palladium-charcoal catalyst, was steam distilled. The distillation residue was studied by paper chromatography with 3:1 phenol:1% formic acid.[23] R_f values of 0.17, 0.56 and 0.91 were observed in agreement with those of glycolic, oxalic and levulinic acid. The ozonolysis was repeated a second time in identical fashion and the products from the two runs were combined.

The solution of non-volatile acids was concentrated to 5 ml. and was adjusted with 1 *N* sodium hydroxide to a *p*H of 5.5. One ml. of 25% calcium acetate solution was added and the precipitate was collected. Analysis of the precipitate[24] indicated that it contained 2.1 mg. of oxalic acid. The filtrate was adjusted to *p*H 4.0 with 0.5 *N* sulfuric acid and was concentrated to near dryness. The concentrate was chromatographed using 75 g. of silicic acid in a column of 50 mm. diameter and a mixture 4:1 chloroform–butanol saturated with 0.5 *N* sulfuric acid.[25] Each 25-ml. fraction was concentrated; the residue was dissolved in ethanol and was titrated to a phenol red end-point with sodium hydroxide. A major peak in elution of acids was noted in fractions 4–8 with a tailing into a minor peak in fractions 36–53. The fractions in the first peak, equivalent to 170 ml. of 0.018 *N* sodium hydroxide, were combined and concentrated to dryness. The infrared spectrum agreed with that of sodium levulinate. The *p*-phenylphenacyl ester was prepared.[26] After crystallization from benzene and from ethanol, it melted at 91–92° and showed the same infrared spectrum as that of an authentic sample. An authentic sample prepared from levulinic acid melted at 94–94.5°. The mixed m.p. of the two samples was 94–95°. *Anal.* Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.22; H, 5.77.

The fractions from the minor second peak observed in chromatography with silicic acid were chromatographed again with 12 g. of silicic acid in a 20 mm. diam. column and 9-ml. fractions were collected. Peaks in acid content were noted in fractions 1–5 and in fractions 14–22. The residue from concentration of the fractions 1–5 was allowed to react with 2 *N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. The precipitate, after crystallization from acetic acid, showed an infrared spectrum identical with that of levulinic acid dinitrophenylhydrazone.

Fractions 14–22, equivalent to 23 ml. of 0.018 *N* sodium hydroxide, were combined and concentrated. The residue was identified as sodium glycolate by infrared spectra. It was converted to the *p*-phenylphenacyl ester which exhibited an infrared spectrum identical with that of authentic *p*-phenylphenacyl glycolate. The authentic sample prepared from glycolic acid[26] melted at 122.5–123.5°. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.16; H, 5.43. The quantity of alkali required for the neutralization of levulinic acid in these titrations was *ca.* 7 times the quantity required for neutralization of the combined oxalic and glycolic acid.

Solanesol Acetate.—A mixture of 1.0 g. of solanesol, 10 ml. of chloroform, 0.14 ml. of pyridine and 0.2 ml. of acetic anhydride was heated under reflux for 3.5 hours. The mixture was diluted with ether and the ethereal solution was washed with 2 *N* sulfuric acid and with water. By chromatographic adsorption on 2:1 silicic acid–Celite, the product was separated into 0.5 g. of solanesol and 0.5 g. of solanesol acetate, m.p. 32–33°. Calcd. for $C_{52}H_{84}O_2$: C, 84.25; H, 11.42. Found: C, 84.12; H, 11.13.

Solanesol 3,5-Dinitrobenzoate.—The 3,5-dinitrobenzoate ester, prepared using benzene as the solvent,[27] was purified by chromatography on silicic acid followed by crystallization from acetone to give a solid melting at 57.5–59.5°. *Anal.* Calcd. for $C_{57}H_{84}N_2O_6$: C, 76.63; H, 9.48; N, 3.14; Found: C, 76.36; H, 9.46; N, 3.33.

Solanesol 3-Nitrophthalate.—The ester, obtained from 1.2 g. of solanesol,[28] was purified by chromatography on silicic acid followed by crystallization from acetone at −27°. The ester, 0.6 g., melted at 60–63° after sintering at 55°. *Anal.* Calcd. for $C_{58}H_{85}NO_6$: C, 78.07; H, 9.53; mol. wt. (neut. equiv.), 892. Found: C, 77.80; H, 9.38; mol. wt. (ebull.), 822; neut. equiv.,[16] 879.

Solanesol *p*-Phenylazobenzoate.—A mixture of 0.47 g. of solanesol, 50 ml. of anhyd. benzene, 0.4 g. of *p*-phenylazobenzoyl chloride and 4 drops of pyridine was heated under reflux for two hours. The product, after standard purification,[29] was extracted with 20 ml. of hexane and the hexane-soluble material was purified by chromatography on silicic acid. Only one colored ester band was noted during chromatography; it was eluted with 3:1 carbon tetrachloride–benzene; yield 0.33 g., m.p. 60–61°. Recrystallization from hexane at −27° did not alter the melting point. *Anal.* Calcd. for $C_{63}H_{90}N_2O_2$: C, 83.38; H, 10.00. Found: C, 83.19; H, 9.88.

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[23] J. B. Stark, A. E. Goodban and H. S. Owens, *Anal. Chem.*, **23**, 413 (1951).

[24] G. W. Pucher, A. J. Wakeman and H. B. Vickery, *Ind. Eng. Chem., Anal. Ed.*, **13**, 244 (1941).

[25] R. Smeby, V. Zbinorsky, B. H. Burris and F. M. Strong, THIS JOURNAL, **76**, 6127 (1954).

