[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

# The Synthesis of Some Fluorene Derivatives[1]

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In work intended to ultimately yield fluorene analogs of Amidone, 9-carbethoxyfluorene was alkylated with several dialkyl aminoalkyl halides. Reaction of the resultant alkylation products with ethylmagnesium bromide reduced the carbethoxy group to an aldehyde group and the mechanism of this reduction is discussed. Alkaline saponification of the same alkylation products was accompanied by decarboxylation to the 9-dialkylaminoalkylfluorenes which were prepared more readily by direct alkylation of fluorene. These latter substances resisted acylation. 9-Ethoxalylfluorene was alkylated (on oxygen) by dialkylaminoalkyl halides with difficulty and acylation of fluorene also proceeded in poor yield. 9-(β-Dimethylaminoethyl)-9-cyanofluorene underwent loss of the cyano group on reaction with ethylmagnesium bromide at 120°. The mechanism of this base-induced elimination is discussed and there are correlated a number of diverse instances of the cleavage of carbon–carbon bonds which are properly viewed as examples of the SN2 concerted displacement reaction.

Some years ago we, in common with other workers,[2a-5] undertook the synthesis of Amidone analogs in which the two phenyl groups were *ortho*-linked in a fluorene ring system. We did not obtain the Amidone analog, which has subsequently been described by Ginsburg and Baizer[4] and by Shapiro,[5] but we did prepare a number of hitherto undescribed fluorene derivatives. Certain reactions of some of these derivatives seem worth recording.

In our first approach we envisaged the alkylation of 9-carbethoxyfluorene with several dialkylaminoalkyl halides, as had been done by Bockmühl and Ehrhart,[6] followed by conversion of the carbethoxy group to a propionyl group by an ethyl Grignard reagent. No particular difficulty was encountered in the alkylation of 9-carbethoxyfluorene with β-dimethylaminoethyl chloride, γ-dimethylaminopropyl chloride and β-dimethylaminopropyl chloride to give the aminoalkyl esters I, II and III, respectively. We made no attempt to prove the structure of III (or any of the other β-dimethylaminopropyl derivatives herein reported) but, because Shapiro[5] found that alkylation of 9-cyanofluorene with either β-dimethylaminopropyl chloride or α-methyl-β-dimethylaminoethyl chloride gave only the β-dimethylaminopropyl alkylated product, we do not believe it likely that our product has the isomeric structure. The reaction of I with ethylmagnesium bromide was run a number of times; in about half of the runs only starting material was obtained from the reaction mixture and in the other runs the product was a mixture of starting material and up to 20% of a different substance which did not give a 2,4-dinitrophenylhydrazone and which, from its percentage composition and boiling point, could only be either the aldehyde IV or the corresponding primary alcohol, formed by reduction of the carbethoxy group by the Grignard reagent. Analogous results were obtained with III and ethylmagnesium bromide. We recently have submitted compounds IV and V to infrared analysis[7] and have obtained confirmation of their structures as the carbonyl compounds: neither compound showed any band in the 2.8–3.2 μ region characteristic of O–H stretching, while IV had a strong band at 5.80 μ and V had a similar one at 5.82 μ in the carbonyl region. Other instances of hindered carbonyl compounds which did not give carbonyl derivatives and could be identified only by their infrared spectra have been reported in the literature,[8] although it is possible that in the present case cyclic dipolar carbinolamine formation between the amine and carbonyl groups could mask the nature of the latter; if this were so, it is problematical whether we would have obtained the strong carbonyl bands in the spectra.

As chemical proof of the structure of these aldehydes one of them, IV, was treated with alkaline silver oxide, which it reduced. Either the intermediate 9-carboxy-9-(β-dimethylaminoethyl)-fluorene underwent decarboxylation during working up of the reaction mixture (see second paragraph below and reference 14), or the alkali effected a base-induced elimination of the formyl group by the mechanism suggested in the Discussion and the produced formic acid caused reduction of the silver oxide. One cannot decide between these two routes, both of which would lead to the product isolated, 9-(β-dimethylaminoethyl)-fluorene (XI), although the experiment did serve to differentiate IV from the corresponding alcohol which would not have been oxidized or suffered elimination under these conditions.

Although we do not know of examples of reduction of an ester to an aldehyde by a Grignard reagent, there is no reason to suppose that a highly hindered ester could not be so reduced since analogous reductions of nitriles,[9] ketones,[10] acid

(1) Paper No. 27 presented before the Division of Medicinal Chemistry, 123rd American Chemical Society Meeting, Los Angeles, California, March 17, 1953; page 15L of meeting Abstracts.

(2) (a) F. F. Blicke and A. J. Zambito, paper No. 5 presented before the Division of Medicinal Chemistry, 111th American Chemical Society Meeting, Atlantic City, N. J., April 16, 1947; page 3K of meeting Abstracts; (b) G. M. Badger, J. W. Cook and F. Schwartz, *J. Chem. Soc.*, 117 (1952).

(3) B. O. Melander, B. Sundbeck and H. C. Willstaedt (to Aktiebolaget Pharmacia), Swedish Patent 128,376, June 6, 1950.

(4) D. Ginsburg and M. M. Baizer, THIS JOURNAL, **71**, 1500 (1949).

(5) D. Shapiro, *J. Org. Chem.*, **14**, 839 (1949).

