylaminoimino-pyrrolidines are the products obtained from ethyl γ -chlorobutyrimidate. A similar case, in which the closure of the triazole ring to obtain a dihydropyrrolotriazole was found to be more difficult than the corresponding closure to a tetrahydrotriazolopyridine, is described. Also the reaction between the imidates and carbethoxy-hydrazine, which gives piperidine and pyrrolidine derivatives, is reported.

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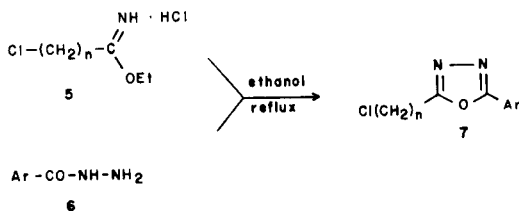
Cycloalkyltriazoles of general formula **1** and **2** are molecules of particular interest in the pharmaceutical field [1].



We have already described two different syntheses [2] for some 3-substituted-4,5-cycloalkyltriazoles of series **1**. In the first, more general instance, *O*-methylvalerolactim is reacted with an hydrazide, the key intermediate being a cyclic acylamidrazone **3** while in the second case, which

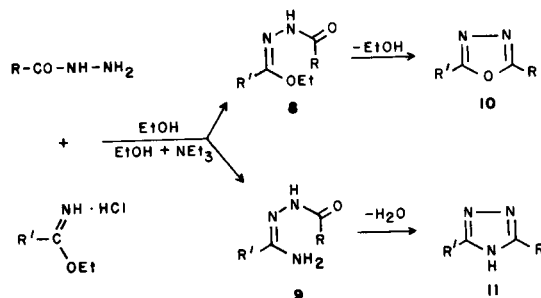


only applies to $n = 4$, a triazolo[4,3-*a*]pyridine **4** is hydrogenated on palladized charcoal to the corresponding tetrahydro derivative **1**. In the present work we wish to report the synthetic approach to some 5-aryl-2,3-cycloalkyltriazoles **2**, starting from ethyl ω -chloroalkylimidates **5** and aroyl hydrazides **6**. It is already known that the reaction between ethyl ω -chloroalkylimidate hydrochlorides **5** and aroylhydrazides **6** in boiling ethanol gives 2-aryl-5- ω -chloroalkyl-1,2,4-oxadiazoles **7** [3,4].



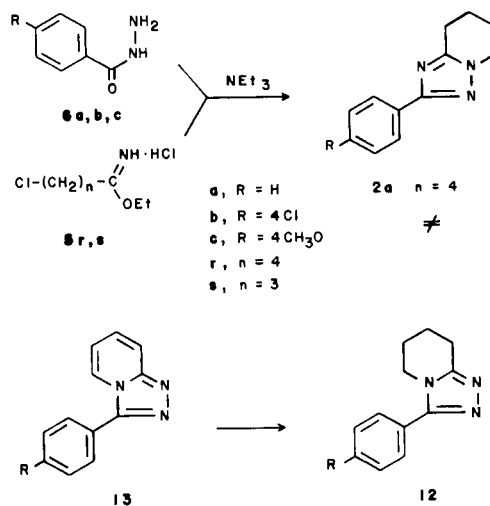
On the other hand it is also known that different products are obtained from the reaction between imidates and hydrazides, depending on the pH of the medium. In fact

the hydrazone esters **8** were obtained from imidate hydrochlorides and hydrazides in ethanol at room temperature, whereas, when an equivalent of an organic tertiary base was added to the reaction mixture, the amidrazones **9** were isolated [5].



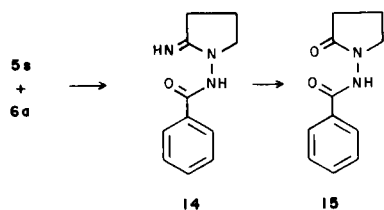
Compounds **8** and **9**, by subsequent heating, lost ethanol or water to give respectively 2,5-disubstituted-1,3,4-oxadiazoles **10** [4] and 3,5-disubstituted 1,2,4-triazoles **11** [6,7].

