easily by the standard methods were so readily hydrolyzed by water that the free furochromones precipitated from the aqueous solutions of their salts almost at once. By treatment with hot alcoholic potassium hydroxide for a short time, the pyridylchromones IIIa and IIIb gave back the corresponding diketones IIa and IIb.

The 2-pyridyl derivative corresponding to visnagin (*i.e.*, IIIa) could be oxidized easily with chromic acid to 6-formyl-7-hydroxy-5-methoxy-2-(3′-pyridyl)-chromone (IV). This reaction, proceeding with the opening of the furan ring and the production of a formylchromone already has been found to occur with visnagin,[3a] khellol[3b] and 5-methoxyfuro-4′,5′,6,7-flavone.[3c]

The pyridylchromones have been found to respond to the usual test for flavones[4]: they give an orange or red color when reduced with magnesium and hydrochloric acid in alcoholic solution.

Experimental[5]

Condensation of Visnaginone (Ia) with Ethyl Nicotinate.—A solution of 6.5 g. of Ia in 30 g. of ethyl nicotinate was treated with 1.6 g. of powdered sodium (prepared under toluene). After the initial reaction has subsided, the mixture was refluxed on a water-bath for 2 hours. It was then left to stand overnight, treated with ice and water and extracted with ether. The aqueous solution, after being freed from ether by a stream of air, was acidified with dilute hydrochloric acid; the crystalline precipitate of **5-nicotinoylaceto-4-methoxy-6-hydroxybenzofuran (IIa)** was filtered off, washed with water and crystallized from dilute ethanol as orange crystals, m.p. 135–136° (red melt), yield 6 g. IIa dissolved in dilute hydrochloric acid and in 4% sodium hydroxide solution, and gave an orange red color with concentrated sulfuric acid; its ferric chloride reaction was brown.

Anal. Calcd. for $C_{17}H_{13}O_5N$: C, 65.6; H, 4.2; N, 4.5. Found: C, 65.4; H, 4.0; N, 4.3.

5-Methoxy-2-(3′-pyridyl)-furo-4′,5′,6,7-chromone (IIIa).—One gram of IIa was refluxed for 30 minutes with a solution prepared by mixing 18 ml. of 92% sulfuric acid with ethanol to make 100 ml. The deep yellow solution thus obtained was cooled, diluted with 100 ml. of water and treated with excess of 20% sodium carbonate solution. The crystalline IIIa which separated out was recrystallized from ethanol as colorless needles, m.p. 226° (brown melt), yield 0.7 g. IIIa was insoluble in cold 4% sodium hydroxide, sparingly soluble in cold ethanol and acetone, and soluble in chloroform and 50% sulfuric acid; in the case of the latter solvent, the free furochromone was reprecipitated on dilution with water. IIIa had a negative ferric chloride reaction and gave an orange-red color on treatment with concentrated sulfuric acid. When magnesium turnings were added to a pale yellow alcoholic solution of IIIa, containing a drop of concentrated hydrochloric acid, as red color was gradually developed.

Anal. Calcd. for $C_{17}H_{11}O_4N$: C, 69.6; H, 3.7; N, 4.8. Found: C, 69.9; H, 3.7; N, 4.5.

The yellow crystalline **hydrochloride of IIIa** was prepared by dissolving the substance in acetone and adding the calculated amount (1 mol.:1 mol.) of 5 *N* hydrochloric acid; the salt which separated out decomposed with evolution of gas above 230°.

IIIa (0.5 g.) was added to a warm solution of 1.2 g. of potassium hydroxide in 10 ml. of alcohol and the mixture was gently warmed to its boiling point and shaken at this temperature for a few minutes until a clear solution was obtained. This was then cooled, diluted with its volume of water and neutralized with dilute acetic acid to give a red precipitate of IIa.