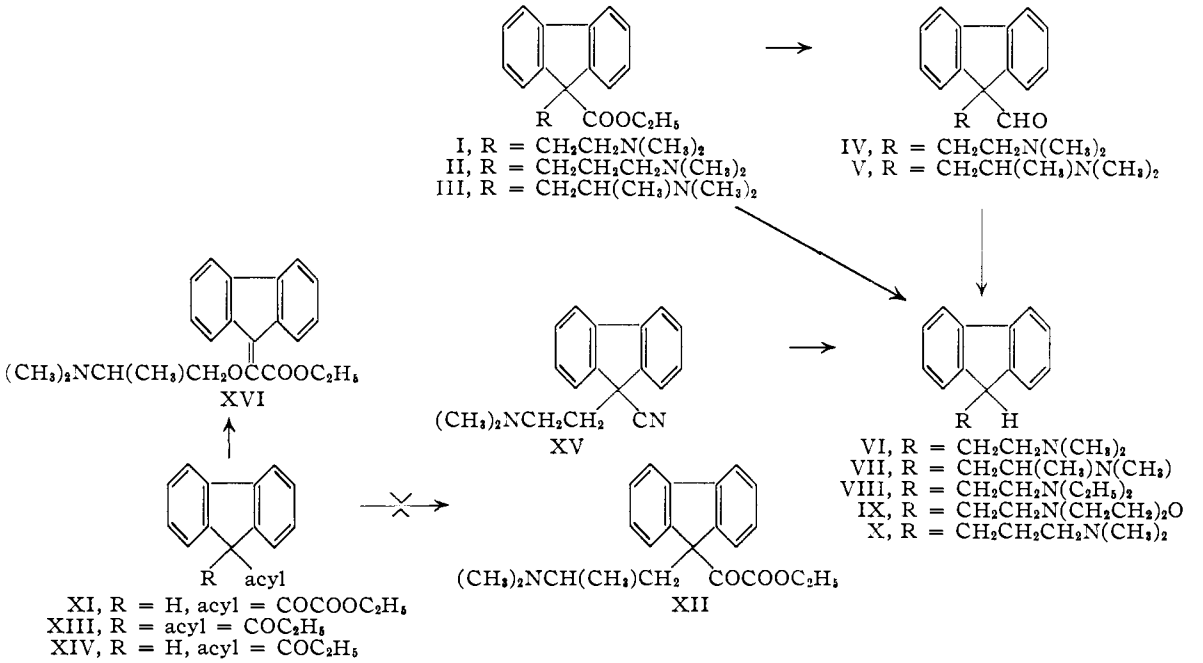
(6) M. Bockmühl and G. Ehrhart (to Winthrop Chemical Company, Inc.), U. S. Patent 2,230,774, Feb. 4, 1941; later published by M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1949).

(7) The substances were run as Nujol mulls, using a Perkin–Elmer model 21 double beam recording infrared spectrophotometer.

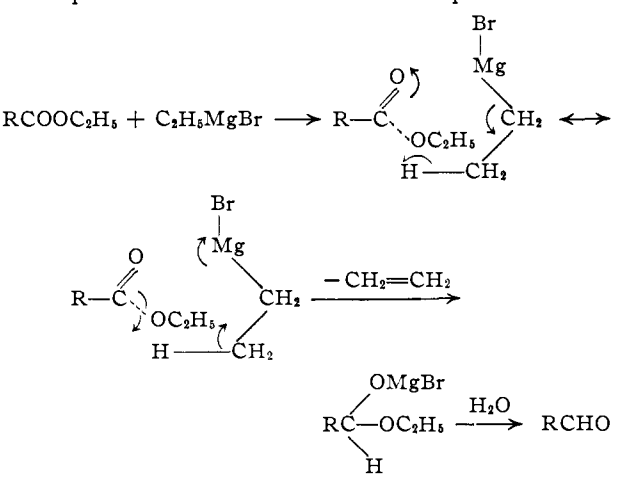
(8) M. S. Newman and W. L. Mosby, THIS JOURNAL, **73**, 3738 (1951); E. C. Horning and A. F. Finelli, *ibid.*, **73**, 3741 (1951); and J. A. Berson, *ibid.*, **74**, 5175 (1952).

(9) H. S. Mosher and W. T. Mooney, *ibid.*, **73**, 3948 (1951). See also reference 2 therein.

(10) H. S. Mosher and E. LaCombe, *ibid.*, **72**, 3994 (1950). See also reference 8 therein. H. S. Mosher and W. M. Foley, paper No. 161 presented before the Division of Organic Chemistry, 118th American Chemical Society Meeting, Chicago, Ill., Sept. 3–8, 1950; page 101N of meeting Abstracts.




chlorides[11] and aldehydes[11] are well-established, albeit not by ethylmagnesium bromide.[12] The mechanism of reduction by a Grignard reagent involves[9,10,13] an internal cyclic rearrangement of a complex which in our cases can be represented as




After it was apparent that the esters I and III underwent reduction rather than addition by ethylmagnesium bromide, it was decided to seek the desired ketones by acylation of the 9-dialkylaminoalkylfluorenes. The latter compounds were available from the alkaline hydrolysis of the esters we had at hand, since the mesomeric stabilization of the 9-fluorenyl anion provided the driving force for the SE1 decarboxylation of the 9-fluorenyl carboxylate anion, as we demonstrated with III.[14] However, we thought it best to prepare the substances directly from fluorene, rather than *via* the esters. Accordingly, the 9-dialkylaminoalkylfluorenes VI–X were prepared, in fair yield, by the sodamide alkylation of fluorene with the appropriate dialkylaminoalkyl chlorides. However, attempts to acylate VI with propionyl chloride by means of either butyllithium or sodamide gave back unchanged starting material so this approach was abandoned.

We next turned to the route consisting of acylating fluorene first and introducing the dialkylaminoalkyl group last. 9-Ethoxalylfluorene (XI) could not be alkylated with γ-dimethylaminopropyl chloride; alkylation with β-dimethylaminopropyl chloride was accomplished, but in poor yield.

We originally considered the alkylation product of XI to be XII but upon being reminded that O-alkylation was sometimes obtained on alkylation of somewhat similar ketones, we looked for and found in the literature a number of such instances[15] and then submitted our alkylation product to infrared analysis in both the sodium chloride and calcium fluoride regions. The spectrum did not resemble that of pyruvic acid or its ethyl ester, which have a broad band from 5.70 to 5.90 μ, but did indicate a structure having a single but conjugated ester group, a strongly hindered car-

(11) F. C. Whitmore, J. S. Whitaker, W. A. Mosher, O. N. Breivik, W. R. Wheeler, C. S. Miner, Jr., L. H. Sutherland, R. B. Wagner, T. W. Clapper, C. E. Lewis, A. R. Lux and A. H. Popkin, THIS JOURNAL, **63**, 643 (1941). Earlier references also are given to the Grignard reduction of both acid chlorides and aldehydes.

(12) Reported examples of reduction by an ethyl Grignard reagent are by W. A. Mosher and L. J. Prucino, paper No. 13 in the Organic Section of the Abstracts of the 4th Meeting in Miniature, Philadelphia, Pa., January 18, 1951, who found that ethylmagnesium bromide gave 95% reduction of benzopinacolone to the corresponding secondary alcohol; by B. F. Landrum and C. T. Lester, THIS JOURNAL, **73**, 4954 (1952); and F. C. Whitmore, *et al.*, ref. 11.

(13) C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951). Also see footnote 2 therein.

(14) W. Wislicenus and W. Mocker, *Ber.*, **46**, 2772 (1913), showed that 9-alkyl-9-carbethoxyfluorenes were decarboxylated on alkaline saponification if the alkyl group was allyl, benzyl, phenacyl and the like.