[26] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd Ed., p. 157.

[27] Reference 26, p. 164.

[28] Reference 26, p. 166.

[29] K. Ladenburg, E. Fernholz and E. S. Wallis, *J. Org. Chem.*, **3**, 294 (1938).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LOUISVILLE]

2-Pyrones. XXII. β-Methylglutaconic Acid, β-Methylglutaconanilic Acids and Related Dianilides, Pyridones and Pyridazones

BY RICHARD H. WILEY AND C. L. DESILVA

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Decarboxylation of β-methylglutaconanilic acids (III) gives three types of products: 6-hydroxy-2-pyridones (IV), senecioanilides (XV) and 3-methyl-3-butenoanilides (XVI) indicating that the glutaconanilic acid reacts as an α,β-unsaturated acid. β-Methylglutaconic acid has been converted to dianilides (VII) and, *via* its anhydride, to γ-arylhydrazono derivatives XIV and pyridazonecarboxylic acids (XIII). A variety of 6-hydroxy-2-pyridones have been coupled with diazonium salts to give arylhydrazono derivatives V which have been converted to pyridazonecarboxylic acids. Dimethyl β-methylglutaconate undergoes coupling with diazonium salts to give mixtures of arylhydrazono derivatives XI and pyridazonecarboxylates XII, both of which have been converted to pyridazonecarboxylic acids and to arylhydrazonopyridazone carboxylates (X).

The discovery that β-methylglutaconic acid and several closely related structures are implicated in the coenzyme A catalyzed biosynthesis of cholesterol[1-3] and the suggestion[4] that the activity of α-phenylbutyramide in reducing blood cholesterol levels may result from its functioning as an antimetabolite in the coenzyme A catalyzed biosynthesis of cholesterol have established the desirability

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[1] K. Block, L. C. Clark and I. Harary, *J. Biol. Chem.*, **211**, 687 (1954).

[2] H. Rudney, THIS JOURNAL, **76**, 2595 (1954); **77**, 1698 (1955).

[3] J. L. Rabinowitz, *ibid.*, **77**, 1295 (1955); **76**, 5168, 3037 (1954).

[4] J. Cottet and J. Redel, *La Presse Medicale*, **62**, 939 (June 16) 1954; *Compt. rend.*, **236**, 2553 (1953).

of providing additional information[5] about the chemistry of β-methylglutaconic acid. We wish to report at this time the results of studies on the preparation, decarboxylation and further reactions of the β-methylglutaconanilic acid (III) and a variety of related structures.

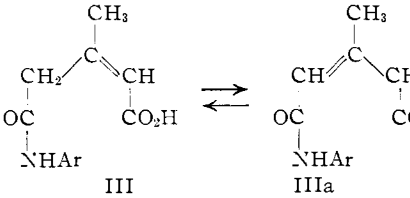
The β-methylglutaconanilic acids (III) described in Table I were readily prepared by the reaction of β-methylglutaconic anhydride with the substituted aniline, or with phenylhydrazine, in benzene solution. Since the anhydride is unsymmetrical, either of two products, in which the double bond is in the α,β-position (III) or in the β,γ-position (IIIa), are possible.

TABLE I

β-METHYLGLUTACONANILIC ACIDS

Compd. Ar of III	M.p., °C.	Yield, %	Nitrogen anal., % Calcd.	Found
C_6H_5	143	93	6.39	6.34
$2\text{-}CH_3C_6H_4$	145	85	6.01	5.97
$4\text{-}CH_3C_6H_4$	155	92	6.01	6.00
$2,6\text{-}(CH_3)_2C_6H_3$	178	95	5.66	5.69[a]
$4\text{-}CH_3OC_6H_4$	168	90	5.62	5.72
$3\text{-}ClC_6H_4$	147	90	5.52	5.39[b]
$4\text{-}ClC_6H_4$	157	95	5.52	5.70
$4\text{-}NO_2C_6H_4$	181	65	10.60	10.68[c]
$4\text{-}(CH_3)_2NC_6H_4$	178	85	10.68	10.66
$2\text{-}C_{10}H_7$	160	90	59.31, 4.95	59.51, 5.04[d]
$4\text{-}HOOCC_6H_4$	221	85	5.20	5.09
$4\text{-}H_2NC_6H_4$	206	75	7.77	7.91
C_6H_5NH	165	80	11.96	11.87
$2\text{-}C_5H_4N$	184	80	12.72	12.68[e]

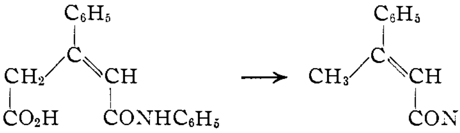
[a] *Anal.* Calcd. for $C_{14}H_{17}NO_3$: neut. equiv., 247. Found: neut. equiv., 246.5. [b] *Anal.* Calcd. for $C_{12}H_{12}NO_3Cl$: neut. equiv., 253.5. Found: neut. equiv., 255.7. [c] *Anal.* Calcd. for $C_{12}H_{12}N_2O_5$: neut. equiv., 264. Found: neut. equiv., 268.7. [d] Carbon–hydrogen analysis. [e] *Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: neut. equiv., 220. Found: neut. equiv., 215.5.



