ppm (1H, s, 3-H). ^{13}C NMR spectrum: 103.3 [$C_{(2)}$], 105.6 [$C_{(4)}$], 111.6 [$C_{(8,8')}$], 121.9 [$C_{(6)}$], 126.0 [$C_{(7,7')}$], 131.8 [$C_{(5)}$], 133.9 [$C_{(1)}$], 134.4 [$C_{(3)}$], 147.6 ppm [$C_{(9)}$].

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3-α-HALOCARBONYL DERIVATIVES OF PYRAZOLO[1,5-a] BENZIMIDAZOLE AND THEIR REACTIONS

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3-(α-haloacyl)-2,4-dialkylpyrazolo[1,5-a]benzimidazoles can be obtained either by brominating 3-acetylpyrazolo[1,5-a]benzimidazoles with bromine in acetic acid, or by acylating the 3-unsubstituted pyrazolobenzimidazoles with haloacetic halides. Halogenation of 3-acetylpyrazolo[1,5-a]benzimidazoles with bromine in acetic acid in the presence of sodium acetate, and bromination with N-bromosuccinimide or 1-chlorobenzotriazole, result in deacylation to give 3,6(7)-dibromo- and 3-chloropyrazolo[1,5-a]benzimidazoles. The mono- and trihaloketones obtained have been used to prepare the corresponding aminoketones, the 3-carboxylic acid, and its derivatives.

Derivatives of pyrazolo[1,5-a]benzimidazole, which is the closest structural analog of the biologically active imidazo[1,2-a]benzimidazole [1, 2], could be of interest for pharmacological study. However, the few investigations of methods of synthesizing functionally substituted derivatives of this heterocycle have mainly been concerned with the difficultly-accessible 4H-pyrazolo-[1,5-a]benzimidazoles [3, 4]. Making use of a simple method which we have developed for the preparation of 3-acyl-2,4-dialkylpyrazolo[1,5-a]benzimidazoles [5], we here examine possible approaches to 3-α-halocarbonyl derivatives of this series, and have obtained therefrom aminoketones, and the 3-carboxylic acid and its esters and hydrazide.

In the halogenation of 3-acetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (I), the high electron density at the 3 position in the heterocycle has a marked deactivating effect on the reactivity of the methyl group attached to the carbonyl carbon, and creates a preference for facile ipso-substitution. For instance, the ketone (I) does not react with bromine in chloroform, alcohol, or carbon tetrachloride. The monoketone (II) can be obtained only in boiling acetic acid, in which case some of the dibromo compound (III) is formed together with the hydrobromide of the starting material, separation of which is possible only after

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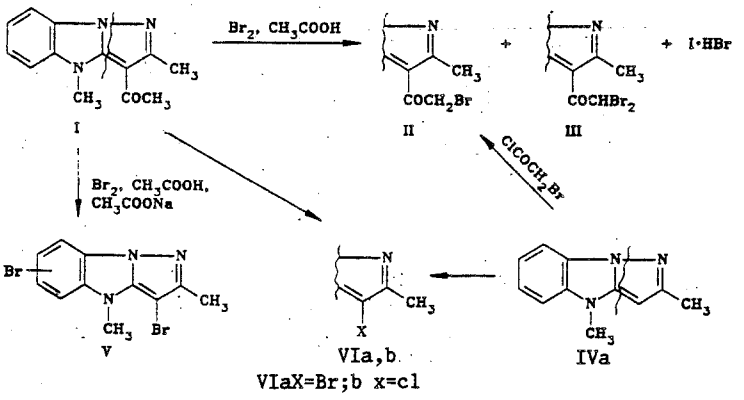
repeated recrystallization from alcohol. When the reaction mixture is sufficiently dilute, and the bromine is added slowly, the formation of these products is largely avoided. Reaction of the ketone (I) with 3-4 moles of bromine gives the dibromoketone (III) in high yield, but it was not possible to introduce a third halogen in this way. In the IR spectra of the haloketones (II) and (III), the position of the carbonyl absorption was scarcely shifted from that in the spectrum of the starting material, occurring at 1645-1650 cm^{-1}. The course of the bromination was confirmed by acid hydrolysis of (II) and (III) to 2,4-dimethylpyrazolo-[1,5-a]benzimidazole (IVa) [5].