(15) N. Sperber, R. Fricano and D. Papa, THIS JOURNAL, **72**, 3068 (1950); W. von E. Doering and S. J. Rhoads, *ibid.*, **73**, 3082 (1951); J. Matti and P. Reynaud, *Bull. soc. chim. Mem.*, [5] **18**, 33 (1951); J. C. Sheehan and C. E. Mumaw, THIS JOURNAL, **72**, 2127 (1950); H. E. Zaugg, M. Freifelder and B. W. Horrom, *J. Org. Chem.*, **15**, 1197 (1950); A. G. Stoll and C. J. Morel, *Helv. Chim. Acta*, **34**, 1937 (1951).

bon–carbon double band and an additional ether band, agreeing with a sharp band at 5.80 $\mu$, a very weak band around 6.00 $\mu$ and an intense broad band at 8.00 $\mu$. It thus is obvious that XI underwent O-alkylation to yield structure XVI.

Acylation of fluorenyllithium with propionyl chloride was effected in only 10% yield to give either the dipropionyl derivative XIII, at room temperature, or the monopropionyl derivative XIV, at reflux temperature. Because of the low yields attendant to these reactions this approach, too, was abandoned.

The position of the two acyl groups in XIII does not seem open to question because it yielded a mono-2,4-dinitrophenylhydrazone, which an isomeric propionyloxypropylidene derivative analogous to XVI could not have done. Furthermore, Greenhow, White and McNeil[16] have recently prepared the latter compound from propionyl chloride and 9-fluorenyl *sodium* and reported it to melt some 10 degrees lower than we found for XIII. These authors have also reviewed the literature on this acylation and concluded that condensation of 9-fluorenyl *lithium* with acid chlorides does indeed yield the 9,9-diacyl derivatives.

Our final approach to the desired compounds was analogous to that successfully used by Ginsburg and Baizer,[4] by Shapiro[5] and by Badger and coworkers.[2] 9-Cyanofluorene was satisfactorily alkylated by $\beta$-dimethylaminoethyl chloride to give the cyano amine XV. However, when XV was treated with ethylmagnesium bromide in xylene at 120–130° it underwent loss of the cyano group and gave entirely 9-($\beta$-dimethylaminoethyl)-fluorene (VI). At this point the demands of other work necessitated the termination of the project.

## Pharmacology

Most of the compounds prepared were tested for morphine-like analgesic activity in rats, using the thermal radiation technique of Ercoli and Lewis.[17] The compounds were administered subcutaneously or orally in doses varying from 200 to 600 mg./kg. (inasmuch as the intravenous $LD_{50}$ values in mice were in the approximate range of 150 to 200 mg./kg., higher doses were not used). The predominant toxic sign was convulsions and none of the substances showed any possible interest as an analgesic.

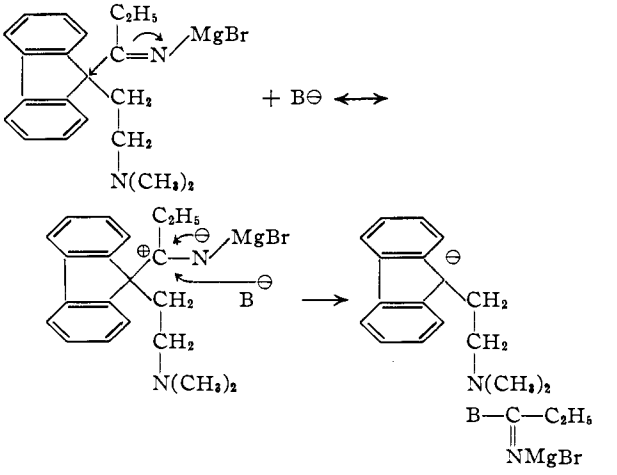
Compounds II and IV were studied for their antispasmodic activity against histamine and acetylcholine spasm of the isolated guinea pig intestine. Each was effective against both of the spasmogens at 20–40 $\gamma$/cc.; Trasentin was effective at 5–10 $\gamma$/cc. against histamine and at 2–5 $\gamma$/cc. against acetylcholine.

We are indebted to Mary N. Lewis and Max Chessin for the analgesic and spasmolytic data, respectively.

## Discussion

The fact that other workers found that a Grignard reagent would add to the cyano group of 9-cyano-9-($\beta$-dimethylaminopropyl)-fluorene at either 75–80°[5] or 95–100°[4] and of 9-cyano-9-($\beta$-diethylaminoethyl)-fluorene at 70–80°,[2] whereas we found the cyano group of 9-cyano-9-($\beta$-dimethylaminoethyl)-fluorene (XV) to be eliminated by this reagent at 120–130° appears worthy of comment. The only reasonable conclusion is that the Grignard reagent also added to XV and that the more vigorous reaction conditions that we used caused elimination of the cyano-derived function.[18]

There is an appreciable tendency for the fluorene molecule to become anionic because of the mesomeric stabilization of the 9-fluorenyl anion, with the consequence that the covalent electron pair of the fluorene $C_9$-acyl bond is considerably displaced toward the fluorene, *i.e.*, it becomes semiionic. (Evidence for the electron deficiency on fluorene-$C_9$ is the tendency for 9-acylfluorenes to exist in the enolic form, as 9-hydroxyalkylidene fluorenes[19,20] and for fluorene itself to undergo typical "reactive methylene group" condensation reactions.[21]) Simultaneously the usual tautomeric displacement of the carbon–nitrogen multiple bond is extant and both factors operate to induce a fractional but real electron deficiency on the acyl carbon atom and render it susceptible to attack by a base (the Grignard reagent). However, there is steric hindrance to the approach of a base to within a covalent bonding radius of this carbon atom and in the reaction conducted at the lower temperatures[2,4,5] no significant change in the molecule takes place. But in our reaction, the higher reaction temperature was able to impart enough energy to the $C_9$-acyl bond to weaken it to incipient ionization, this process being driven to completion by simultaneous nucleophilic attack by the base on the departing cationic fragment and by the mesomeric stabilization of the 9-fluorenyl anion produced




It is not necessary and is probably even false to

(16) E. J. Greenhow, E. N. White and D. McNeil, *J. Chem. Soc.*, 3099 (1953).

(17) N. Ercoli and M. N. Lewis, *J. Pharmacol. Exptl. Therap.*, **84**, 301 (1945).