III IIIa

The α,β-unsaturated acid structure [III, Ar = C_6H_5] was first assigned[6] to the anilic acid for no stated reason. Soon after this, evidence was presented[7] to support the conclusion that the structure of α-methylglutaconanilic acid, similarly prepared, was that of a β,γ-unsaturated acid. This was based on the observation that oxidation of α-methylglutaconanilic acid, m.p. 189°, gave malonic acid, m.p. 132°. An isomeric α-methylglutaconanilic acid, m.p. 165°, had been reported previously,[8] and this had been assigned the α,β-unsaturated acid structure, although it may be that this isomer is one of a *cis–trans* pair. Recently[9] the decarboxylation of β-phenylglutaconanilic acid has been shown to give β-methylcinnamanilide which suggests, subject to the unreliability of thermal decarboxylation as a method of structural proof, that structure of the β-phenylglutaconanilic acid is that of a β,γ-unsaturated acid.

$$HO_2CCH_2CH{=}C(CH_3)CONHC_6H_5 \xrightarrow{\text{(Oxid.)}} HO_2CCH_2CO_2H$$



Our investigation of the thermal decarboxylation of the β-methylglutaconanilic acids has shown that three products are formed: a pyridone (IV), a senecioanilide (XV) and a 3-methyl-3-butenoanilide (XVI). In the three examples studied (*o*- and *p*-tolyl and *p*-chlorophenyl) the products were obtained in the ratio of one part of senecioanilide, five parts of butenoanilide and eight parts of hydroxypyridone. The senecionanilides, which were less soluble than the isomeric butenoanilides and were therefore more readily isolated and purified, were identified by comparison of melting points and infrared spectra with authentic senecioanilides, several of which are described in Table III. The isomeric butenoanilides showed a strong infrared absorption band at 11.2 μ characteristic of the C–H deformation vibrations of the terminal olefinic bond ($C{=}CH_2$).[10] Heating[6,11] the β-methylglutaconanilic acids gives 30–60% yields of anils, having the 1-aryl-4-methyl-6-hydroxy-2-pyridone structure IV, listed in Table II.

TABLE II

HYDROXYPYRIDONES

Compd. Ar of IV	M.p., °C.	Re-crystd.[a] from	Yield, %	Nitrogen anal., % Calcd.	Found
C_6H_5	164	B–P	35	6.96	6.93[b]
$2\text{-}CH_3C_6H_4$	121	B–P	25	6.51	6.48
$4\text{-}CH_3C_6H_4$	163	B–P	30	6.51	6.36
$2,6\text{-}(CH_3)_2C_6H_3$	228	M	60	6.11	5.99[c]
$2,5\text{-}(CH_3O)_2C_6H_3$	149	B–P	50	5.36	5.35[d]
$3\text{-}ClC_6H_4$	151	M	30	5.95	6.09[e]
$4\text{-}ClC_6H_4$	178	M	45	5.95	5.97
$2\text{-}NO_2C_6H_4$	170	B–P	25	11.38	11.40[f]
$4\text{-}(CH_3)_2NC_6H_4$	233	M	25	11.47	11.24
$4\text{-}(C_2H_5)_2NC_6H_4$	182	M	20	10.29	10.13

[a] B–P, benzene–petroleum ether; M, methanol. [b] *Anal.* Calcd. for $C_{12}H_{11}NO_2$: neut. equiv., 201. Found: neut. equiv., 210. [c] *Anal.* Calcd. for $C_{14}H_{15}NO_2$: neut. equiv., 229. Found: neut. equiv., 226. [d] *Anal.* Calcd. for $C_{14}H_{15}NO_4$: neut. equiv., 261. Found: neut. equiv., 262. [e] *Anal.* Calcd. for $C_{12}H_{10}NO_2Cl$: neut. equiv., 236. Found: neut. equiv., 226. [f] *Anal.* Calcd. for $C_{12}H_{10}N_2O_4$: neut. equiv., 246. Found: neut. equiv., 239.

The availability of this additional information about the products formed on decarboxylation makes possible a re-evaluation of the significance

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[5] For previous papers from our laboratories on β-methylglutaconic acid and its derivatives see: (a) R. H. Wiley and C. H. Jarboe, Jr., THIS JOURNAL, **77**, 403 (1955); (b) R. H. Wiley, E. L. DeYoung and N. R. Smith, *ibid.*, **76**, 1675 (1954); (c) R. H. Wiley and N. R. Smith, *ibid.*, **74**, 3893 (1952).

[6] J. F. Thorpe and H. Rogerson, *J. Chem. Soc.*, **87**, 1692 (1905).

[7] F. B. Thole and J. F. Thorpe, *ibid.*, **99**, 2214 (1911).

[8] F. Feist and G. Pomme, *Ann.*, **370**, 71 (1909).

[9] S. S. Karmarkar and V. M. Bhave, *J. Ind. Chem. Soc.*, **31**, 455 (1954); **30**, 689 (1953).

[10] J. A. Anderson and W. D. Seyfried, *Anal. Chem.*, **20**, 998 (1948).

[11] F. Fichter and J. Schwab, *Ann.*, **348**, 255 (1906).