The bromination of (I) proceeds differently in acetic acid in the presence of sodium acetate, to give the deacylated product 3,6(7)-dibromo-2,4-dimethylpyrazolo[1,5-a]benzimidazole (V). In this case, use of equimolar amounts of the reactants gives a mixture of the dibromo-compound (V) (33%), the monobromoketone (II) (26%), the dibromoketone (III) (7%), and starting material. If 2-3 moles of bromine and sodium acetate are used, (V) is formed in 80% yield. This mode of reaction is probably due to the formation in the reaction mixture of acetylhypobromite, which is known to be a more powerful brominating agent than bromine itself [6]. Substitution by halogen in the 3-position of the heterocycle and in the benzene ring in (V) follows from the PMR spectrum, in which there is no signal characteristic of the 3-H proton at 5 ppm or of the acetyl group. The integral intensity of the aromatic protons, which are present as two doublets (7.35 and 7.04 ppm, J = 9 Hz) and the singlet at 7.63 ppm, correspond to three proton units, but it is difficult to make a choice between the two possible sites of secondary bromination (6 or 7).

Reaction of the acetyl compound (I) with N-bromosuccinimide likewise fails to give the bromoketones (II) and (III). With one mole of N-bromosuccinimide in chloroform, carbon tetrachloride, or acetic acid at 25°C, 3-bromo-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIa) was obtained. This reaction takes place with particular ease in acetic acid, and with two moles of N-bromosuccinimide at 80°C, the dibromo compound (V) is obtained in 65% yield.

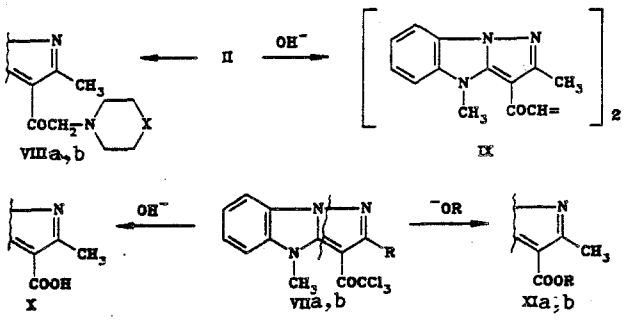
A similar result was obtained on attempted chlorination of (I) with 1-chlorobenzotriazole in methylene chloride, when instead of the expected chloroketone of type (II), there was obtained 3-chloropyrazolo[1,5-a]benzimidazole (VIb). 3-Halo-compounds identical with (VIa) and (VIb) were obtained also by halogenating 2,4-dimethylpyrazolo[1,5-a]benzimidazole (IVa).



The poor selectivity of monobromination of the ketone (I) and the unsuccessful attempts to introduce a third halogen atom into the acetyl group by halogenation stimulated an examination of the reaction of 2,4-dialkylpyrazolo[1,5-a]benzimidazoles (IV) with haloacetyl halides. Acylation of (IV) with bromoacetyl and trichloroacetyl chlorides proceeds quite readily even in boiling benzene, but the yields of bromoketone (II) and trichloroketone (VII) did not exceed 40%, because half of the starting material formed a salt with hydrogen chloride evolved, and did not undergo further acylation. This drawback was overcome by using xylene, a higher boiling solvent.

In order to obtain pyrazolo[1,5-a]benzimidazoles with functional substituents, haloketones (II) and (VII) were used in typical reactions with nucleophiles. Reaction of the monobromoketone (II) with secondary amines in boiling benzene gave high yields of the aminoketones (VIIIa, b). Heating the monobromoketone (II) in aqueous alcoholic alkali gave a high-melting yellow solid, which from its spectral data, elemental analysis, and by analogy with earlier work [7] was 1,4-di-(2,4-dimethylpyrazolo[1,5-a]benzimidazol-3-yl)but-2-ene-1,4-dione (IX). This compound may be formed by dimerization of the carbene formed by

α-elimination of hydrogen bromide from the monobromoketone (II). The IR spectrum of (IX) retains the carbonyl absorption at 1635 cm^{-1}. In the aliphatic region of the PMR spectrum, in addition to two singlets for the methyl groups, there is seen a signal for the methine proton at 4.58 ppm.



VIII a X=N, b X=O; VII, XI a R=CH_3, b R=C_2H_5

Compound (IX), rather than the expected pyrazolobenzimidazole-3-carboxylic acid (X), is obtained from the ketone (I) under the conditions of the haloform reaction. However, the authentic trichloroketone (VIIa) is readily cleaved by alkali to the acid (X). Brief heating of the trichloroketone (VIIa) with sodium alkoxides in the appropriate alcohol gives 90% of the esters (XI). Reaction of (VIIa) with boiling hydrazine hydrate affords the hydrazide (XII). It is worthy of mention that as a result of the inadequate electrophilicity of the carbonyl carbon, the esters (XI) fail to react with hydrazine.