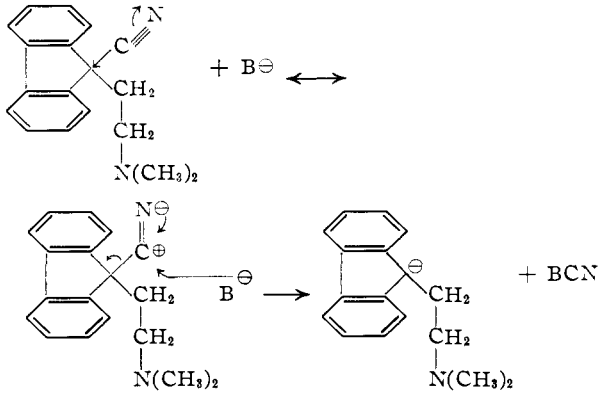
(18) Steric factors can be discounted because E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949), noted that in the analogous diphenylacetonitrile series the $\beta$-dimethylaminopropyl and $\beta$-dimethylaminoethylnitriles offered little resistance to attack of a reagent at the nitrile carbon atom (although the $\alpha$-methyl-$\beta$-dimethylaminoethyl compound was resistant, presumably due to steric hindrance).

(19) W. Wislicenus and M. Waldmuller, *Ber.*, **42**, 785 (1909).

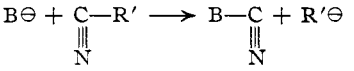
(20) R. Kuhn and E. Levy, *ibid.*, **61**, 2240 (1928).

(21) I. Von and E. C. Wagner, *J. Org. Chem.*, **9**, 155 (1944).

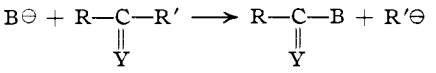
assume that all instances or even the entire amount of any given instance of elimination of a cyano group by a Grignard reagent must proceed through preliminary addition of a molecule of RMgX to the carbon–nitrogen triple bond to yield an intermediate ketimine; e.g.



It is thus seen that this elimination



is in reality but a special case of nucleophilic displacement on carbon in the system



wherein Y is a negative function and R′ is a radical capable of resonance stabilization, and that as such it is fundamentally the same mechanism as has been advanced by other authors for the reversal of the Claisen (or aldol) condensation (in its broadest sense). Inasmuch as there have been reported in the literature a great number of reactions which we believe are examples of this displacement, but many of which have not been recognized as such, it seems pertinent to at least mention some of them.

In the fluorene series there may be noted the reaction of propylene oxide with potassium 9-cyanofluorene to yield 9-isopropenylfluorene[2,22]; in the present work the production of dipropionylfluorene at room temperature but monopropionylfluorene under reflux conditions[23]; and the conversion of 9-formylfluorene by alkaline formaldehyde to 9-fluorenylcarbinol, which Burr[24] recognized as proceeding *via* the unstable 9-hydroxymethyl-9-formylfluorene by a mechanism essentially identical with the one mentioned above. In connection with these 9-acylfluorenes we also wish to mention the factor of steric strain; although the principal studies on the facilitation of reactions by steric strain, where the transition state affords a decrease in strain, have been with carbonium ion reactions[25] there is no reason to assume that a different situation exists in carbanion formation or that a 9-substituted 9-fluorenyl anion is not less strained than a 9,9-disubstituted fluorene molecule. Thus, conversion of a 9,9-disubstituted fluorene molecule to a 9-monosubstituted 9-fluorenyl anion would be expected to be aided by the decrease in strain of the ion over that of the original molecule.

Ordinarily the corresponding elimination of a cationic acyl fragment from a benzhydryl type compound requires more drastic reaction conditions (stronger base, higher temperature or longer time) because the mesomeric stabilization of the benzylhydryl anion is less than that of the corresponding 9-fluorenyl anion. This reaction has been used by a number of people for the elimination, expected or otherwise, of cyano and acetyl groups by a means of a Grignard reagent,[26–32] ethyl lithium,[30] potassium hydroxide[29,33] or sodamide[6,30,34–40] in a variety of substituted diphenylacetonitriles or analogous compounds. None of these people, to our knowledge, has suggested the manner in which these eliminations occur; we believe them to be merely additional instances of the general SN2 displacement by the mechanism under discussion.[41]

(22) Here the KOH generated in the intermediary formation of 9-cyano-9-isopropenylfluorene effects cyano removal from the latter substance.

(23) We believe that the dipropionyl derivative was formed in both cases but that at reflux temperature the base present, in this case the 9-fluorenyl anion, converted what little dipropionyl derivative formed back to the monoderivative.

(24) J. G. Burr, THIS JOURNAL, **73**, 5179 (1951).

(25) H. C. Brown, Abstracts of Twelfth National Organic Symposium, pp. 14–15 (1951); H. C. Brown and R. S. Fletcher, THIS JOURNAL, **71**, 1845 (1949); **72**, 1223 (1950); H. C. Brown and A. Stern, *ibid.*, **72**, 5068 (1950); H. C. Brown and H. L. Berneis, *ibid.*, **75**, 10 (1953); H. C. Brown and R. B. Johanneson, paper No. 26 before the Division of Organic Chemistry, 109th American Chemical Society Meeting, April, 1946.

(26) M. Ramart-Lucas and F. Salmon-Legagneur, *Bull. soc. chim.*, [4] **43**, 321 (1928).

(27) J. L. E. Erickson and M. M. Barnett, THIS JOURNAL, **57**, 560 (1935).

(28) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2906 (1948).

(29) E. M. Schultz, *ibid.*, **74**, 5793 (1952).

(30) (a) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *ibid.*, **73**, 5752 (1951); (b) N. Sperber, D. Papa and E. Schwenk (to Schering Corporation), U. S. Patent 2,604,473 (July 22, 1953).

(31) N. R. Easton, L. R. Bartron, F. L. Meinhofer and V. B. Fish, THIS JOURNAL, **75**, 2086 (1953).

(32) W. B. Wheatley, *J. Org. Chem.*, **19**, 434 (1954).

(33) E. L. May and E. Mosettig, *ibid.*, **13**, 459 (1948).

(34) British Intelligence Objective Subcommittee Final Report 116, Item No. 24, pp. 49–50, E. H. M. Stationery Office, London (1945); see also PB 981, p. 42, PB L74031, PB L57794 and PB 241, Office of the Publication Board, Department of Commerce, Washington, D. C.

(35) M. M. Klenk, C. M. Suter and S. Archer, THIS JOURNAL, **70**, 3846 (1948).

(36) M. Jackman, C. Bolen, F. C. Nachod, B. F. Tullar and S. Archer, *ibid.*, **71**, 2301 (1949).

(37) E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949).

(38) M. Jackman, F. C. Nachod and S. Archer, THIS JOURNAL, **72**, 716 (1950).

(39) A. W. Ruddy, *ibid.*, **73**, 4096 (1951).