Condensation of Khellinone (Ib) with Ethyl Nicotinate.—Six and one-half grams of khellinone was condensed with ethyl nicotinate in the presence of sodium, using the same procedure and amounts as for the preparation of IIa. **5-Nicotinoylaceto-4,7-dimethoxy-6-hydroxybenzofuran (IIb)** crystallized from dilute ethanol as orange crystals, m.p. 129–130°, yield 5.9 g. IIb was insoluble in water and soluble in dilute hydrochloric acid and 4% sodium hydroxide; it gave a brown ferric chloride reaction and dissolved in concentrated sulfuric acid with a brown-red color.

Anal. Calcd. for $C_{18}H_{15}O_6N$: C, 63.4; H, 4.4; N, 4.1. Found: C, 63.7; H, 4.5; N, 3.9.

5,8-Dimethoxy-2-(3′-pyridyl)-furo-4′,5′,6,7-chromone (IIIb).—One gram of IIb was cyclized to IIIb by using the same procedure as in the cyclization of IIa. The pale yellow needles of IIIb, m.p. 213–214° (brown-red melt), obtained in 65% yield, gave a negative ferric chloride reaction and dissolved in concentrated sulfuric acid with a red color. IIIb was very sparingly soluble in water, moderately soluble in alcohol, and freely soluble in chloroform and glacial acetic acid. The magnesium–hydrochloric acid test, done under the conditions described for IIIa, gave a red color.

Anal. Calcd. for $C_{18}H_{13}O_5N$: C, 66.9; H, 4.0; N, 4.3. Found: C, 67.3; H, 3.9; N, 3.9.

The hydrochloride of IIIb was prepared by the addition of the calculated amount (1 mol.:1 mol.) of 5 *N* hydrochloric acid to a solution of IIIb in acetone, m.p. 233° dec., and the sulfate by recrystallizing IIIb from ethanol containing excess of sulfuric acid, m.p. 250° (red-brown melt). These yellow crystalline salts dissolved in water giving pale yellow solutions from which the free base precipitated spontaneously on keeping for a few minutes.

The conversion of IIIb back to IIb was effected by alcoholic potassium hydroxide as described for IIIa.

Oxidation of IIIa with Chromic Acid.—One gram of IIIa dissolved in 20 ml. of glacial acetic acid was treated with stirring and at room temperature (20°) with 4 ml. of 25% sulfuric acid and 6.6 ml. of 30% sodium dichromate. The mixture warmed up to about 40°, while its color was changing from yellow to deep brown. After standing for 30 minutes, the mixture was diluted with 120 ml. of water and extracted with 50 ml. of chloroform. The chloroform extract then was washed with water and extracted with 20 ml. of 4% sodium hydroxide. The yellow alkaline extract yielded on acidification with dilute acetic acid colorless **6-formyl-7-hydroxy-5-methoxy-2-(3′-pyridyl)-chromone (IV)**, which was filtered off and crystallized from ethanol as hairy yellowish crystals, m.p. 223° (dec., evolution of gas), yield 0.6 g. IV was insoluble in water and dilute acetic acid and sparingly soluble in alcohol and acetone. It gave a red ferric chloride reaction and dissolved in both 4% sodium hydroxide and concentrated sulfuric acid with a yellow color; a deep orange color was produced when an alcoholic solution of IV was mixed with an alcoholic solution of *p*-phenylenediamine. The magnesium–hydrochloric acid test done as with IIIa gave an orange color.

Anal. Calcd. for $C_{15}H_{11}O_5N$: C, 64.7· H, 3.7; N, 4.7. Found: C, 64.9; H, 3.7; N, 4.7.

Oxime of IV.—A mixture of 0.2 g. of IV, 0.2 g. of hydroxylamine hydrochloride, 0.4 g. of sodium acetate and 300 ml. of ethanol was refluxed for one hour and cooled. The crystalline oxime which separated out had m.p. 253° (brown melt) and was very sparingly soluble in alcohol; its ferric chloride reaction was red-brown.

Anal. Calcd. for $C_{15}H_{12}O_5N_2$: N, 9.0. Found: N, 8.7.

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(3) (a) A. Schönberg, N. Badran and N. A. Starkowsky, THIS JOURNAL, **75**, 4992 (1953); (b) **77**, 1019 (1955); (c) **77**, 5390 (1955).