EXPERIMENTAL

IR spectra were obtained on a UR-20 in vaseline oil, and PMR spectra on Tesla BS-467 (60 MHz) and Tesla BS-487 (80 MHz) instruments, internal standard HMDS. The reactions were followed and the purity of the products established by TLC on plates with alumina grade III activity, eluent benzene or chloroform, visualized with iodine vapor.

3-Bromoacetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (II). A. To a boiling solution of 2.27 g (0.01 mole) of 3-acetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole [5] in 30 ml of glacial acetic acid was added slowly with stirring 1.60 g (0.01 mole) of bromine in 5 ml of acetic acid, at such a rate as to avoid accumulation of bromine in the reaction mixture. A solid separated from the hot solution, and after cooling this was filtered off and washed with ether. It was then suspended in 50 ml of water, treated with 10% sodium bicarbonate solution until weakly alkaline, filtered off, and washed with water. Recrystallization from butanol gave 2.32 g (75%) of colorless crystals, mp 200-201°C, R_f 0.65 (benzene). Found: C 51.1; H 3.6; Br 25.8%. $C_{13}H_{12}BrN_3O$. Calculated: C 51.1; H 3.9; Br 26.1%.

B. To a boiling solution of 5.55 g (0.03 mole) of 2,4-dimethylpyrazolo[1,5-a]benzimidazole [5] in 60 ml of dry xylene was added dropwise 4.72 g (0.03 mole) of bromoacetyl chloride, and the mixture boiled with stirring for 1 h. After cooling, the solid was filtered off and washed with small amounts of alcohol and ether, to give 6.7 g of product. Evaporation of the mother liquors gave a further 1.3 g of material which was purified on an alumina column (3 × 20 cm), eluent chloroform. Yield 8 g (87%).

3-Dibromoacetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (III). To a boiling solution of 2.27 g (0.01 mole) of the 3-acetyl compound (I) in 30 ml of acetic acid was added dropwise over 40 min 4.8 g (0.03 mole) of bromine. The hydrobromide of the monoketone which separated initially changed its appearance as the bromine was added. After 1 h, the mixture was cooled, and the solid filtered off and washed with ether. It was then suspended in water, treated with 10% sodium bicarbonate solution until weakly alkaline, and quickly filtered off to give 3.4 g (89%) of pale yellow crystals, mp 196-198°C (decomp., from butanol), R_f 0.8 (benzene). PMR spectrum (CF_3COOH): 2.65 (3H, s, C–CH_3), 3.95 (3H, s, N–CH_3), 6.35 (1H, s, CH), 7.33-7.5 ppm (4H, m, 5–8-H). Found: C 40.8; H 3.1; Br 41.6; N 10.6%. $C_{13}H_{11}Br_2N_3O$. Calculated: C 40.5; H 3.1; Br 41.5; N 10.9%.

Bromination of Kétone (I) with 1 Mole of Bromine in Acetic Acid in the Presence of Sodium Acetate. To a boiling solution of 2.27 g (0.01 mole) of the ketone (I) and 0.80 g (0.01 mole) of fused sodium acetate in 30 ml of acetic acid was added dropwise with stirring a solution of 0.5 ml (0.01 mole) of bromine in 5 ml of acetic acid. After 30 min, the mixture was cooled, and 0.37 g of

the dibromo compound (V) filtered off. The mother liquors were poured into 150 ml of water, and the solid which separated (2.35 g) was filtered off. Recrystallization of this from alcohol gave 0.8 g (26%) of the monobromoketone (II). The alcoholic mother liquors were evaporated to dryness, and the residue chromatographed on an alumina column (3 × 40 cm), eluting first with a 1:1 mixture of benzene and light petroleum to give 0.76 g of (V). Yield of 3,6(7)-dibromo-2,4-dimethylpyrazolo[1,5-a]benzimidazole (V) 1.13 g (33%), colorless needles, mp 177-178°C (from alcohol), R_f 0.9 (benzene). PMR spectrum (CF_3COOH): 2.20 (3H, s, C–CH_3), 3.72 (3H, s, N–CH_3), 7.04 (1H, d, J = 9 Hz), 7.35 ppm (1H, d, J = 9 Hz), 7.63 ppm (1H, s). Found: C 38.7; H 2.7; Br 46.3; N 12.3%. $C_{11}H_9Br_2N_3$. Calculated: C 38.4; H 2.9; Br 46.5; N 12.0%. The column was then eluted with benzene to give successively 0.27 g (7%) of the dibromoketone (III) and a difficultly-separable mixture of (II) and the starting material. Bromoketones (II) and (III) were identical in their physicochemical properties to those described above.

