nitrotrifluoromethyldiphenyl sulfone isomer (IIa'), which had been isolated in the process of the preparation of sulfone IIa, was subjected to reduction by the stannous chloride procedure. From 500 mg. (1.1 mmoles) of IIa' there was obtained 290 mg. (67%) of yellow, granular crystals, m.p. 236–237°.

Anal. Calcd. for $C_{14}H_{10}F_6N_2O_2S$: C, 43.75; H, 2.62; S 8.34. Found: C, 43.78; H, 2.62; S, 8.59.

Acknowledgment. We wish to express our appreciation to Dr. Ewald Rohrmann, Dr. W. S. Boniece, and Mr. F. Streightoff of the Lilly Research Laboratories, Indianapolis, Ind., for the chemotherapy screening results reported in this article. We also wish to thank Dr. John D. Roberts for a stimulating discussion in regard to the oxidation of sulfides.

PULLMAN, WASH.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

1,2,2-Triarylethylenes Substituted with Higher Alkyl Groups

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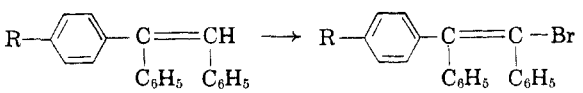
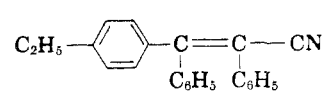
A number of 1-bromo- and 1-cyano-1,2,2-triarylethylenes, bearing higher alkyl groups, and possessing only a weak estrogenic activity, have been synthesized for biological investigation as potential chemical inhibitors of the anterior pituitary secretions.

1,2,-Triarylethylenes, especially those bearing a halogen or a cyano substituent in the ethylene bridge, form a biologically interesting group comprising several substances of remarkably high estrogenic potency (as for instance, 1-bromo- and 1-cyano-1,2,2-triphenylethylene,[1] 1-bromo-1-phenyl-2,2-di(4-ethoxyphenyl)ethylene, 1-chloro-1,2,2-trianisylethylene,[2] etc.) These estrogenic 1,2,2-triarylethylenes are also chemical inhibitors of the secretions of the anterior pituitary,[3] especially of the somatotrophic hormone, and some have found practical use in the chemotherapy of cancer[4]; in this series, the estrogenic activity is known to decrease sharply with the introduction of alkyl substituents in *para-* positions.[1] Now, it has recently been found that some 1,2,-triarylethylenes bearing higher alkyl groups, such as 1-bromo-1,2-diphenyl-2-(4-*n*-butylphenyl)ethylene (III), are good inhibitors of growth in mice, while displaying only a negligible estrogenic activity[5]; compound III inhibits also the effect of gonadotrophin on the ovaries in female mice, but has little action on the development of the testicles in male animals. These observations led us to synthesize, for biological evaluation in this domain, a number of homologs and analogs of compound (III) bearing higher alkyl groups or other bulky substituents in the benzene rings.

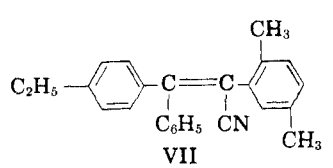


I; R = *n*-C_5H_{11}
II; R = *n*-C_6H_{13}
III; R = *n*-C_4H_9
IV; R = *n*-C_5H_{11}
V; R = *n*-C_6H_{13}

The reaction of benzylmagnesium chloride on 4-*n*-amyl- and 4-*n*-hexylbenzophenone yielded tertiary alcohols which were directly dehydrated with formic acid to 1,2-diphenyl-2-(4-*n*-amylphenyl)- (I) and 1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (II), respectively; these liquid hydrocarbons readily underwent bromination to give 1-bromo-1,2-diphenyl-2-(4-*n*-amylphenyl)- (IV) and 1-bromo-1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (V), both of which were well crystallized compounds. In these bromination reactions, it was observed that only one of the two possible stereoisomeric ethylenes was formed; on the other hand, the sodium amide–catalyzed condensation of 4-ethylbenzophenone with benzyl cyanide[6] yielded 1,2-diphenyl-2-(4-ethylphenyl)acrylonitrile (VI) in both stereoisomeric forms.



VI



VII

(1) Lacassagne, Buu-Hoï, Corre, Lecocq, and Royer, *Experientia*, **2**, 70 (1946); Robson, Schönberg, and Tadros, *Nature*, **150**, 22 (1942).

(2) Thompson and Werner, *Proc. Soc. Exp. Biol. Med.*, **77**, 484 (1951).

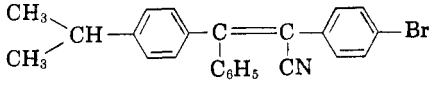
(3) Zondek, *Lancet*, **1**, 10 (1936); **2**, 842 (1936); Noble, J., *Physiol.*, **94**, 177 (1938); *J. Endocrinol.*, **1**, 216 (1939).