(4) For references to the reaction of flavones with magnesium and hydrochloric acid, see T. A. Geissman and R. O. Clinton, *ibid.*, **68**, 700 (1946).

(5) All melting points are uncorrected. For the ferric chloride reactions, a drop of an aqueous solution of ferric chloride was added to the substance dissolved in 95% ethanol. Elementary microanalyses were made by Drs. Weiler and Strauss, Oxford.

Benzoylcyanamide from Ethyl Benzoylthioncarbamate

BY GLENN S. SKINNER AND H. C. VOGT

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In an attempt to condense N-benzoyl-O-ethylisourea with ethyl malonate in alcoholic sodium ethox-

ide it was found that the substance suffered loss of alcohol to give benzoylcyanamide.

The needed N-benzoyl-O-ethylisourea was prepared by modifications of the methods of Wheeler and Johnson.[1] In the preparation of ethyl benzoylthioncarbamate the reaction with alcohol must be conducted below 25° to avoid mercaptan formation. Temperatures above 70° in the removal of the solvent also lowered the yield. The highest yield of N-benzoyl-O-ethylisourea was obtained when exactly two moles of ammonia were used for each mole of thion ester.

Experimental

Ethyl Benzoylthioncarbamate.—To a stirred mixture of 52.4 g. (0.54 mole) of dry powdered potassium thiocyanate and 38 cc. of toluene was added 70.3 g. (0.50 mole) of benzoyl chloride. The temperature was increased to gentle reflux which was maintained for 24 hours. The mixture was cooled to 15–17° and 35 cc. (0.59 mole) of absolute alcohol was added. After standing 24 hours at this temperature 90.4 g. (80%) of product was obtained by filtration and removal of the solvent under diminished pressure. It crystallized from absolute alcohol in long needles, m.p. 73–74° (lit.[1] 73–74°).

N-Benzoyl-O-ethylisourea.—Five grams (0.024 mole) of ethyl benzoylthioncarbamate was dissolved in 50 cc. of absolute alcohol containing 0.82 g. (0.048 mole) of anhydrous ammonia. Evolution of hydrogen sulfide began at once. After three days at room temperature the alcohol was distilled at atmospheric pressure. The residue then was treated with 50 cc. of water to which had been added 1 cc. of 1% potassium hydroxide solution. The filtered dry product weighed 4.11 g. (89.5%). Long colorless needles were obtained by crystallization from petroleum ether; m.p. 74–75° (lit.[1] 74–75°). Mixed with the starting material the melting point dropped to 45° (lit.[1] 45°).

Benzoylcyanamide.—To a stirred solution of sodium ethoxide prepared from 14 g. (0.60 mole) of sodium and 220 cc. of absolute alcohol was added at room temperature 38.4 g. (0.20 mole) of N-benzoyl-O-ethylisourea. The mixture was warmed slowly to 60° and kept at this temperature for 8 hours. After standing at room temperature the sodium salt of benzoylcyanamide was filtered, dissolved in ice-cold water and converted to benzoylcyanamide by an excess of hydrochloric acid, yield 25.53 g. (87.5%). It was recrystallized by adding petroleum ether to a saturated solution in ether; m.p. 141–142°. It was identical with a sample of the known compound prepared from calcium cyanide (m.p. 141–142°).

Anal. Calcd. for $C_8H_6ON_2$: N, 19.22. Found: N, 19.05.

(1) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **24**, 189 (1900).