TABLE III

SENECIOANILIDES

Compd. Ar of XVI	M.p., °C.	Yield, %	Nitrogen anal., % Calcd.	Found
C_6H_5	130	80	7.99	8.21
$2\text{-}CH_3C_6H_4$	100	85	7.40	7.61
$4\text{-}CH_3C_6H_4$	105	90	7.40	7.53
$2,6\text{-}(CH_3)_2C_6H_3$	125	85	6.89	7.04
$2\text{-}CH_3OC_6H_4$	65	80	6.82	6.84
$4\text{-}CH_3OC_6H_4$	90	85	6.82	6.77
$2,5\text{-}(CH_3O)_2C_6H_3$	88	75	5.95	5.74
$3\text{-}ClC_6H_4$	111	85	6.68	6.63
$4\text{-}ClC_6H_4$	122	90	6.68	6.63

of such data in establishing the structure of the β-methylglutaconanilic acids. The isolation of both senecio- and buteno-anilides on thermal decarboxylation indicates an accompanying rearrangement which apparently negates the possibility of assigning a structure to the starting material. It can be argued, however, that since the products are less readily interconverted by rearrangement, at least under some conditions, than are the glutaconanilic acids, a partial rearrangement precedes decarboxylation giving a smaller amount, under non-equilibrium conditions, of the decarboxylated rearranged product—the senecioanilide. This indicates an α,β-structure III for the β-methylglutaconanilic acids. The α,β-structure is also indicated as that which would be formed by the reaction of the aniline with the anhydride at the saturated carbonyl carbon rather than at the α,β-unsaturated carbonyl in keeping with prior reports[12,13] that the carbonyl group of saturated esters is more readily attacked on saponification than is the carbonyl of an α,β-unsaturated ester. Although a final structural assignment cannot be made on the basis of the available data, the α,β-unsaturated acid structure provides a consistent explanation of the reactions and behavior of the β-methylglutaconic acids.

The infrared absorption data for β-methylglutaconic acid, the anilic acids, the senecioic anilides and butenoic anilides provide no basis for a final structural assignment to the anilic acids. β-Methylglutaconic acid shows double acid carbonyl absorption bands at 5.88 and 5.90 μ. Since malonic acid also absorbs at these two wave lengths, there is no evidence of a shift in the carbonyl absorption resulting from the conjugated unsaturation. The anilic acids show an absorption band at 5.88–5.90 μ, which may be either the acid or amide carbonyl, with no marked shift attributable to conjugated unsaturation. They also show a band at 6.45–6.52 μ attributable to the amide carbonyl, again in its normal position. The C–H deformation band is at 11.36–11.42 μ in both the acid and the anilic acids. This is shifted from the 11.6–11.9 μ position for this band in the butenoanilides but provides no structural clue.

Apparently, the only previous reports on studies of the reactions of 6-hydroxy-2-pyridones with aryldiazonium salts are a mention of color formation in such a reaction[6] with 4,5-dimethyl-6-hydroxy-2-pyridone and diazotized p-nitroaniline and the formation of a yellow solid from the reaction of benzenediazonium chloride with 2,6-dihydroxypyridone.[14] The 1-aryl-4-methyl-1,2,5,6-tetrahydro-2,6-diketo-5-arylhydrazonopyridines V listed in Table VI were obtained in essentially quantitative yield by adding a diazotized aniline to a cold sodium carbonate solution of the pyridone. They have been assigned arylhydrazone structures by analogy with the γ-arylhydrazonoglutaconic anhydrides XIV. Hydrolysis of these pyridone derivatives gives the same 1-aryl-3-carboxy-4-methyl-6-pyridazone structure XIII that is obtained by hydrolysis of either the anhydride XIV or the coupled products obtained from the ester (XI, XII).

TABLE IV

β-METHYLGLUTACONANILIDES

Compd. Ar of VII	M.p., °C.	Nitrogen anal., % Calcd.	Found
C_6H_5	177	9.52	9.48
$2\text{-}CH_3C_6H_4$	131	8.69	8.48
$4\text{-}CH_3C_6H_4$	185	8.69	8.47
$2\text{-}CH_3OC_6H_4$	146	7.91	7.61
$4\text{-}CH_3OC_6H_4$	147	7.91	7.74
$2,6\text{-}(CH_3)_2C_6H_3$	217	7.99	8.12
$2,5\text{-}(CH_3O)_2C_6H_3$	142	6.76	6.86
$3\text{-}ClC_6H_4$	142	7.71	7.81
$4\text{-}ClC_6H_4$	201	7.71	7.51
$4\text{-}(CH_3)_2NC_6H_4$	183	14.73	14.61
$4\text{-}(C_2H_5)_2NC_6H_4$	198	13.05	12.86
$2\text{-}C_{10}H_7$	240	7.10	6.97

TABLE V

γ-KETO-β-METHYLGLUTACONIC ANHYDRIDE ARYLHYDRAZONES

Compd. Ar' of XIV	M.p., °C.	Re-crystd.[a] from	Color	Nitrogen anal., % Calcd.	Found
$2,6\text{-}(CH_3)_2C_6H_3$	160	EA	Pink	10.86	11.14
$2,5\text{-}(CH_3O)_2C_6H_3$	180	EA	Scarlet	9.65	9.65
$4\text{-}ClC_6H_4$	228	GA	Yellow	10.60	10.47
$2\text{-}CH_3\text{-}4\text{-}NO_2C_6H_3$	218	GA	Yellow	14.42	14.53
$2\text{-}HOOC\text{-}(4,6\text{-}(I_2)C_6H_2$	246	GA	Orange	5.53	5.09
$2\text{-}HOOCC_6H_4$	288	NB	Yellow	10.22	10.14

[a] EA, ethyl acetate; GA, glacial acetic acid. Prepared by the method of reference.[5a]

The reaction of aryldiazonium salts with dimethyl β-methylglutaconate is much more complex than is the corresponding reaction with dimethyl glutaconate.[15] With the latter, a γ-arylhydrazono derivative is obtained when the reactants are combined in a one to one ratio and an α-arylazo-γ-arylhydrazono derivative when a two to one ratio is used. Cyclization of the last takes place readily to give a 1-aryl-3-carbomethoxy-5-arylazo-6-pyridazone. These reactions have been checked with the p-chlorophenyl derivatives whose properties are recorded. Dimethyl β-methylglutaconate coupled readily with only one molecule of diazonium salt using either one to one or one to two ratios of reactants. The γ-arylhydrazono derivatives XI can be isolated but often they are rearranged on recrystallization to give as the reaction product the pyridazone XII. The pyridazone acids (XIII), obtained on hydrolysis of these esters are identical with those prepared by other routes. Although no arylazoarylhydrazono types IX were isolated, the rearranged 1-aryl-5-arylazo-3-carbo-

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[12] E. Schjanberg, *Z. physik. Chem.*, **A174**, 465 (1935).