(40) H. S. Mosher and J. E. Tessieri, *ibid.*, **73**, 4925 (1951). These authors noted that an extended reflux period decreased the yield of phenyl-3-pyridylacetonitrile obtained in the sodamide alkylation of phenylacetonitrile with 3-bromopyridine, we believe by cyano elimination from the alkylated product.

(41) The elimination of groups such as cyano, benzyl and others from tertiary and quaternary carbon atoms by sodium (C. F. Koelsch, *ibid.*, **56**, 1605 (1934), potassium (A. H. Beckett and W. J. Linnell, *J. Pharm. Pharmacol.*, **2**, 418 (1950)), sodium plus alcohol (L. A. Walter and S. M. McElvain, THIS JOURNAL, **56**, 1614 (1934); E. C. Horning, M. G. Horning, M. S. Fish and M. W. Rutenberg, *ibid.*, **74**, 773 (1952)) and the like is not by the same mechanism, is probably free-radical in nature, and is beyond the scope of the present discussion.

We also consider it probable that a mechanism of this sort rather than the complicated one suggested by the authors is responsible for the genesis of the alkyl cyanides obtained when Blicke and Tsao[42] treated benzhydryl-type nitriles with alkylmagnesium halides.

## Experimental[43]

**Fluorene-9-carboxylic acid**, m.p. 228–230°, was prepared by the butyllithium alternative described by Burtner and Cusic[44] and was converted to its *ethyl ester*, b.p. 150–160° (1.1–1.6 mm.) by the procedure of Adickes[45] in 55% yield.

**9-(γ-Dimethylaminopropyl)-9-carbethoxyfluorene (II).**—This procedure is a modification of that of Bockmühl and Ehrhart[6] who prepared the piperidinoethyl and morpholinoethyl derivatives and is representative for our compounds I, II and III. To a solution of 9-carbethoxyfluorene (23.0 g., 0.096 mole) in ether (170 cc.), maintained in a hydrogen atmosphere, there was added 4.0 g. (0.101 mole) of finely cut potassium. When a yellow solid began to separate there was added 4.6 g. (0.10 mole) of ethanol and after all of the potassium had dissolved there was added, dropwise during one-half hour, a solution of γ-dimethylaminopropyl chloride (15.0 g., 0.123 mole) in dry benzene (100 cc.), while the reaction mixture was held at reflux. Refluxing was continued as an additional 100 cc. of benzene was slowly added, the condenser water was turned off, and the mixture was stirred at reflux on the steam-bath for a total of 2.5 hours. The cooled solution was decomposed with water and the benzene layer was distilled on the steam-bath at 1 mm. to remove the solvent and any unchanged aminoalkyl chloride. The residue was taken up in ether and then extracted with dilute hydrochloric acid. The acidic solution was made alkaline with sodium carbonate and extracted with ether; the ethereal extract was dried over magnesium sulfate and treated with dry hydrogen chloride. The product, after recrystallization from a mixture of dioxane and ethyl acetate, weighed 12.0 g. (35% yield) and melted at 147°.

*Anal.* Calcd. for $C_{21}H_{25}NO_2 \cdot HCl$: C, 70.08; H, 7.28; N, 3.89; Cl, 9.85. Found: C, 69.96; H, 7.56; N, 4.15; Cl, 9.78.

**9-(β-Dimethylaminoethyl)-9-carbethoxyfluorene (I).**—Prepared analogously from 36.6 g. of 9-carbethoxyfluorene and 15.9 g. of β-dimethylaminoethyl chloride, this was obtained in 45% yield. The base boiled at 165–167° (1 mm.) and the hydrochloride melted at 153°.

*Anal.* Calcd. for $C_{20}H_{23}NO_2 \cdot HCl$: N, 4.05; Cl, 10.25. Found: N, 4.04; Cl, 10.35.

**9-(β-Dimethylaminopropyl)-9-carbethoxyfluorene (III).**—Sixteen and two-tenths grams of 9-carbethoxyfluorene and the base from 13.2 g. of β-dimethylaminopropyl chloride hydrochloride, by the above procedure, gave an 18% yield of product hydrochloride, m.p. 221° after recrystallization from dioxane.

*Anal.* Calcd. for $C_{21}H_{25}NO_2 \cdot HCl$: C, 70.08; H, 7.28; N, 3.89; Cl. 9.85. Found: C, 69.88; H, 7.05; N, 4.00; Cl, 9.75.

**9-(β-Dimethylaminoethyl)-9-formylfluorene (IV).**—To a solution of ethylmagnesium bromide prepared from ethyl bromide (2.0 g., 18 millimoles) and magnesium (0.6 g., 24 millimoles) in ether (65 cc.) there was added a solution of 9-carbethoxy-9-(β-dimethylaminoethyl)-fluorene (6.9 g., 22 millimoles) in ether (50 cc.). After the mixture had been refluxed 30 minutes the Michler ketone test for a Grignard reagent was negative and the reaction mixture was decomposed with saturated aqueous ammonium chloride solution. The ethereal layer was dried over magnesium sulfate and then treated with dry hydrogen chloride to yield an ether-insoluble oil (in two other runs the material in the ethereal extract was distilled, b.p. 160° (1.2 mm.), 165–168° (1.6 mm.), prior to precipitation of the hydrochloride with no appreciable influence on the yield or outcome of the reaction). Trituration of the oil with ethyl acetate produced a solid which after repeated extraction with ethyl acetate and recrystallization from dioxane–ether and from ethyl acetate was separated into about 4 g. of starting material hydrochloride, m.p. 148–149°, and 1.33 g. (20% yield) of product hydrochloride, m.p. 189°.

*Anal.* Calcd. for $C_{18}H_{19}NO \cdot HCl$: C, 71.64; H, 6.68; N, 4.64; Cl, 11.75. Found: C, 71.35; H, 7.14; N, 4.41; Cl, 11.48.

Some of the calculated values for the anticipated product, 9-(β-dimethylaminoethyl)-9-propionylfluorene, and its possible further reaction product 9-(β-dimethylaminoethyl)-9-(α-ethyl-α-hydroxypropyl)-fluorene are appreciably different from the found values. Those for the further reduction product, 9-(β-dimethylaminoethyl)-9-hydroxymethylfluorene, are not sufficiently different from the found values to permit a choice of structure on the basis of the analysis.