3,6(7)-Dibromo-2,4-dimethylpyrazolo[1,5-a]benzimidazole (V). To a boiling solution of 2.27 g (0.01 mole) of the ketone (I) and 0.24 g (0.03 mole) of fused sodium acetate in 20 ml of acetic acid was added dropwise with stirring a solution of 1.5 ml (0.03 mole) of bromine in 5 ml of acetic acid, and the mixture boiled for 30 min. On cooling, (V) separated, and was filtered off (2.0 g). Dilution of the mother liquors with water gave a further 0.7 g of product. Yield 2.7 g (80%).

3-Bromo-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIa). A. To a solution of 0.45 g (2 mmole) of the ketone (I) in 5 ml of glacial acetic acid was added 0.36 g (2 mmole) of N-bromosuccinimide, and the mixture stirred for 1 h at 20°C. The mixture was then poured into 20 ml of water, and the solid which separated was filtered off and washed with water, to give 0.42 g (79%) of product, mp 135-136°C (from heptane). Found: C 49.9; H 3.5; Br 30.0%. $C_{11}H_{10}BrN_3$. Calculated: C 50.0; H 3.8; Br 30.3%.

B. To a stirred solution of 0.37 g (2 mmole) of 2,4-dimethylpyrazolo[1,5-a]benzimidazole in 10 ml of dry chloroform was added dropwise a solution of 0.1 ml (2 mmole) of bromine in 3 ml of chloroform. The solid (VIa) hydrobromide which separated was filtered off, washed with acetone, and treated with 10% ammonia to give 0.48 g (90%) of colorless crystals, identical to those described in method A.

3-Chloro-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIb). A. A solution of 0.45 g (2 mmole) of the ketone (I) and 0.3 g (2 mmole) of 1-chlorobenzotriazole in 15 ml of dry carbon tetrachloride was boiled for 30 min. The solvent was then evaporated to dryness, and the residue chromatographed on a column (2 × 20 cm) of alumina, eluent benzene, the first fraction being collected. Yield 0.34 g (68%), rose-pink prisms, mp 119-120°C (from isooctane). Found: C 59.9; H 4.5; Cl 16.0; N 19.0%. $C_{11}H_{10}ClN_3$. Calculated: C 60.1; H 4.6; Cl 16.2; N 19.1%.

B. To a solution of 0.37 g (2 mmole) of 2,4-dimethylpyrazolo[1,5-a]benzimidazole in 20 ml of dichloromethane was added 0.3 g (2 mmole) of 1-chlorobenzotriazole, and the mixture stirred at 25°C for 30 min. The solvent was then evaporated to dryness, the residue chromatographed on a column (2 × 10 cm) of alumina, eluent benzene, and the fraction with R_f 0.8 was collected. Yield 0.4 g (91%). The compound gave no depression of melting point on admixture with material from method A.

3-Trichloromethyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIIa). To a boiling solution of 5.55 g (0.03 mole) of 2,4-dimethylpyrazolo[1,5-a]benzimidazole in 60 ml of dry xylene was added slowly with stirring 3.3 ml (0.03 mole) of trichloroacetyl chloride. After 1 h, the mixture was cooled, and the solid filtered off to give 8.7 g (86%) of product, pale yellow needles, mp 192-193°C (from alcohol). IR spectrum (chloroform): 1655 cm^{-1} (C=O). Found: C 46.9; H 2.9; Cl 32.0; N 12.4%. $C_{13}H_{10}Cl_3N_3O$. Calculated: C 47.2; H 3.0; Cl 32.2; N 12.7%.

3-Trichloroacetyl-2-ethyl-4-methylpyrazolo[1,5-a]benzimidazole (VIIb) was obtained similarly to (VIIa), yield 80%, pale yellow needles, mp 157-158°C (from alcohol). Found: C 49.2; H 3.6; Cl 31.2% $C_{14}H_{12}Cl_3N_3O$. Calculated: C 48.8; H 3.5; Cl 30.9%.