[13] H. Pohl, *J. prakt. Chem.*, **141**, 44 (1934).

[14] L. Gattermann and A. Skita, *Ber.*, **49**, 500 (1916).

[15] F. Henrich and W. Thomas, *ibid.*, **40**, 4924 (1907).

TABLE VI

1-ARYL-1,2,5,6-TETRAHYDRO-2,6-DIKETO-4-METHYL-5-ARYLHYDRAZONOPYRIDINES

Compd. V	M.p., °C.	Recrystd.[a] from	Color	Yield, %	Anal., % Calcd.	Found
(Ar = C_6H_5) Ar′ =						
4-ClC_6H_4	239	EA	Yellow	90	C 63.62	63.63
					H 4.15	4.26
2,6-$(CH_3)_2C_6H_3$	192	M	Yellow	80	N 12.61	13.09
1,4-C_6H_4-	242	C, EA	Scarlet	80	N 15.78	15.51
1-$C_{10}H_7$	302	C	Orange	85	N 11.84	12.05
2-$C_{10}H_7$	254	C, PE	Orange	85	N 11.84	11.92
(Ar = 4-$CH_3C_6H_4$) Ar′ =						
4-$CH_3OC_6H_4$	221	EA	Brown	80	C 68.75	68.80
					H 5.48	5.45
4-ClC_6H_4	241	EA	Yellow	90	C 64.51	64.49
					H 4.56	4.49
2,6-$(CH_3)_2C_6H_3$	204	M	Yellow	80	N 12.10	11.95
(Ar = 2,6-$(CH_3)_2C_6H_3$) Ar′ =						
C_6H_5	82	EA	Yellow	85	N 12.61	12.50
2-$CH_3OC_6H_4$	213	M	Orange	80	N 11.56	11.82
4-$CH_3OC_6H_4$	169	M	Orange	90	N 11.56	11.76
2,5-$(CH_3O)_2C_6H_3$	210	EA	Grey	85	N 10.68	10.68
4-$(CH_3)_2NC_6H_4$	190	M	Black	80	N 14.88	14.99
4-$(C_2H_5)_2NC_6H_4$	149	PE	Black	85	N 13.86	13.96
4-ClC_6H_4	200	EA, PE	Red	90	N 11.41	11.04
Ar = 4-ClC_6H_4						
Ar′ = 4-$CH_3OC_6H_4$	249	EA	Orange	90	N 11.37	11.58
Ar = 2,5-$(CH_3O)_2C_6H_3$						
Ar′ = 4-ClC_6H_4	208	B, PE	Brown	90	N 10.51	10.69

[a] M, methanol; PE, petroleum ether; B, benzene; EA, ethyl acetate; C, chloroform.