**9-(β-Dimethylaminopropyl)-9-formylfluorene (V).**—A solution of 9-(β-dimethylaminopropyl)-9-carbethoxyfluorene (6.5 g., 20 millimoles) in toluene (50 cc.) was added to a Grignard solution prepared from magnesium (0.57 g., 23.5 millimoles) and ethyl bromide (2.6 g., 23.8 millimoles) in ether (25 cc.). The ether was removed by distillation, the mixture was refluxed 1.5 hours, and then decomposed with saturated ammonium chloride solution. The dried benzene layer was treated with dry hydrogen chloride and from the oily precipitate there was obtained by tedious fractional crystallization from ethyl acetate 1.27 g. (20% yield) of product hydrochloride, m.p. 181–182°.

*Anal.* Calcd. for $C_{19}H_{21}NO \cdot HCl$: C, 72.26; H, 7.02; N, 4.44; Cl, 11.23. Found: C, 71.91; H, 7.47; N, 4.28; Cl, 11.15.

As in the case of the β-dimethylaminoethyl homolog, some of the calculated values for the anticipated product, 9-(β-dimethylaminopropyl)-9-propionylfluorene, and the possible further reaction product 9-(β-dimethylaminopropyl)-9-(α-ethyl-α-hydroxypropyl)-fluorene are appreciably different from the found values, although those of the analogous carbinol here too are close enough to exclude decision from microanalysis alone.

**9-(β-Dimethylaminoethyl)-fluorene (VI).**—The following procedure is representative of that used for our compounds VI–X. A solution of 120 g. (0.72 mole) of fluorene in 250 cc. of toluene was refluxed with 15 g. (0.575 mole) of sodamide for 1.5 hours, then there was added the base liberated from 57 g. (0.395 mole) of β-dimethylaminoethyl chloride hydrochloride dissolved in 150 cc. of toluene. The mixture was refluxed another four hours, then cooled and decomposed with sufficient 4 *N* hydrochloric acid to render it acid to congo red. The organic layer was washed twice with dilute hydrochloric acid and evaporated to leave about 50 g. of unreacted fluorene. The aqueous acidic layers were combined, made alkaline, and extracted with ether. Fractional distillation of the dried ethereal extract gave 44.2 g. (0.162 mole, 41% yield) of crude product, b.p. 156–165° (2 mm.). The product, dissolved in 200 cc. of warm alcohol, was treated with 400 cc. of hot 5% perchloric acid solution; the perchlorate melted at 206–208° after recrystallization from water.

*Anal.* Calcd. for $C_{17}H_{19}N \cdot HClO_4$: C, 60.44; H, 5.97; N, 4.15. Found: C, 60.39; H, 5.60; N, 4.33.

The recrystallized perchlorate was dispersed in a mixture of 300 cc. of hot water and 100 cc. of hot benzene and the mixture then made alkaline, vigorously mixed and the benzene layer separated. The benzene extraction was repeated, the extracts were combined and distilled to give 28 g. (0.102 mole, 34% yield over-all) of pure product, b.p. 153–154° (1.7 mm.), $n^{28}D$ 1.5970. The hydrochloride and picrate, just as the perchlorate, were identical with those described below, in the last paragraphs of the Experimental section.

**Silver Oxide Conversion of 9-(β-Dimethylaminoethyl)-9-formylfluorene (IV) to 9-(β-Dimethylaminoethyl)-fluorene (VI).**—A solution of 9-(β-dimethylaminoethyl)-9-formylfluorene hydrochloride (400 mg., 1.3 millimoles) in 10 cc. of water was added to a suspension in 10 cc. of water of silver oxide prepared from 1.0 g. (0.6 millimole) of silver nitrate. To this mixture there was added 5.0 cc. of 0.15 *N* sodium hydroxide and the resultant mixture was diluted with an equal volume (25 cc.) of alcohol. The mixture was heated on the steam-bath for 1.5 hours (it was still strongly basic), then 1.0 cc. of 5 *N* sodium hydroxide was added and

(42) F. F. Blicke and E. P. Tsao, THIS JOURNAL, **75**, 5587 (1953).

(43) Melting points and boiling points are uncorrected. Microanalyses were carried out by or under the supervision of Louis Dorfman.

(44) R. B. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(45) F. Adickes, *J. prakt. Chem.*, **146**, 235 (1936).

heating was continued for another hour and a half. During the heating period the volume of the mixture was concentrated to about 5 cc. The black precipitate was removed by filtration and washed repeatedly with alcohol. The combined filtrate and washings was evaporated to dryness on the steam-bath, the residue was taken up in ether and the ethereal solution was dried over magnesium sulfate. Evaporation of the dried ethereal solution left an oily residue. A small portion of this oil was redissolved in ether and treated with ethereal hydrogen chloride to yield an oily precipitate that could not be induced to crystallize on seeding with the starting hydrochloride. Another portion of the oily residue was converted to its perchlorate that was recrystallized from dioxane. The product melted at 207° alone or mixed with an authentic sample of 9-(β-dimethylaminoethyl)-fluorene perchlorate. A third portion of the oily residue was converted to its picrate that melted at 173–175° and did not depress the melting point (176°) when mixed with an authentic sample of 9-(β-dimethylaminoethyl)-fluorene picrate.

**9-(β-Dimethylaminopropyl)-fluorene (VII).**—The crude base boiled at 165–169° (2.5 mm.) and the hydrochloride melted at 256–257.5° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{18}H_{21}N\cdot HCl$: C, 75.11; H, 7.71; N, 4.87; Cl, 12.32. Found: C, 74.98; H, 7.76; N, 4.96; Cl, 12.10.

The same material was obtained when a mixture of 8.3 g. of 9-(β-dimethylaminopropyl)-9-carbethoxyfluorene, 10 g. of sodium hydroxide, 10 cc. of water and 90 cc. of alcohol was refluxed five hours. The mixture was evaporated to dryness, the residue taken up in water, extracted with ether and the dried ethereal extract treated with hydrogen chloride.

**9-(β-Diethylaminoethyl)-fluorene (VIII),** b.p. 195–197.5° (4 mm.), $n^{27}D$ 1.5665, was prepared by the procedure of Eisleb.[46] Although this material yielded an acid sulfate, m.p. 217–218°, as reported, it was found best to purify the substance *via* its perchlorate, m.p. 181.5–182.5°, after recrystallization from ethanol. The purified free base, liberated from the perchlorate in the same manner as described in the case of the dimethyl homolog, boiled at 165° (1 mm.) and had $n^{28}D$ 1.5800. The same material has also been described subsequently by Badger, Cook and Schwartz,[2] who also found it expedient to use the perchlorate for purification of the base.

**9-(β-Morpholinoethyl)-fluorene (IX).**—The material was purified *via* its picrate, m.p. 181–182° after recrystallization from acetone, which was not analyzed. The purified base boiled at 195–198° (1 mm.) and had $n^{22}D$ 1.6040.