(4) Watkinson, Delory, King, and Haddow, *Brit. Med. J.*, **2**, 492 (1944); Berger and Buu-Hoï, *Lancet*, **2**, 172 (1947).

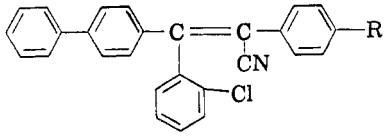
(5) Buu-Hoï, Xuong, and Beauvillain, *Experientia*, in press.

(6) Bodroux, *Bull. soc. chim. France*, **9**, 758 (1911); Buu-Hoï and Lecocq, *J. Chem. Soc.*, 641 (1947); Buu-Hoï, Lecocq, and Hoán, *Bull. soc. chim. France*, **14**, 816 (1947); Buu-Hoï, Hoán, Lecocq, and Declercq, *Rec. trav. chim.*, **67**, 796 (1948).

The isolation of two stereoisomeric compounds is not possible in all the Bodroux syntheses of 1,2,2-triarylacrylonitriles. For instance, the condensation of 4-ethylbenzophenone with 2,5-dimethylbenzyl cyanide yielded only one 1-(2,5-dimethylphenyl)-2-phenyl-2-(4-ethylphenyl)acrylonitrile (VII); similarly, in the reaction of 4-isopropylbenzophenone with *p*-bromobenzyl cyanide, only one 1-(4-bromophenyl)-2-phenyl-2-(4-isopropylphenyl)acrylonitrile (VIII) could be isolated.



VIII



IX; R = Br
X; R = Cl

Other 1,2,2-triarylacrylonitriles with bulky substituents were prepared by the Bodroux condensation of 2-chloro-4′-phenylbenzophenone with *p*-bromo- and *p*-chlorobenzyl cyanide, which afforded 1-(4-bromophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (IX) and 1-(4-chlorophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (X), respectively.

The estrogenic activity of all these new compounds, determined by means of the Allen-Doisy test in rats, was found to be of a very low order; the other biological properties are being investigated.

EXPERIMENTAL

4-n-Amylbenzophenone. To a water-cooled solution of 23 g. of *n*-amylbenzene (prepared from *n*-valerophenone by Kishner-Wolff reduction, using Huang-Minlon's technique[7]) and 32 g. of benzyl chloride in 200 ml. of dry carbon disulfide, 36 g. of finely powdered aluminum chloride was added in small portions with stirring, and the mixture left overnight at room temperature. After decomposition with ice, the organic layer was washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, and the solvent was distilled. Vacuum-fractionation of the residue gave 23 g. of a pale yellow oil, b.p. 232°/18 mm., n_D^{23} 1.5708.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.8; H, 8.0.

The corresponding *2,4-dinitrophenylhydrazone* crystallized from ethanol in shiny yellow leaflets, m.p. 160°.

Anal. Calcd. for $C_{24}H_{24}N_4O_4$: N, 12.9. Found: N, 12.6.

1,2-Diphenyl-2-(4-n-amylphenyl)ethylene (I). To an ice-cooled Grignard solution prepared from 3 g. of magnesium and 12 g. of benzyl chloride in anhydrous ether, 15 g. of the foregoing ketone was added in small portions with stirring, and the mixture refluxed for 10 min. on the water bath. After treatment with an ice-cooled dilute aqueous solution of sulfuric acid, the organic layer was washed with water, the ether was distilled off, and the oily residue was added to 15 g. of pure formic acid. The mixture was then refluxed for 5 min., and water was added after cooling. The dehydration product was taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. Yield: 17 g. of a pale yellow, viscous oil, b.p. 271–272°/25 mm., n_D^{22} 1.6233.

Anal. Calcd. for $C_{25}H_{26}$: C, 92.0; H, 8.0. Found: C, 92.1; H, 8.1.

1-Bromo-1,2-diphenyl-2-(4-n-amylphenyl)ethylene (IV). Bromination in acetic acid medium and in the cold was unsatisfactory, and the following procedure was adopted. To a solution of 6.5 g. of the foregoing ethylene in 30 ml. of dry chloroform, 3.2 g. of bromine (in 20 ml. of chloroform) was added in small portions with stirring, and the mixture heated for 2 hr. at 50–60° on the water bath. The residue from evaporation of the solvent was washed with water and recrystallized twice from acetic acid or ethanol, giving fine colorless prisms, m.p. 100°. Yield: 6 g. No isomer was found in the mother liquors.

Anal. Calcd. for $C_{25}H_{25}Br$: C, 74.1; H, 6.2. Found: C, 74.2; H, 6.0.