TABLE VII

ARYLDIAZONIUM COUPLING PRODUCTS FROM DIMETHYL β-METHYLGLUTACONATE

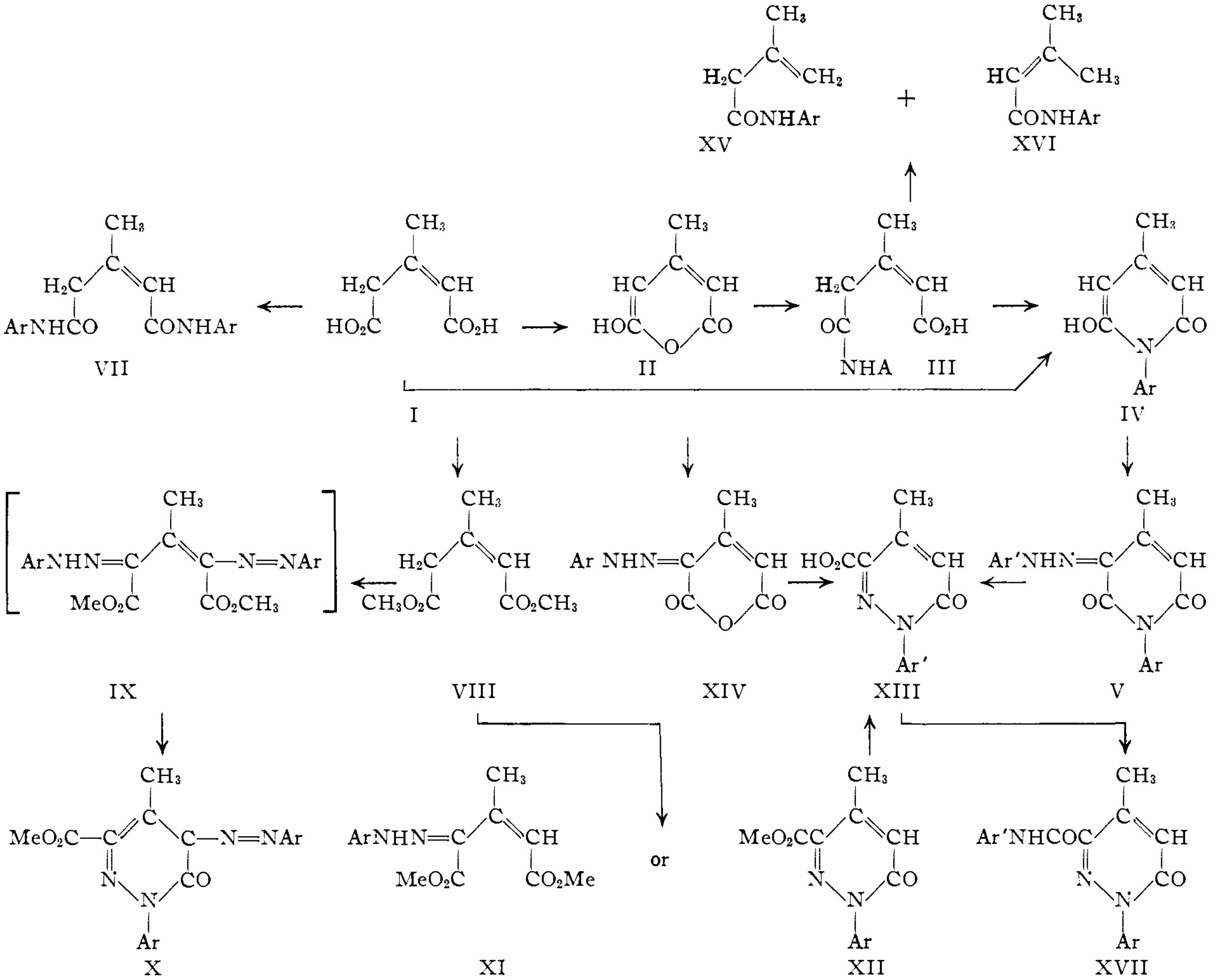
Compound		M.p., °C.	Recrystd.[a] from	Color	Yield, %	Nitrogen anal., % Calcd.	Found
Ar = C_6H_5	X	216	M	Pale yell.	10	16.08	15.53
	XII	127	M	White	20	11.47	11.59
Ar = 4-$(CH_3)C_6H_4$	XI	81	PE	Red-brown	20	9.65	9.85
	XII	148	B, PE	Beige	30	10.85	11.14
Ar = 4-$CH_3OC_6H_4$	X	140	B, PE	Beige	35	13.72	13.84
	X	180	EA, PE	Chocolate brown	10	13.72	13.81
XII		158	M	Light brown	15	10.21	10.60
Ar = 2,5-$(CH_3O)_2C_6H_3$, XI		114	M	Yellow	50	8.33	8.57
Ar = 3-ClC_6H_4, XI		140	M	Pale yell.	10	9.02	8.70
Ar = 3-BrC_6H_4, XI		125	M	Pale yell.	10	7.89	8.16
Ar = 4-IC_6H_4, XI		185	M	Yellow	10	6.97	7.19
Ar = 4-ClC_6H_4, XII		162	EA, PE	Beige	35	10.05	9.96

[a] M, methanol; B, benzene; PE, petroleum ether; EA, ethyl acetate.

methoxy-4-methyl-6-pyridazone structure was obtained in reactions with benzene and *p*-methoxybenzenediazonium chloride. In fact, two products were isolated which correspond to this structure (X, Ar = *p*-methoxyphenyl) from diazotized anisidine. The data are summarized in Table VII.

The β-methylglutaconanilides (VII) (Table IV), a previously undescribed class of compounds, were prepared from β-methylglutaconyl chloride and the aniline. Of all the amines used in this reaction only 2-aminopyrimidine gave the pyridone (IV, Ar = 2-pyrimidyl). The previously unrecorded γ-arylhydrazono-β-methylglutaconic anhydrides (XIV) listed in Table V were prepared as previously described.[5a] The 1-aryl-3-carboxy-4-methyl-6-pyridazones (XIII) described in Table VIII were prepared by three reactions: (a) from γ-arylhydrazono-β-methylglutaconic anhydrides (XIV)[5a]; (b) from 1-aryl-1,2,5,6-tetrahydro-2,6-diketo-4-methyl-5-arylhydrazono pyridines (V); and (c) from dimethyl γ-arylhydrazono-5β-methylglutaconates.

Acknowledgments.—The authors wish to express their appreciation for a grant from the Damon Runyon Memorial Fund which provided a graduate research assistantship from February, 1954, through June, 1955, and to the National Cancer Institute of the U. S. Public Health Service for a graduate research assistantship from July, 1955, to March, 1956, held by C. L. dS. Partial additional support for the research program described herein was also provided by these grants. C. L. dS. also wishes to express appreciation for a Fulbright Travel Grant.



Experimental

Typical procedures will be given for each type of preparation of each type of compound listed in the tables. Exceptional behavior is noted.

β-Methylglutaconanilic Acid (III, Ar = C_6H_5–).—A solution of 4 g. (0.03 mole) of β-methylglutaconic anhydride in 10 ml. of dry benzene was added to a solution of 3 g. (0.03 mole) of freshly distilled aniline in 10 ml. of dry benzene. The reaction mixture was warmed on a water-bath for 20 minutes. The precipitated crude product was collected, washed with benzene, dried and recrystallized from aqueous methanol to give 6.5 g. (93%) of the product, m.p. 143°.

