945. *Pyrimido*[3,4-a]*benzimidazole: A Novel Ring System*

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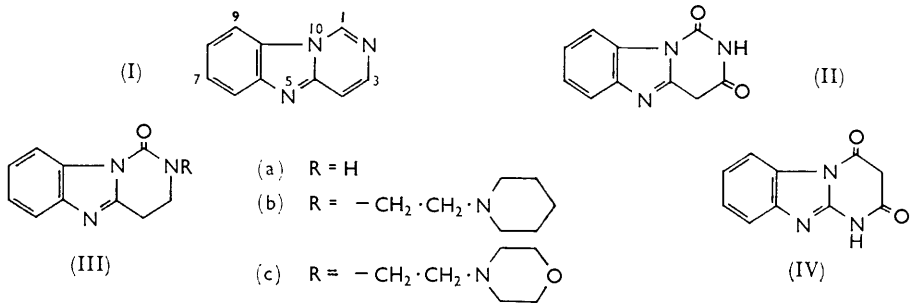
Many polycyclic heterocyclic compounds in which a nitrogen atom bears a dialkylaminoalkyl side-chain possess pharmacological activity and therapeutic usefulness. A recent review [1] indicates both the diversity of ring systems and the uses to which such compounds are put. In a search for such compounds, examples of the system pyrimido[3,4-*a*]benzimidazole (I), hitherto unreported, were prepared, namely pyrimido[3,4-*a*]benzimidazole-1,3(2*H*,4*H*)-dione (II) and 3,4-dihydropyrimido[3,4-*a*]benzimidazol-1(2*H*)-one (IIIa).

Pyrimido[3,4-*a*]benzimidazole-1,3(2*H*,4*H*)-dione was prepared by the catalytic hydrogenation of 1-(*o*-nitrophenyl)barbituric acid (from diethyl malonate and *o*-nitrophenylurea). Cyclisation took place spontaneously between the amino-group thus generated and the carbonyl group at position 6 in the barbituric acid. Cyclisation could have occurred with the carbonyl group at position 2, to give a compound with structure (IV). This structure, however, can be eliminated by an examination of the infrared spectrum of the compound, which shows bands at 1722 and 1750 cm.$^{-1}$, characteristic of diacyl imides (–CO–NH–CO–).

Ethyl [2-(2-benzimidazolyl)ethyl]carbamate was prepared from 2-(2-aminoethyl)-benzimidazole dihydrochloride [2] and diethyl carbonate in the presence of sodium ethoxide.

[1] E. Jucker, *Angew. Chem. Internat. Edn.*, 1963, **3**, 493.
[2] F. Sorm and J. Urban, *Coll. Czech. Chem. Comm.*, 1950, **15**, 196.



The hydrochloride of this carbamate has been reported.[2] Both ethyl [2-(2-benzimidazolyl)ethyl]carbamate and its hydrochloride were converted into 3,4-dihydropyrimido-[3,4-*a*]benzimidazol-1(2*H*)-one, the former by heating at 170°, and the latter by treatment with warm aqueous sodium carbonate solution.

Attempted alkylation (at N-2) of pyrimido[3,4-*a*]benzimidazole-1,3(2*H*,4*H*)-dione with sodamide and dialkylaminoalkyl chlorides yielded only intractable gums, but 3,4-dihydropyrimido[3,4-*a*]benzimidazol-1(2*H*)-one gave 3,4-dihydro-2-(2-piperidinoethyl)- (IIIb), and 3,4-dihydro-2-(2-morpholinoethyl)-pyrimido[3,4-*a*]benzimidazol-1(2*H*)-one (IIIc) on treatment with sodamide and *N*-(2-chloroethyl)piperidine, and *N*-(2-chloroethyl)morpholine, respectively, in dioxan.

Experimental.—1-(o-*Nitrophenyl*)*barbituric acid.* To a solution of sodium (1·27 g., 2 mol.) in dry methanol (40 ml.) were added diethyl malonate (4 g., 1 mol.), and a solution of *o*-nitrophenylurea (5 g., 1 mol.) in warm dry methanol (50 ml.). The solution was heated under reflux, with stirring and exclusion of moisture, on a steam-bath for 6 hr. When cool, the solution was poured into a mixture of water (100 ml.) and concentrated hydrochloric acid (10 ml.). The precipitated solid was collected, washed with water, and crystallised from water to give 1-(o-*nitrophenyl*)*barbituric acid* (3·2 g.) as a yellow microcrystalline powder, m. p. 246—249° (decomp.) (Found: C, 48·2; H, 3·3; N, 16·9. $C_{10}H_7N_3O_5$ requires C, 48·2; H, 2·8; N, 16·7%).