On account of these facts we reacted ethyl γ -chlorobutyrimidate hydrochloride **5s** and ethyl δ -chlorovalerimidate

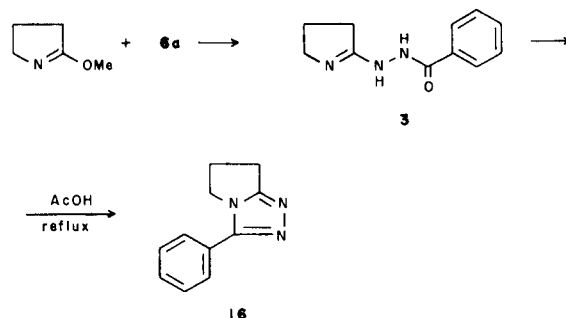
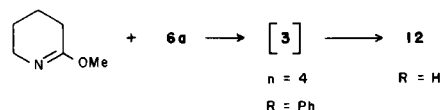


hydrochloride **5r** with various aroyl hydrazides (**6a**, **b**, **c**) in the presence of two molecular equivalents of triethylamine. As expected, the presence of triethylamine drastically affected the course of the reactions and consequently the tetrahydro-1,2,4-triazolo[1,5-*a*]pyridine **2a** ($n = 4$) was obtained from **5r** and **6a**.

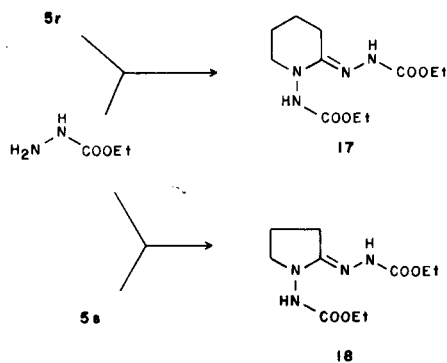
The structure of the tetrahydro-1,2,4-triazolopyridine, for the compound obtained, resulted from the analytical values and the spectral properties. Of the two possible isomers **2a** and **12**, the latter was discarded since the compound **12** had been obtained by selective reduction of the known 3-phenyl-1,2,4-triazolo[4,3-*a*]pyridine **13** [8] and found to be different from **2a**. Not even the least trace of **12** was found in the crude mixture obtained from the reaction between **5r** and **6a**. It is interesting to point out that **2a** and **12**, in spite of their very similar structures, show very different physical properties (compare the uv, nmr, mp, solubility and tlc behaviour in the experimental). The reaction follows the same course when substituted aroyl hydrazides are used at the place of **6a**. So, by reacting **5r** with **6b** and **6c**, **2b** and **2c** are respectively obtained. On the contrary when the lower homologues of **5r**, *i.e.* **5s**, is reacted with **6a**, the corresponding cycloalkyltriazole is not obtained. In fact the elemental analysis of the compound isolated corresponds to $C_{11}H_{13}N_3O$. By alkaline hydrolysis this product loses ammonia to give a compound which corresponds to the formula $C_{11}H_{12}N_2O_2$, showing in the ir spectrum two carbonyl bands, the higher of which is typical of a cyclic five-membered lactam. These results suggest structure **14** for the above-mentioned compound and **15** for its hydrolysis product.



With regard to obtaining a triazole ring through cyclization, it is interesting to point out that cyclization turns out to be easier when the triazole is fused to a tetrahydropyridine ring rather than with a dihydropyrrole ring. As a matter of fact, when in the synthesis of tetrahydro-1,2,4-triazolo[4,3-*a*]pyridine (see above), *O*-methylvalerolactim was reacted with **6a** in order to obtain the intermediate cyclic amidrazone **3** ($n = 4$, $R = Ph$), the amidrazone itself was not isolated since it very quickly cyclized under the reaction conditions. In contrast when *O*-methylbutyrolactim was reacted with **6a**, under the same conditions, the corresponding **3** ($n = 3$, $R = Ph$) was easily isolated and its ring closure to the 5*H*-6,7-dihydropyrrolo-1,2,4-triazole **16** was achieved only after long refluxing in acetic acid.



One must exercise caution in attempts to correlate reported results. It is indeed well known that the course of the reaction between imidates and primary amines or hydrazines in alkaline medium is affected not only by small pH variations of the medium, as outlined above, but also by the p*K* of the basic component, both from a preparative and from a mechanistic point of view. As a matter of fact when either **5r** or **5s** were reacted in boiling ethanol in the presence of two molecular equivalents of triethylamine with carbethoxyhydrazine, two similar products, arising from the combination of two moles of hydrazide with one mole of imidate, were obtained. The structures **17** and **18** are assigned to the two compounds.



EXPERIMENTAL

Melting points were determined in capillary tubes (Bücher melting point apparatus) employing a thermometer for partial immersion. The ir spectra were measured with a Perkin-Elmer Model 257 spectrophotometer in potassium bromide or chloroform. The nmr spectra were obtained with a Perkin-Elmer Hitachi R-24 spectrometer with TMS as the internal standard. The uv spectra were taken with a Beckmann DK₂ spectrometer. The tlc were performed on Kieselgel Merck F 254 plates and the spots detected by uv show lamp or exposure to iodine vapor. No attempt has been made to optimize the yields of the reactions described.