4-n-Hexylbenzophenone. Prepared, as for the lower homolog, from 65 g. of *n*-hexylbenzene, 75 g. of benzoyl chloride, and 85 g. of aluminum chloride in carbon disulfide medium, this *ketone* was a pale yellow, viscous oil, b.p. 239–240°/18 mm., n_D^{24} 1.5621. Yield: 83 g.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.6; H, 8.2.

The *2,4-dinitrophenylhydrazone* crystallized from ethanol in shiny yellow leaflets, m.p. 154°.

Anal. Calcd. for $C_{25}H_{26}N_4O_4$: N, 12.6. Found: N, 12.4.

1,2-Diphenyl-2-(4-n-hexylphenyl)ethylene (II). Obtained from 26 g. of the foregoing ketone and an ethereal solution of benzyl magnesium chloride prepared from 20 g. of benzyl chloride and 4 g. of magnesium, this *hydrocarbon* was a pale yellow, viscous oil, b.p. 280–281°/20 mm., n_D^{24} 1.6109. Yield: 30 g.

Anal. Calcd. for $C_{26}H_{28}$: C, 91.7; H, 8.3. Found: C, 91.8; H, 8.2.

1-Bromo-1,2-diphenyl-2-(4-n-hexylphenyl)ethylene (V). Prepared from 10.2 g. of the foregoing ethylene and 4.8 g. of bromine in chloroform, this *compound* crystallized from ethanol in fine colorless prisms, m.p. 93°.

Anal. Calcd. for $C_{26}H_{27}Br$: C, 74.5; H, 6.4. Found: C, 74.2; H, 6.3.

1,2-Diphenyl-2-(4-ethylphenyl)acrylonitriles (VI). To a solution of 12 g. of benzyl cyanide in 250 ml. of anhydrous ether, 8 g. of finely powdered sodium amide was added in small portions, and the mixture refluxed for 15 min. on the water bath. After cooling, 25 g. of 4-ethylbenzophenone was added portionwise, and the mixture refluxed for six more hours. After decomposition with ice and acidification with acetic acid, the ethereal layer was washed with water and dried over sodium sulfate. The solvent was distilled off and the residue vacuum-fractionated. The portion boiling at 275°/18 mm. yielded on recrystallization from acetic acid the *first isomer*, in the form of fine, shiny, colorless prisms, m.p. 130°. Yield: 9 g.

Anal. Calcd. for $C_{23}H_{19}N$: C, 89.3; H, 6.2. Found: C, 89.2; H, 6.4.

Concentration of the mother liquors gave an oil which solidified on prolonged standing; repeated crystallization from acetic acid afforded the *isomeric compound* (1 g.) in the form of fine colorless prisms, m.p. 111°. The melting point of this compound was depressed on admixture with the foregoing isomer. Both isomers gave a violet coloration with hot sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}N$: C, 89.3; H, 6.2. Found: C, 89.5; H, 6.3.

1-(2,5-Dimethylphenyl)-2-phenyl-2-(4-ethylphenyl)acrylonitrile (VII). This compound was similarly prepared from 5 g. of 4-ethylbenzophenone, 5.5 g. of 2,5-dimethylbenzyl cyanide, and 3 g. of sodium amide in anhydrous ether. The portion boiling at 280°/15 mm. yielded on recrystallization

(7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2478 (1946).

from acetic acid only one isomer, in the form of fine colorless prisms, m.p. 138°, giving a violet coloration in hot sulfuric acid. Yield: 3.5 g.

Anal. Calcd. for $C_{25}H_{23}N$: C, 89.0; H, 6.9; N, 4.2. Found: C, 89.2; H, 6.6; N, 4.0.

1-(4-Bromophenyl)-2-phenyl-2-(4-isopropylphenyl)acrylonitrile (VIII). Prepared from 9 g. of 4-isopropylbenzophenone, 9.5 g. of 4-bromobenzyl cyanide, and 5 g. of sodium amide, this product, b.p. 298–300°/13 mm., crystallized from acetic acid in fine colorless prisms, m.p. 148°.

Anal. Calcd. for $C_{24}H_{20}BrN$: C, 71.6; H, 5.0; N, 3.5. Found: C, 71.3; H, 5.0; N, 3.3.

1-(4-Bromophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (IX). Prepared from 8 g. of 2-chloro-4′-phenylbenzophenone, 8 g. of 4-bromobenzyl cyanide, and 5 g. of sodium amide, this product crystallized from acetic acid in fine colorless needles, m.p. 210°.

Anal. Calcd. for $C_{27}H_{17}BrClN$: C, 68.9; H, 3.6; N, 3.0. Found: C, 68.6; H, 3.4; N, 2.8.