Infrared absorption spectra for the *p*-tolyl, *o*-tolyl and *p*-chlorophenyl β-methylglutaconanilic acids show absorption bands at 5.88–5.90 μ (acid or amide I carbonyl), 6.03–6.05 μ, 6.18–6.25 μ (phenyl), 6.45–6.52 μ (amide II carbonyl), 6.84–6.92 μ and 11.36–11.42 μ (C–H deformation vibration of trisubstituted olefin). β-Methylglutaconic acid shows absorption bands at 5.91 and 5.96 μ (dibasic acid double carbonyl), 6.06, 6.86 and 11.40 μ (C–H deformation).

The 1-aryl-4-methyl-6-hydroxy-2-pyridones IV given in Table II were prepared by three different procedures.

(1) **By Heating Together β-Methylglutaconic Acid and an Amine. 1-*p*-Tolyl-4-methyl-6-hydroxy-2-pyridones (IV, Ar = *p*-$CH_3C_6H_4$–).**—A mixture of 3.0 g. (0.02 mole) of dry β-methylglutaconic acid and 2.0 g. (0.02 mole) of *p*-toluidine was heated in a test-tube to 150° for 2 hr. The cooled residue was recrystallized first from benzene and then from ligroin–ethyl acetate or benzene–petroleum ether to give 1.2 g. (30%) of the product, m.p. 163°. The aniline derivative was prepared similarly. The *m*-chlorophenyl and *o*-tolyl analogs were purified by removal of the impurities on an alumina chromatographic column. The remaining compounds listed in the table were isolated by extracting a benzene solution of the crude reaction mixture, after it had been washed with water to remove unreacted acid, with sodium carbonate to remove the pyridone which was precipitated by acidification. The *p*-dimethylaminophenyl derivative was precipitated from the alkaline solution by acidification with acetic acid to *p*H 5–6.

(2) **By Refluxing a Mixture of β-Methylglutaconic Acid with an Amine in Benzene Solution. 1-(*p*-Dimethylaminophenyl-4-methyl-6-hydroxy-2-pyridone (IV, Ar = *p*-$Me_2NC_6H_4$–).**—The benzene layer obtained by extracting a solution of 4.0 g. (0.028 mole) of *p*-dimethylaminoaniline hydrochloride made alkaline with aqueous sodium hydroxide was dried and refluxed under a Barrett moisture test receiver with 2.0 g. (0.014 mole) of β-methylglutaconic acid. After 18 hr., 0.35 ml. (theory 0.50 ml.) of water had been collected. The benzene solution was extracted first with water to remove unreacted acid and then with 20% aqueous sodium bicarbonate to remove the pyridone. Acidification of the alkaline solution to a *p*H of 5–6 with acetic acid precipitated the crude pyridone. Recrystallization from methanol gave 0.5 g. (10%) of the product.

(3) **By Thermal Decarboxylation of β-Methylglutaconanilic Acids.**—This process gives the 6-hydroxy-2-pyridone, senecioanilide and a 3-methyl-3-butenoanilide.

One gram of 4-methyl-β-methylglutaconanilic acid (III, Ar = *p*-$CH_3C_6H_4$–) was heated for 20 minutes at 175°. A benzene solution of the residue was extracted with 20% aqueous sodium carbonate to remove the hydroxypyridone. Acidification of this solution precipitated the crude pyridone which was purified by recrystallization and observed to be identical with that prepared as described above.

The carbonate-extracted benzene solution was washed with dilute hydrochloric acid. The benzene solution was then washed with water and evaporated to a semi-crystalline mass. By recrystallization from both methanol and ligroin, this was separated into a higher melting, less soluble, minor fraction, m.p. 105°, which was identical on the basis of comparisons of infrared absorption spectra, with a sample of senecio-*p*-toluidide prepared as described in a following paragraph (and in Table III) and an isomeric more soluble, lower melting fraction, m.p. 71°, which on the basis of a strong absorption band at 11.20 μ characteristic of the $=CH_2$ group has been assigned the structure 3-methyl-3-buteno-*p*-toluidide.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 7.40. Found: N, 7.29.

TABLE VIII

1-ARYL-3-CARBOXY-4-METHYL-6-PYRIDAZONES

Compd. Ar' of XIII	M.p., °C.	Nitrogen anal., % Calcd.	Found
4-$CH_3C_6H_4$	213	11.47	11.47
2,6-$(CH_3)_2C_6H_3$	224	10.85	10.61[a]
4-$CH_3OC_6H_4$	221	10.77	10.68[b]
2,5-$(CH_3O)_2C_6H_3$	206	9.65	9.74
4-ClC_6H_4	216	10.59	10.47[c]
2-$HOOCC_6H_4$	231	10.22	10.22
4-$(CH_3)_2NC_6H_4$	251	15.38	15.58
4-$(C_2H_5)_2NC_6H_4$	187	13.95	13.95
1-$C_{10}H_7$	236	10.00	9.85
2-$C_{10}H_7$	240	10.00	9.97

[a] *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$: neut. equiv., 258. Found: neut. equiv., 253. [b] *Anal.* Calcd. for $C_{13}H_{12}O_4N_2$: neut. equiv., 260. Found: neut. equiv., 254. [c] *Anal.* Calcd. for $C_{12}H_9O_3N_2Cl$: neut. equiv., 264. Found: neut. equiv., 260.

The decarboxylation of the *o*-tolyl and *p*-chlorophenyl analogs gave mixtures of hydroxypyridone, senecioanilide and 3-methyl-3-butenoanilides which were separated and identified in a similar fashion. The senecioanilide and butenoanilide from *o*-toluidine melted at 99 and 100°, respectively, but showed a large depression of m.p. on admixture and distinctly different infrared absorption spectra. The senecioanilide from each was recrystallized up to ten times to obtain a pure fraction having no infrared absorption in the 11.2 μ region. Complete data on the infrared absorption characteristics of these compounds are given in Table IX. The products were present in a weight ratio of approximately one part of the senecioanilide, to five parts of the butenoanilide and eight parts of the hydroxypyridone.