*Anal.* Calcd. for $C_{19}H_{21}NO$: C, 81.63; H, 7.58; N, 5.03. Found: C, 81.68; H, 7.48; N, 5.04.

The perchlorate melted at 186–188° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{19}H_{21}NO\cdot HClO_4$: C, 60.08; H, 5.84; N, 3.69. Found: C, 60.32; H, 5.64; N, 3.44.

**9-(γ-Dimethylaminopropyl)-fluorene (X).**—The crude base boiled at 184–205° (4.5 mm.) and was converted to the hydrochloride which melted at 187.5–188.5° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{18}H_{21}N\cdot HCl$: C, 75.11; H, 7.71; N, 4.87; Cl, 12.32. Found: C, 75.18; H, 7.71; N, 4.86; Cl, 12.50.

**9-Ethoxalylfluorene (XI),**[47] m.p. 74–76°, was prepared in 90% yield by essentially the procedure described by Kuhn and Levy[20] for the methyl ester. Thirteen attempts to alkylate this material with γ-dimethylaminopropyl chloride, under various conditions, all led to either cleavage of ethoxalyl group[48] or tar formation, although alkylation with β-dimethylaminopropyl chloride was successful.

**Ethyl 9-Fluorenylidene-β-dimethylaminopropyloxyacetate (XVI).**—To a solution of 9-ethoxalylfluorene (2.5 g., 9.4 millimoles) in benzene (100 cc.) there were added potassium (0.4 g., 10.2 millimoles) and absolute alcohol (0.44 g., 9.6 millimoles) and the mixture was refluxed until all the potassium had dissolved. There was then added β-dimethylaminopropyl chloride (1.3 g., 8.2 millimoles), the mixture was refluxed another hour and 10 cc. of alcohol was added. The mixture was decomposed with water, the organic layer was separated, dried and treated with hydrogen chloride to give the hydrochloride of the product which, after successive recrystallization from alcohol–ether and dioxane–ether, melted at 181°.

*Anal.* Calcd. for $C_{22}H_{25}NO_3\cdot HCl$: C, 67.46; H, 6.62; N, 3.74; Cl, 9.48. Found: C, 67.17; H, 6.43; N, 3.66; Cl, 9.64.

**9,9-Dipropionylfluorene (XIII).**—Fluorenyllithium was prepared in the usual manner from fluorene (47 g., 0.283 mole), lithium (7 g., 1.00 mole) and butyl chloride (28 g., 0.51 mole) in ether (200 cc.). The orange-brown solution of fluorenyllithium was dropped into a stirred solution of propionyl chloride (60 g., 0.65 mole) in ether (100 cc.) at room temperature and was decolorized as it entered the acid chloride solution. The mixture was allowed to stand at room temperature overnight and then decomposed with water. The organic layer was separated and dried and the solvent removed to leave a residue from which fluorene crystallized. After filtration, the filtrate was washed with dilute ammonia, then dried and fractionally distilled to give more fluorene and a higher-boiling fraction which after two redistillations weighed 7.8 g. (10% yield) and boiled at 182–184° (1.5–2.0 mm.). This material solidified and, after recrystallization from ligroin (b.p. 35–60°), melted at 80°.

*Anal.* Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.26; H, 6.51.

This material yielded a mono-2,4-dinitrophenylhydrazone, m.p. 124°, after recrystallization from aqueous methanol.

*Anal.* Calcd. for $C_{25}H_{22}N_4O_5$: C, 65.49; H, 4.83; N, 12.22. Found: C, 65.12; H, 5.12; N, 11.77.

**9-Propionylfluorene (XIV).**—Fluorenyllithium, prepared from lithium (10.5 g., 1.50 moles), butyl chloride (142 g., 1.53 moles) and fluorene (82 g., 0.495 mole) in ether (400 cc.), was added to a stirred ice-cooled solution of propionyl chloride (200 g., 2.16 moles) in ether (200 cc.). The mixture was allowed to warm to room temperature, was then refluxed one hour and allowed to stand overnight. After decomposition of the reaction mixture with water the organic layer was washed with dilute ammonia and the solvent evaporated from the washed solution. The residue, on standing several days, deposited fluorene which was removed by filtration. Distillation of the filtrate gave 11 g. (10% yield) of product, b.p. 145–180° (3 mm.) which solidified and melted at 103–104° after recrystallization from ligroin (b.p. 35–60°).

*Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.34. Found: C, 86.22; H, 6.30.

This ketone failed to give a 2,4-dinitrophenylhydrazone but did give an oxime that melted at 240° after recrystallization from aqueous alcohol. The oxime was not analyzed.

**9-Formylfluorene** was prepared by the potassium methoxide condensation of fluorene with ethyl formate in ether by a procedure adapted from Wislicenus and Waldmuller.[49] This was converted to its **oxime** by the method of Wislicenus and Russ,[50] whose procedure was also followed for the thionyl chloride dehydration of the oxime to **9-cyanofluorene,** m.p. 151–152°. It is significant that the cyano compound could be obtained in 53% over-all yield from fluorene by avoiding purification of the intermediates.

**9-(β-Dimethylaminoethyl)-9-cyanofluorene (XV).**—This compound was prepared fundamentally by the procedure used by Shapiro[5] for the β-dimethylaminopropyl homolog. The product distilled at 173° (1.1 mm.).

*Anal.* Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.49; H, 6.76; N, 10.60.

The hydrochloride melted, after recrystallization from ethanol, at 253°.

*Anal.* Calcd. for $C_{18}H_{18}N_2\cdot HCl$: C, 72.35; H, 6.41; N, 9.38; Cl, 11.87. Found: C, 72.23; H, 6.55; N, 9.51; Cl, 12.09.

**Grignard Reaction on 9-(β-Dimethylaminoethyl)-9-cyanofluorene (XV).**—To a Grignard solution prepared from 2.43

(46) O. Eisleb, *Ber.*, **74**, 1433 (1941). Also subsequently described by M. Bockmühl and G. Ehrhart (to Winthrop-Stearns, Inc.), U. S. Patent 2,446,522 (August 10, 1948).

(47) W. Wislicenus, *ibid.*, **33**, 771 (1900).

(48) W. Wislicenus and W. Mocker, *ibid.*, **46**, 2772 (1913), also found some cleavage to fluorene when they alkylated ethoxalylfluorene with benzyl chloride.

(49) W. Wislicenus and M. Waldmuller, *ibid.*, **42**, 785 (1909).