Pyrimido[3,4-a]*benzimidazole*-1,3(2H,4H)-*dione* (II). 1-(*o*-Nitrophenyl)barbituric acid (2 g.) in glacial acetic acid was hydrogenated at atmospheric pressure over 10% palladium–charcoal catalyst; 600 ml. of hydrogen were absorbed (Calc. 540 ml.). The mixture was heated on a steam-bath to dissolve the product, filtered, and the filtrate evaporated to dryness. The residue was crystallised from glacial acetic acid (charcoal) to give the *dione* (0·6 g.) as a brownish-pink microcrystalline solid, m. p. 303—305° (decomp.) in an apparatus preheated to 290° (Found: C, 60·0; H, 3·8; N, 20·3. $C_{10}H_7N_3O_2$ requires C, 59·7; H, 3·5; N, 20·9%).

Ethyl [2-(*2-benzimidazolyl*)*ethyl*]*carbamate.* To a solution of sodium (2·3 g., 4 mol.) in dry ethanol (60 ml.) were added 2-(2-aminoethyl)benzimidazole dihydrochloride (5·85 g., 1 mol.), and diethyl carbonate (2·96 g., 2·5 mol.), and the resultant mixture was stirred, under reflux, on a steam-bath, with exclusion of moisture, for 6 hr., then cooled. The sodium chloride was filtered off and washed with a little ethanol. The combined filtrate and washings were evaporated to dryness. The residue was crystallised from water (charcoal) to give ethyl [2-(2-benzimidazolyl)ethyl]carbamate (2 g.) as short white needles, m. p. 158—161° (Found: C, 61·5; H, 6·9; N, 17·9. $C_{12}H_{15}N_3O_2$ requires C, 61·8; H, 6·5; N, 18·0%).

3,4-*Dihydropyrimido*[3,4-a]*benzimidazol*-1(2H)-*one* (IIIa). (*a*) Ethyl [2-(2-benzimidazolyl)-ethyl]carbamate (1 g.) was heated at 170° in an oil-bath for 75 min. The carbamate melted and the melt then slowly solidified. The crude product was crystallised from ethanol (charcoal) to give 3,4-*dihydropyrimido*[3,4-a]*benzimidazol*-1(2H)-*one* (0·31 g.) as small white flattened needles, m. p. 245—248° (Found: C, 64·4; H, 5·1; N, 22·3. $C_{10}H_9N_3O$ requires C, 64·4; H, 4·9; N, 22·5%).

(*b*) Ethyl [2-(2-benzimidazolyl)ethyl]carbamate hydrochloride (17 g.) was dissolved in warm water (500 ml.) and sodium carbonate (25 g.) was added cautiously with stirring. The liquid, which now contained a bulky precipitate, was boiled for a few minutes and allowed to cool. The solid was collected, washed with water, and dried. Crystallisation from ethanol gave 3,4-dihydropyrimido[3,4-*a*]benzimidazol-1(2*H*)-one (5·3 g.), m. p. and mixed m. p. 245—258°

The identity of the compounds prepared by the two methods was confirmed by a comparison of their infrared spectra.

3,4-*Dihydro*-2-(2-*piperidinoethyl*)*pyrimido*[3,4-a]*benzimidazol*-1(2H)-*one* (IIIb). 3,4-Dihydropyrimido[3,4-*a*]benzimidazol-1(2*H*)-one (3 g., 1 mol.), sodamide (0·7 g., 1·1 mol.), and *N*-(2-chloroethyl)piperidine (2·6 g., 1·1 mol.) in anhydrous dioxan (200 ml.) were heated under reflux, with stirring and exclusion of moisture, until evolution of ammonia ceased, and then cooled. Methanol (20 ml.) was added to destroy unreacted sodamide. The solid was filtered off, and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate and extracted with 2N-hydrochloric acid. The aqueous layer was separated, made basic with 6N-ammonia solution, and the precipitated base isolated with ethyl acetate, dried ($MgSO_4$), and crystallised from light petroleum (b. p. 80—100°) to give **3,4-*dihydro*-2-(2-*piperidinoethyl*)-*pyrimido*[3,4-a]*benzimidazol*-1(2H)-*one*** (1 g.) as irregular off-white crystals, m. p. 81—84° (Found: C, 68·3; H, 7·6; N, 19·0. $C_{17}H_{24}N_4O$ requires C, 68·4; H, 7·4; N, 18·8%).

3,4-*Dihydro*-2-(2-*morpholinoethyl*)*pyrimido*[3,4-a]*benzimidazol*-1(2H)-*one* (IIIc). This compound was prepared in a similar manner to the last from 3,4-dihydropyrimido[3,4-*a*]benzimidazol-1(2*H*)-one (5 g.), sodamide (1·14 g.), and *N*-(2-chloroethyl)morpholine (4·4 g.) in anhydrous dioxan (200 ml.). Crystallisation from light petroleum (b. p. 80—100°) gave **3,4-*dihydro*-2-(2-*morpholinoethyl*)*pyrimido*[3,4-a]*benzimidazol*-1-(2H)-*one*** (2·7 g.) as nacreous flakes, m. p. 116—119° (Found: C, 63·6; H, 6·8; N, 18·6. $C_{16}H_{20}N_4O_2$ requires C, 63·6; H, 7·3; N, 18·5%).

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