2-Aryl-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-*a*]pyridines (**2a**, **b**, **c**).

General Procedure.

Triethylamine (0.05 mole) and the appropriate aroylhydrazide (0.025 mole) were successively added to a suspension of ethyl δ -chlorovalerimidate hydrochloride [9] (0.025 mole) in 50 ml of absolute ethanol. The reaction mixture was refluxed for 1 hour, concentrated at reduced pressure to a small volume and poured into cold water. The crude reaction product was extracted with chloroform. Evaporation of the dried solvent gave a residue which was then crystallized from ethanol or ethyl acetate.

2-Phenyl-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-a]pyridine (2a).

This compound had mp 163-165° (from ethanol); yield 35%, nmr (deuteriochloroform): δ 8.1 (m, 2H), 7.4 (m, 3H), 4.1 (t, 2H), 2.9 (t, 2H), 1.9 (m, 4H); uv (95° ethanol): λ max 245 ($\epsilon = 16,600$) nm; tlc (benzene-ethyl acetate-diethylamine 7:2:1): Rf = 0.6.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.41; H, 6.55; N, 21.02.

2-*p*-Chlorophenyl-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-a]pyridine (2b).

This compound had mp 176-177° (from ethyl-acetate), yield 26%, nmr (deuteriochloroform): δ 8.0 (m, 2H), 7.4 (m, 2H), 4.1 (t, 2H), 2.9 (t, 2H), 2.0 (m, 2H).

Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98. Found: C, 61.47; H, 5.11; N, 17.77.

2-*p*-Methoxyphenyl-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-a]pyridine (2c).

This compound had mp 125-127° (from ethyl-acetate), yield 28%, nmr (deuteriochloroform): δ 7.9 (m, 2H), 6.9 (m, 2H), 4.1 (t, 2H), 3.8 (s, 3H), 2.9 (t, 2H), 2.0 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.85; H, 6.56; N, 18.08.

3-Phenyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyridine (12) from 3-Phenyl-1,2,4-triazolo[4,3-a]pyridine (13).

Ten g (0.062 mole) of **13** [10] was suspended in 200 ml of ethanol and dissolved by adding the calculated amount of hydrochloric acid. The solution, after addition of 1 g of 5% palladized charcoal was hydrogenated at 70 psi at room temperature. The catalyst was filtered, the ethanolic solution concentrated under reduced pressure and the residue dissolved in water, treated with 8% sodium hydroxide and extracted with ethyl acetate. The evaporation of the solvent gave **12** as a solid residue, which was then recrystallized from benzene, 6 g, mp 158-160°; nmr (deuteriochloroform): δ 7.8-7.3 (m, 5H), 4.0 (t, 2H), 3.0 (t, 2H), 1.9 (m, 4H); uv (95° ethanol): λ max 238.5 ($\epsilon = 11,700$) nm; tlc (benzene-ethyl acetate-diethylamine 7:2:1): Rf = 0.3.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.11; H, 6.53; N, 20.89.

1-Benzoylamino-2-imino-2,3,4,5-tetrahydropyrrolole (14).

Triethylamine (5 g, 0.05 mole) and benzoylhydrazine (3.4 g, 0.025 mole) were successively added to a suspension of ethyl γ -chlorobutyrimidate hydrochloride [13] (4.65 g, 0.025 mole) in 25 ml of absolute ethanol. The mixture was refluxed for 1 hour, concentrated at reduced pressure to a small volume, then poured into cold water and extracted with chloroform. Evaporation of the dried solvent gave a residue which was recrystallized from ethyl acetate to give **14** (2 g), mp 208-209°; nmr (deuterium oxide): δ 8.1-7.4 (m, 5H), 3.95 (t, 2H), 3.15 (t, 2H), 2.0-2.5 (m, 4H).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 64.96; H, 6.48; N, 20.92.

The hydrochloride had mp 319° (from 95% ethanol-water).

Anal. Calcd. for Cl⁻, 14.79. Found: Cl⁻, 14.75.

N-(Benzoylamino)-2-pyrrolidone (15).

A solution of **14** (2.0 g, 0.01 mole) in 40 ml of water-95% ethanol was refluxed for 3 hours. The cold solution was extracted with ethyl ether and concentrated to dryness. The crude solid residue was recrystallized from ethanol to give **15** (0.3 g), mp 159-161°; nmr (deuteriochloroform): δ 10.30 (broad s, 1H), 7.80-7.45 (m, 3H), 7.45-6.90 (t, 2H), 3.65 (t, 2H), 2.70-1.60 (m, 4H). The ir spectrum (chloroform): shows at 1710 cm^{-1} a strong band typical of a cyclic five membered lactam [14].

