A Convenient Preparation of Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones

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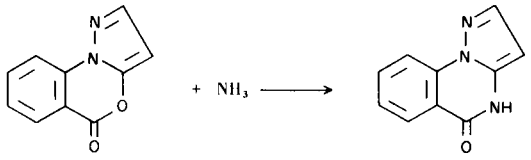
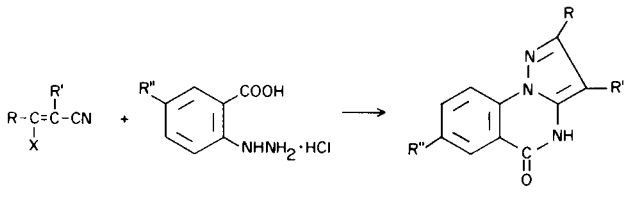
The pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one ring system (I) has not been investigated to any extent. The only reference to these compounds is in a publication by Michaelis (1), who prepared compounds of this type by reaction of the anhydride II with ammonia. The preparation of the anhydride II involved several steps from suitable starting materials.



II I

We have found that compounds of the type I can be prepared conveniently in essentially a one-step reaction starting with *o*-hydrazinobenzoic acid hydrochloride (2) (III, R″=H). Briefly, the method consists of using *o*-hydrazinobenzoic acid hydrochloride as the arylhydrazine in methods that have been used for the preparation of 1-aryl-5-aminopyrazoles. Under the conditions of the reaction, the *o*-carboxylic acid group condenses with the amino group in the 5-position of the pyrazole ring initially formed to give pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones. Thus, *o*-hydrazinobenzoic acid hydrochloride when refluxed with 3-aminocrotononitrile (IV, R=CH_3, R′=H, X=NH_2) in dilute hydrochloric acid solution gave 2-methylpyrazolo-[1,5-*a*]quinazolin-5(4*H*)-one (Va) in 72% yield after recrystallization.



IV III V

X = NH_2, OC_2H_5 or CN

a. R = CH_3, R′ = H, R″ = H
b. R = H, R′ = $COOC_2H_5$, R″ = H
c. R = CH_3, R′ = $COOC_2H_5$, R″ = H
d. R = C_2H_5, R′ = $COOC_2H_5$, R″ = H
e. R and R′ = CN, R″ = H
f. R = CH_3, R′ = H, R″ = Cl

Furthermore, this method permits the synthesis of new derivatives of the pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one system that cannot be synthesized conveniently by Michaelis' method.

Treatment of *o*-hydrazinobenzoic acid hydrochloride with ethyl 2-cyano-3-ethoxyacrylates (IV, R′=$COOC_2H_5$, X=OC_2H_5) gave the corresponding ethyl pyrazolo[1,5-*a*]-quinazolin-5(4*H*)-one-3-carboxylates (Vb, Vc and Vd). One of the esters prepared (*viz* Vb) was saponified to the corresponding acid.

Treatment of *o*-hydrazinobenzoic acid hydrochloride with tetracyanoethylene (3) (IV, R, R′ and X=CN) gave pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-2,3-dicarbonitrile (Ve) in 63% yield.

One substituted *o*-hydrazinobenzoic acid, namely 5-chloro-2-hydrazinobenzoic acid hydrochloride (III, R″=Cl), was also used in this reaction. Treatment of this acid with 3-aminocrotononitrile gave 7-chloro-2-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (Vf) in 57% yield.

EXPERIMENTAL

All melting points are corrected.

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2-Methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)one (Va).

To a solution of 37.72 g. (0.2 mole) of *o*-hydrazinobenzoic acid hydrochloride in 160 ml. of water was added 40 ml. of concentrated hydrochloric acid and then, with stirring, 16.4 g. (0.2 mole) of 3-aminocrotononitrile. The mixture was heated under reflux for 2.5 hours, allowed to cool and was filtered. The solid was washed with water and recrystallized from ethanol. There was obtained 29.35 g. (73%) of matted tan needles melting at 286-288°. Further recrystallization from ethanol gave colorless needles melting at 288-289° (4); uv λ max (ethanol), 225.5 (ϵ = 24,250), 231 (ϵ = 26,000), 258 mμ (ϵ = 22,270); λ max (0.1*N* ethanolic hydrochloric acid), 225 (ϵ = 24,170), 231 (ϵ = 26,000), 258 mμ (ϵ = 22,300); λ max (0.1*N* ethanolic potassium hydroxide), 224 (ϵ = 27,920), 259 (ϵ = 22,460), 282 sl.sh. (ϵ = 7400), 313 (ϵ = 5,000), 321 mμ sl.sh. (ϵ = 5,000); ir (nujol mull) 3100 (NH), 1680 (C=O) cm^{-1}; nmr (DMSO-d_6) δ 2.3 (S, 3, CH_3), 5.8 (S, 1, CH=), 12.1 (S, 1, NH).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.33; H, 4.41; N, 21.20.

Ethyl Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-3-carboxylate (Vb).

A mixture of 9.93 g. (0.05 mole) of *o*-hydrazinobenzoic acid hydrochloride (2), 100 ml. of ethanol, 8.46 g. (0.05 mole) of ethyl 2-cyano-3-ethoxyacrylate and 25 ml. of water was heated on the steam bath for 10 minutes and allowed to stand overnight at room temperature. The mixture was filtered. There was obtained 10.85 g. (85%) of fine colorless needles melting at 200-202°. Recrystallization of a sample from a large volume of 80% ethanol (*ca.* 200 ml./g.) gave material melting at 204-204.5°.