3-Piperidinoacetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIIIa). A solution of 1.1 g (3 mmole) of the bromoketone (II) and 0.52 ml (6 mmole) of piperidine in 15 ml of dry benzene was boiled for 30 min. The solvent was then removed, and the residue washed with water. Yield 0.9 g (100%), colorless crystals, mp 109-110°C (from isooctane). IR spectrum (chloroform): 1650 cm^{-1} (C=O). Found: C 69.5; H 6.8; N 18.3%. $C_{18}H_{22}N_4O$. Calculated: C 69.7; H 7.1; N 18.0%.

3-Morpholinoacetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (VIIIb) was obtained as for (VIIa), yield quantitative, mp 115-116°C (from heptane). Found 65.2; H 6.5; N 17.7%. $C_{17}H_{20}N_4O_2$. Calculated: C 65.4; H 6.4; N 17.9%.

1,4-Di-(2,4-dimethylpyrazolo[1,5-a]benzimidazol-3-yl)but-2-ene-1,4-dione (IX). A. To a suspension of 0.61 g (2 mmole) of the bromoketone (II) in 10 ml of alcohol was added 1 ml of 20% caustic alkali, and the mixture boiled for 30 min. After cooling, the bright yellow solid which separated was filtered off and washed with water to give 0.35 g (77%) of product, mp 279-280°C (from DMF). IR spectrum: 1635 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 2.65 (3H, s, C–CH_3), 3.95 (3H, s, N–CH_3), 4.58 (1H, s, =CH), 7.25-7.5 ppm (4H, m, arom). Found: C 69.3; H 4.9; N 18.7%. $C_{26}H_{22}N_6O_2$. Calculated: C 69.3; N 4.9; N 18.7%.

B. To a stirred solution of 0.68 (3 mmole) of the ketone (I) in 30 ml of dioxane was added 5 ml of 10% sodium hydroxide, followed by the dropwise addition of a solution of 3 g of iodine and 6 g of potassium iodide in 30 ml of water, initially at 20°C (until a persistent dark color was present), then at 70-80°C. After 20-25 min, a yellow solid began to separate. This was filtered off and washed with water to give 0.37 g (56%) of product. A mixed melting point with the material obtained by method A gave no depression.

2,4-Dimethylpyrazolo[1,5-a]benzimidazole-3-carboxylic acid (X). A suspension of 0.99 g (3 mmole) of the trichloroketone (VIIa) in 15 ml of 5% sodium hydroxide was boiled for 10 min. After cooling, the solution was acidified cautiously with acetic acid to pH 5, and the solid which separated was filtered off and washed with water to give 0.6 g (87%) of product, mp 203-205°C (decomp.) (from butanol). Found: C 63.2; H 5.0; N 18.2%. $C_{12}H_{11}N_3O_2$. Calculated: C 62.9; H 4.8; H 18.3%.

3-Ethoxycarbonyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (XIb). To a solution of sodium ethoxide, obtained from 0.2 g of sodium and 10 ml of absolute ethanol, was added portionwise 0.99 g (3 mmole) of the trichloroketone (VIIa). When the vigorous reaction had subsided, the mixture was boiled for 5 min, cooled, and the solid which separated filtered off (0.53 g). Dilution of the mother liquors with water gave a further 0.18 g of material. Yield 0.71 g (92%), colorless needles, mp 131-132°C (from heptane). IR spectrum (chloroform): 1680 cm^{-1} (C=O). Found: C 65.6; H 5.9; N 16.2%. $C_{14}H_{15}N_3O_2$. Calculated: C 65.3; H 5.9; N 16.3%.

3-Methoxycarbonyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (XIa) was obtained as described for (XIb), yield 93%, colorless crystals, mp 165-166°C (from heptane). Found: C 64.3; H 5.1; N 17.2%. $C_{13}H_{13}N_3O_2$. Calculated: C 64.2; H 5.3; N 17.3%.

2,4-Dimethylpyrazolo[1,5-a]benzimidazole-3-carbohydrazide (XII). A suspension of 0.66 g (2 mmole) of the trichloroketone (VIIa) in 7 ml of hydrazine hydrate was boiled for 2 h, cooled, and the solid filtered off and washed with water, yield 0.48 g (100%), mp 224-225°C (from alcohol). IR spectrum (thin film): 1625 (C=O), 3210, 3320 cm^{-1} (NH_2). Found: C 59.5; H 5.2; N 29.1%. $C_{12}H_{13}N_5O$. Calculated: C 59.2; H 5.3; N 28.9%.

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