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.45; H, 5.98; N, 13.78.

3-Phenyl-5,6,7,8-tetrahydro-s-triazolo[4,3-a]pyridine 12 from *O*-Methylvalerolactim and Benzoylhydrazine 6a.

Benzoylhydrazine (8.56 g, 0.063 mole) was added to 7.15 g (0.063 mole) of *O*-methylvalerolactim [12] dissolved in 100 ml of xylene. The mixture was refluxed for 1 hour and the solvent removed at reduced pressure. The crude residue, recrystallized from ethyl acetate, gave 3.6 g of **12** as colourless solid, mp 158-159° (also in mixture with the product as above).

3*H*-2-Benzoylhydrazino-4,5-dihydropyrrolole 3 (n = 3, R = Ph).

A mixture of benzoylhydrazine (3.5 g, 0.025 mole) and of *O*-methylbutyrolactim [11] (2.5 g, 0.025 mole) in 10 ml of benzene, was refluxed for 1 hour. After cooling, the solid separated was filtered and recrystallized from methanol to give **3** (n = 3, R = Ph), 3.0 g, mp 230-231°; nmr (trifluoroacetic acid): δ 9.80 (broad s, 1H), 8.85 (s, 1H), 8.10-7.35 (m, 5H), 3.95 (t, 2H), 3.25 (t, 2H), 2.90-2.10 (m, 2H).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 64.83; H, 6.29; N, 20.43.

5*H*-6,7-Dihydro-3-phenylpyrrolole[2,1-c]-1,2,4-triazole (16).

One g (0.005 mole) of **3** was dissolved in 10 ml of glacial acetic acid and refluxed overnight. The solution was concentrated to dryness and the solid residue was recrystallized from absolute ethanol to give **16** (0.4 g), mp 186-188°; nmr (trifluoroacetic acid): δ 7.80-7.50 (m, 3H), 7.50-7.10 (m, 2H), 4.10 (t, 2H), 3.0-2.4 (m, 4H).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.32; H, 5.98; N, 22.69. Found: C, 71.18; H, 6.00; N, 22.62.

N-Carbomethoxyamino-2-piperidonecarbomethoxyhydrazone (17).

Triethylamine (10 g, 0.1 mole) and carbomethoxyhydrazine (5.2 g, 0.05 mole) were successively added to a suspension of ethyl δ -chlorovalerimidate hydrochloride (10 g, 0.05 mole) in 50 ml of absolute ethanol. The mixture was refluxed for 1 hour, concentrated at reduced pressure to a small volume and poured into cold water. The aqueous solution salted with sodium chloride was extracted twice with ether, the ethereal solution evaporated to dryness and the residue (3.7 g) crystallized twice from ethyl acetate gave **17** (0.3 g), mp 119-121°; nmr (deuteriochloroform): δ 7.30 (broad s, 2H), 4.15 (superimposed 2q, 2H + 2H), 3.45 (t, 2H), 2.55 (t, 2H), 1.85 (m, 4H), 1.25 (superimposed 2t, 3H + 3H).

Anal. Calcd. for $C_{11}H_{20}N_4O_4$: C, 48.51; H, 7.40; N, 20.58. Found: C, 48.45; H, 7.49; N, 20.49.

N-Carbomethoxyamino-2-pyrrolidonecarbomethoxyhydrazone (18).

Triethylamine (10 g, 0.1 mole) and carbomethoxyhydrazine (5.2 g, 0.05 mole) were successively added to a suspension of ethyl γ -chlorobutyrimidate hydrochloride (9.3 g, 0.05 mole) in 50 ml of absolute ethanol. The mixture was refluxed for 1 hour, concentrated at reduced pressure to a small volume and poured into cold water. The aqueous solution, salted with sodium chloride was extracted with chloroform. Evaporation of the dried solvent gave a residue (4 g) which was crystallized twice from ethyl acetate to give **18** (2.7 g), mp 131-132°; nmr (deuteriochloroform): δ 7.40 (broad s, 2H), 4.20 (superimposed 2q, 2H + 2H), 3.55 (t, 2H), 2.90-2.45 (m, 2H), 2.40-1.70 (m, 2H), 1.25 (superimposed 2t, 3H + 3H).

Anal. Calcd. for $C_{10}H_{16}N_4O_4$: C, 46.49; H, 7.02; N, 21.70. Found: C, 46.62; H, 7.09; N, 21.49.

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