(50) W. Wislicenus and K. Russ, *ibid.*, **43**, 2719 (1910).

g. (0.100 mole) of magnesium and 8.86 g. (0.081 mole) of ethyl bromide in 100 cc. of ether there was added a solution of 5.2 g. (0.020 mole) of 9-(β-dimethylaminoethyl)-9-cyanofluorene in a mixture of 100 cc. of ether and 150 cc. of xylene. The solution was heated to 120–130° for three hours, during which the greenish-black solution turned yellow. The reaction mixture was decomposed with dilute ammonia, the organic layer was separated, dried and the solvent was evaporated to leave a residue which practically all distilled at 159–161° (2 mm.) and analyzed for 9-(β-dimethylaminoethyl)-fluorene.

*Anal.* Calcd. for $C_{17}H_{19}N$: C, 86.05; H, 8.07; N, 5.90. Found: C, 85.16; H, 8.12; N, 6.11.

The hygroscopic hydrochloride melted at 172–174°.

*Anal.* Calcd. for $C_{17}H_{19}N\cdot HCl$: N, 5.20. Found: N, 4.85.

The perchlorate was prepared by adding 10 cc. of hot 5% perchloric acid to a solution of 1 g. of the material in 5 cc. of alcohol. It melted, after three recrystallizations from dioxane, at 207–208°.

*Anal.* Calcd. for $C_{17}H_{19}N\cdot HClO_4$: C, 60.44; H, 5.97 N, 4.15. Found: C, 60.75; H, 5.78; N, 4.41.

The picrate melted at 181–183°.

*Anal.* Calcd. for $C_{17}H_{19}N\cdot C_6H_3N_3O_7$: C, 59.22; H, 4.76; N, 12.01. Found: C, 59.22; H, 4.81; N, 11.73.

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

# Synthesis of Flavone- and Flavonol-6-carboxylic Acid and Related Derivatives

BY D. N. SHAH, S. K. PARIKH AND N. M. SHAH

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Using 2-hydroxy-5-carboxyacetophenone as starting material, flavone- and flavonol-6-carboxylic acids and their various derivatives have been synthesized for the first time.

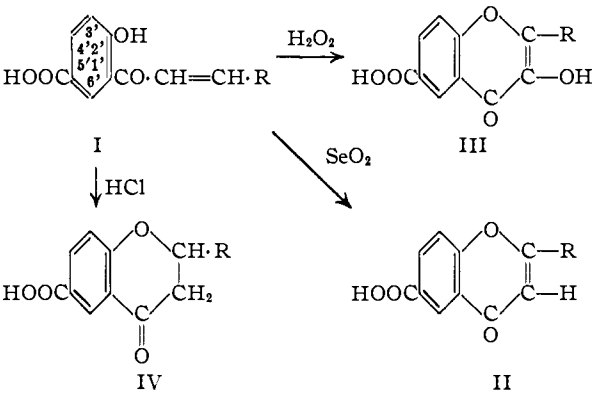
In connection with their work on the Fries migration of *p*-acetoxybenzoic acid, Shah and Shah[1] obtained 2-hydroxy-5-carboxyacetophenone, a substance of much potential value for synthetic work. Its easy accessibility opens the way for the synthesis of chromones, flavones and related substances containing the carboxyl group. A perusal of the literature shows that several chromonecarboxylic acids are known, but such carboxylated flavonoid compounds have not been described except the recently reported 3′,4′-dihydroxy-6-carboxyflavonol.[2]

The present work was undertaken as a part of a systematic study of such heterocyclic compounds and synthesis of flavone-6-carboxylic acid, flavonol-6-carboxylic acid and several of their derivatives is described in this paper. That such compounds may possess vitamin-p like activity adds to the interest of this work.

The Kostanecki–Robinson acetylation of 2-hydroxy-5-carboxyacetophenone or its methyl ester was fruitless and failed to yield 2-methylchromone-6-carboxylic acid. It has been observed in other instances also that the carboxyl group inhibits or hinders the above acetylation. Efforts to synthesize the above chromone acid by other methods are in progress. Hence attention was diverted to the building of the heterocyclic ring by other methods.

When 2′-hydroxy-5′-carboxychalcone (I) and its 4-methoxy and 3-hydroxy derivatives, previously prepared[3] by the condensation of 2-hydroxy-5-carboxyacetophenone and the appropriate aldehyde with ethanolic potassium hydroxide, were oxidized with selenium dioxide in amyl alcohol according to Venkataraman,[4] flavone-6-carboxylic acid (II) and its 4′-methoxy and 3′-hydroxy derivatives, respectively, were obtained. When these three chalcones and in addition the 4-hydroxy derivative were subjected to the Algar–Flynn oxidation[5] with hydrogen peroxide in the presence of cold alkali, flavonol-6-carboxylic acid (III) and its derivatives were obtained in good yield.

The *p*-methoxychalcone was isomerized also by dilute alcoholic hydrochloric acid treatment to the corresponding flavanone (IV).




R = either $C_6H_5$, $-C_6H_4OH$-*p*, $-C_6H_4OCH_3$-*p* or $-C_6H_4OCH_3$-*m*

It is evident from the above results that a carboxyl group in the benzene nucleus does not exert any retarding influence on the above reactions for the ring formation.

## Experimental

**Flavone-6-carboxylic Acid.**—Selenium dioxide (1 g.) was added to 2′-hydroxy-5′-carboxychalcone (1 g.) dissolved in dry amyl alcohol (30 ml.) and the mixture was refluxed at 140–150° for about 12 hours ($CaCl_2$ guard-tube). The precipitated selenium then was filtered off and the filtrate was subjected to steam distillation. After the removal of amyl alcohol, the solid that separated in the flask was collected and crystallized from acetic acid as small white granules, m.p. 302°, yield 0.4 g. It dissolves in sodium bicarbonate solution with effervescence and in alkali solution with yellow color.

(1) D. N. Shah and N. M. Shah, *J. Indian Chem. Soc.*, **26**, 235 (1949).

(2) T. Nagano and K. Matsumura, THIS JOURNAL, **75**, 6237 (1953).

(3) G. N. Vyas and N. M. Shah, *J. Indian Chem. Soc.*, **28**, 43 (1951).

(4) K. Venkataraman, *et al.*, *J. Chem. Soc.*, 866 (1935); 569 (1936); D. Chakravarti and J. Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939).

(5) J. Algar and J. Flynn, *Proc. Roy. Irish Acad.*, **B42**, 1 (1934); *cf.* T. Oyamada, *J. Chem. Soc., Japan*, **55**, 1256 (1934).