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.58; H, 4.65; N, 16.30.

Ethyl 2-Methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-3-carboxylate (Vc).

A stirred mixture of 9.15 g. (0.05 mole) of ethyl α-cyano-β-ethoxycrotonate, 9.93 g. (0.05 mole) of *o*-hydrazinobenzoic acid hydrochloride, 100 ml. of ethanol and 25 ml. of water was heated under reflux for one hour, allowed to cool at room temperature and was filtered. There was obtained 2.60 g. of material melting at 185-187°. Recrystallization from ethanol gave 2.35 g. of matted colorless needles melting at 193-194°.

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 61.78; H, 4.65; N, 15.66.

Ethyl 2-Cyano-3-ethoxy-2-pentenoate.

A mixture of 36.2 g. (0.32 mole) of ethyl cyanoacetate, 56.4 g. (0.32 mole) of triethylorthopropionate and 75.8 g. (0.74 mole) of acetic anhydride was refluxed for six hours and then concentrated under reduced pressure. The residue was dried in a desiccator over sodium hydroxide and then distilled through an 8-inch vigreux column. There was obtained 17.0 g. of material boiling at 156-158° (13 mm.), which solidified upon standing. Recrystallization from petroleum ether gave colorless prisms melting at 64-66°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.98; H, 7.72; N, 7.15.

Ethyl 2-Ethylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-3-carboxylate (Vd).

A solution of 9.0 g. (0.0455 mole) of ethyl 2-cyano-3-ethoxy-2-pentenoate, 8.6 g. (0.0455 mole) of *o*-hydrazinobenzoic acid hydrochloride, 90 ml. of ethanol and 20 ml. of water was refluxed for 18 hours. The mixture was allowed to cool overnight and the solid was removed by filtration and recrystallized from ethanol. There was obtained 1.80 g. of matted colorless needles melting at 159-160°.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.48; N, 14.95.

Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-3-carboxylic Acid.

A mixture of 4.51 g. (0.01753 mole) of ethyl pyrazolo[1,5-*a*]-quinazolin-5(4*H*)-one-3-carboxylate, 100 ml. of dioxane, 2 g. of sodium hydroxide and 60 ml. of water was heated under reflux for 5 hours and allowed to stand at room temperature overnight. The solid was removed by filtration and the mother liquors were evaporated to dryness. The combined residue and precipitate was dissolved in 100 ml. of water and the solution clarified by filtration through celite. Acidification of the filtrate with acetic acid gave 3.78 g. (93.5%) of material melting at 285° dec.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.47; H, 2.95; N, 18.33.

Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one-2,3-dicarbonitrile (Ve).

A mixture of 9.43 g. (0.05 mole) of *o*-hydrazinobenzoic acid hydrochloride, 6.41 g. (0.05 mole) of tetracyanoethylene, 100 ml. of ethanol and 75 ml. of water was stirred for one hour at room temperature and then stirred and heated under reflux for an additional hour. The mixture was allowed to cool and the solid removed by filtration, 7.40 g. (63%), m.p. > 310°. Recrystallization from dioxane gave yellow prisms possessing the same melting point; ir (nujol mull), 2900 (NH), 2240 and 2230 (–C≡N), 1705 (C=O), cm^{-1}.

Anal. Calcd. for $C_{12}H_5N_5O$: C, 61.28; H, 2.18; N, 29.78. Found: C, 61.12; H, 2.14; N, 29.52.

7-Chloro-2-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (Vf).

To a stirred mixture of 22.31 g. (0.1 mole) of 5-chloro-2-hydrazinobenzoic acid hydrochloride (5), 160 ml. of water and 40 ml. of concentrated hydrochloric acid was added 8.2 g. (0.1 mole) of 3-aminocrotononitrile. The mixture was stirred 30 minutes at room temperature and then refluxed for 5 hours. The mixture was allowed to cool, was filtered and the precipitate washed with water. After recrystallization from ethanol there was obtained 13.1 g. (57%) of colorless matted needles melting at 304-305°; uv λ (ethanol), 203 (ε = 29,200), 222 sl.sh. (ε = 21,300), 228 (ε = 22,700), 264 mμ (ε = 27,650); λ max (0.1*N* ethanolic hydrochloric acid), 203 (ε = 29,000), 222 sl.sh. (ε = 21,300), 227 (ε = 22,500), 264 mμ (ε = 27,450); λ max (0.1*N* ethanolic potassium hydroxide), 225 (ε = 28,850), 239 (ε = 9,200), 266 (ε = 27,100), 291 sl.sh. (ε = 6,200), 328 mμ (ε = 4,250); ir (nujol mull), 3100 (NH), 1690 (C=O), cm^{-1}.

Anal. Calcd. for $C_{11}H_8ClN_3O$: C, 56.55; H, 3.45; Cl, 15.17; N, 17.98. Found: C, 56.86; H, 3.65; Cl, 15.35; N, 18.18.

REFERENCES

(1) A. Michaelis, *Ann.*, 373, 129 (1910).

(2) Obtained from Distillation products Industries, Eastman Organic Chemicals Department.

(3) *cf.* C. L. Dickinson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, 29, 1915 (1964).

(4) Michaelis (*cf.* Reference 1) reported a melting point of 275-276°.

(5) J. S. Morley, *J. Chem. Soc.*, 2280 (1959).

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