1-(4-Chlorophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (X). This compound was prepared from 10 g. of 2-chloro-4′-phenylbenzophenone, 9 g. of 4-chlorobenzyl cyanide, and 4.2 g. of sodium amide; the portion boiling at 325–328°/13 mm. crystallized from acetic acid in colorless leaflets, m.p. 201°, giving a violet coloration in hot sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}Cl_2N$: C, 76.1; H, 4.0; N, 3.3. Found: C, 75.8; H, 3.8; N, 3.0.

PARIS (VE), FRANCE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, M.R. SCIENCE INSTITUTE, GUJARAT COLLEGE]

Chalcones and Related Compounds Derived from 2-Hydroxy-5-acetaminoacetophenone II. Flavones and Flavonols

A. A. RAVAL AND N. M. SHAH[1]

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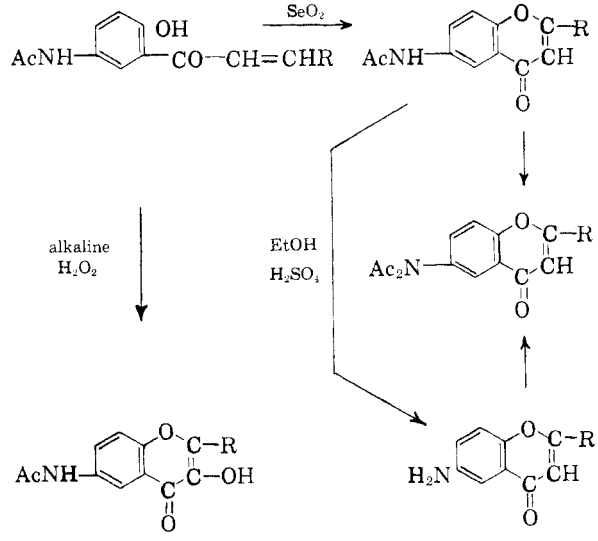
The selenium dioxide oxidation and Algar-Flynn oxidation of some acetaminochalcones derived from 2-hydroxy-5-acetaminoacetophenone have been studied. 6-Acetaminoflavones and flavonols have been synthesized. The 6-acetaminoflavones have been deacetylated by means of ethanolic sulfuric acid, the corresponding 6-aminoflavones being obtained.

In a previous paper[2], the authors have described various chalcones derived from 2-hydroxy-5-acetaminoacetophenone by condensing it with various aldehydes and the chalcones obtained have been cyclized to the corresponding 6-aminoflavanones. The work has now been extended to the synthesis of other heterocyclic compounds, and the synthesis of 6-aminoflavones and 6-acetaminoflavanols from the above chalcones is described in this paper.

When the acetaminochalcones were subjected to selenium dioxide oxidation,[3] 6-acetaminoflavones were obtained, which on deacetylation by ethanolic sulfuric acid, gave the corresponding 6-aminoflavones.

The chalcones were then subjected to Algar-Flynn oxidation[4] using alkaline hydrogen peroxide. Under these conditions, the corresponding 6-acetaminoflavonols were obtained.

Neither selenium dioxide nor Algar-Flynn oxidation of 2,2′-dihydroxy-5′-acetaminochalcone succeeded.



R = C_6H_5; *p*-$C_6H_4OCH_3$; 3,4-$C_6H_3(CH_2O_2)$; *m*-C_6H_4OH.

EXPERIMENTAL

6-Acetaminoflavone. A mixture of 2′-hydroxy-5′-acetaminochalcone (0.5 g.) and selenium dioxide (0.5 g.) in dry isoamyl alcohol (15 ml.) was refluxed on an oil bath at 160–170° for 12 hr. The reaction mixture was then filtered while hot to remove precipitated selenium, and the filtrate was steam-distilled to remove isoamyl alcohol. A dark brown solid, along with some pasty mass, separated; this was filtered, dried, and extracted with benzene; the solid obtained after the removal of benzene was recrystallized twice from ethanol, producing yellowish brown needles, m.p. 174°. Yield, 0.3 g.

Anal. Calcd. for $C_{17}H_{13}O_3N$: C, 73.12; H, 4.66; N, 5.02. Found: C, 73.05; H, 4.47; N, 4.48.

It is soluble in ethanol, acetic acid, benzene, and chloroform. It gives greenish fluorescence with concentrated H_2SO_4. It does not give the $FeCl_3$ color test. It is insoluble in dilute alkali and dilute hydrochloric acid.

The *diacetyl* derivative prepared by the acetic anhydride-

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(3) K. Venkataraman *et al.*, *J. Chem. Soc.*, 866 (1935); 569 (1936).

(4) J. Algar and J. Flynn, *Proc. Roy. Irish Acad.*, **B 42**, 1 (1934).