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7-*t*-Butyl-2,4-quinazolinedione

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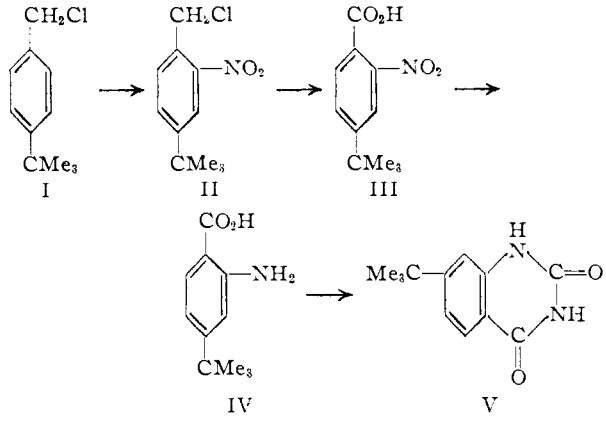
The monochloromethylation of *t*-butylbenzene gives a product which is almost entirely the *para* isomer.[1] This result appeared to afford a suitable synthetic route to 7-*t*-butyl-2,4-quinazolinedione (VI) according to the scheme shown.



The desired product was obtained but in poor over-all yield. The product containing II is evidently a mixture of isomers, since from the oxidation product there were isolated III and the known 4-*t*-butyl-3-nitrobenzoic acid. This oxidation was the most difficult step and succeeded only after preheating II with potassium hydroxide solution followed by long oxidation with permanganate.

The nitro acid III was reduced smoothly. The amino acid IV was insoluble in dilute hydrochloric acid and was unsuited for conversion to V through the ureide. The amino acid thereupon was fused with urea to yield V since 2,4-quinazolinedione had been made in a similar manner from anthranilic acid.[2]

7-*t*-Butyl-2,4-quinazolinedione[3] showed no hypnotic activity. The acute intraperitoneal toxicity LD-50 in mice is 421 ± 38.4 mg./kg. The compound is inactive against influenza virus PR8 *in ovo*. It is inactive against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Brucella abortus, Proteus vulgaris, Hemophilus pertussis, Microsporum audouini, Trichophyton mentagrophytes, Aspergillus niger, Candida albicans* and *Blastomyces dermatitidis*. It does inhibit *Mycobacterium tuberculosis in vitro* if more than 400 micromolar in dimethylformamide.

Experimental

3-*t*-Butyl-6-chloromethylnitrobenzene (II).—The procedure for the nitration[4] of *t*-butylbenzene was used. From 400 g. (2.195 moles) of I, 195 g. (2.195 moles) of nitric acid (d. 1.42) and 237 cc. of sulfuric acid (d. 1.84) there was obtained 316 g. of reddish oil, b.p. 133–140° (1.25 mm.), $n^{25}D$ 1.5433. The analytical sample had b.p. 117–119° (0.5 mm.), $n^{25}D$ 1.5431, d^{25}_4 1.1644.

Anal. Calcd. for $C_{11}H_{14}O_2NCl$: N, 6.15; Cl, 15.57; M_D 61.34. Found: N, 5.94; Cl, 15.84; M_D 61.64.

4-*t*-Butyl-2-nitrobenzoic Acid (III).—A mixture of the above product II (25 g., 0.11 mole), 62.5 cc. of 10% potassium hydroxide solution and 125 cc. of water was stirred and refluxed for one hour. More of the potassium hydroxide solution (75 cc.) and 24.2 g. (0.153 mole) of potassium permanganate were added dropwise during 40 minutes while the mixture was stirred and refluxed. The stirring and refluxing were continued for 13 hours. Refluxing 20 to 37 hours did not affect the yield and the product became dark in color. The excess of permanganate was destroyed with methanol. The hot mixture was filtered through Super-cel and the cake was washed three times with boiling water. The cold alkaline filtrate was extracted with benzene. The water layer was concentrated to about 200 cc. by distillation under diminished pressure. The ice-cold concentrate was acidified with hydrochloric acid to give an oily product which solidified after collection in ether and removal of the ether under diminished pressure. To the hot filtered solution in benzene was added hexane to incipient cloudiness. On standing large crystals formed. The product III had m.p.

(1) G. S. Skinner, J. A. Gladner and R. F. Heitmiller, THIS JOURNAL, **73**, 2330 (1951).

(2) M. T. Bogert and G. Scatchard, *ibid.*, **41**, 2052 (1919).

(3) Pharmacological tests by Sharp and Dohme, West Point, Penna.

(4) D. Craig, THIS JOURNAL, **57**, 195 (1935).