TABLE IX

INFRARED ABSORPTION DATA[a]

Senecioanilides *o*-Tolyl	*p*-Tolyl	*p*-Chloro	3-Methyl-3-buteno-anilides *o*-Tolyl	*p*-Tolyl	*p*-Chlorophenyl
3.04s	3.03s	3.03s	3.07s	3.04s	3.06s
6.00m	6.05s	6.03s	6.05s	6.04s	6.05s
6.09s	6.13s	6.11s			
6.28m	6.27ms	6.16s	6.28m	6.22m	6.24m
6.53s	6.56s	6.56s	6.53s	6.58s	6.50s
		6.71s			6.69m
6.86m	6.91m	6.93m	6.87m	6.89m	6.84m
7.33w	7.14m	7.18m	7.39m	7.09m	7.14m
7.73s	7.65ms	7.67m	7.75m	7.59s	7.66m
7.95s	8.03s	8.04s	7.97s	7.98s	8.02s
8.59s	8.65s	8.64s	8.49s	8.63s	8.61s
		9.20s			9.10s
		10.00m	9.64m		9.87m
10.05m	10.09m	10.11m	10.33m	10.06w	
11.60s	11.87s	11.91m	11.14s	11.16m	11.20m
12.21m	12.30s	12.14s		12.22s	12.11s
13.26s	12.73m	12.85m	13.21s		12.82m
13.44s	13.47m	13.6m	13.45s	13.42m	

[a] m, medium; s, strong; w, weak.

3-Methyl-3-buteno-*o*-toluidide (XV, Ar = *o*-$CH_3C_6H_4$–), m.p. 99°.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 7.40. Found: N, 7.57.

3-Methyl-3-buteno-*p*-chloroanilide (XV, Ar = *p*-ClC_6H_4–), m.p. 72°.

Anal. Calcd. for $C_{11}H_{12}ClNO$: N, 6.68. Found: N, 6.85.

Senecio-*p*-toluidide (XVI, Ar = *p*-$CH_3C_6H_4$–).—Senecioic acid (2.0 g., 0.02 mole) was converted to its acid chloride by reaction with thionyl chloride. After removal of the volatile products the residual solid crude acyl chloride was dissolved in 20 ml. of dry benzene and 4.3 g. (0.04 mole) of *p*-toluidine was added. After warming 10 minutes, the benzene solution was washed with water, dilute acid and again with water. Evaporation left the crude product which was purified by recrystallization from benzene–petroleum ether. The substituted senecioanilides whose properties are given in Table III were prepared similarly.

The β-methylglutaconanilides VII were prepared from β-methylglutaconyl chloride. A typical example of the procedure used in the preparation of the anilides listed in Table IV follows.

β-Methylglutaconanilide (VII, Ar = C_6H_5–).—Five grams (0.035 mole) of powdered dry acid and 6 ml. (0.07 mole) of thionyl chloride were cautiously mixed. Considerable effervescence and decomposition took place. The excess thionyl chloride was removed under vacuum and the residue distilled under vacuum to give a fraction b.p. 85–90° (10 mm.), m.p. 55°. The solid was recrystallized from benzene–ligroin mixtures.

A solution of 0.35 g. (0.002 mole) of the acid chloride and 0.74 g. (0.004 mole) of aniline was dissolved in 15 ml. of dry benzene and warmed for 5–10 minutes on a water-bath. The benzene solution was washed with water to remove the precipitated aniline hydrochloride and with dilute acid (except for the dialkylamino derivatives) to remove unreacted aniline. The crude solid obtained on evaporation of the benzene was recrystallized from methanol to give 1.0 g. (90%) of the anilide, m.p. 177°.

The 1-aryl-1,2,5,6-tetrahydro-2,6-diketo-4-methyl-5-arylhydrazonopyridines V listed in Table VI were prepared by coupling diazonium salts with N-aryl-6-hydroxy-2-pyridones IV. A typical experimental procedure is given. The *p*-dimethylamino- and *p*-diethylaminophenyl derivatives were purified by deposition from benzene on an alumina column followed by elution with a benzene–ligroin mixture.

1-Phenyl-4-methyl-1,2,5,6-tetrahydro-2,6-diketo-5-(*p*-chlorophenyl)-hydrazonopyridine (V, Ar' = *p*-ClC_6H_4–; Ar = C_6H_5–).—A diazotized solution of 1.3 g. (0.01 mole) of *p*-chloroaniline was added to an ice-cold solution of 2.0 g. (0.01 mole) of 1-phenyl-4-methyl-6-hydroxy-2-pyridone and 0.5 g. (0.005 mole) of sodium carbonate in 25 ml. of water. The yellow precipitate was collected, washed, dried and recrystallized from ethyl acetate to give 2.3 g. (90%) of the product, m.p. 239°.

The reaction of dimethyl β-methylglutaconate with aryldiazonium salts gave complex mixtures from which dimethyl γ-arylhydrazono-β-methylglutaconates XI, 1-aryl-5-arylazo-4-methyl-3-carbomethoxy-6-pyridazones X and 1-aryl-4-methyl-3-carbomethoxy-6-pyridazones XII were isolated by chromatography. The procedure is similar to that previously used[16] for this type of reaction.

An ice-cold solution of diazotized aniline (2.7 g., 0.03 mole) was added to a solution of 5.0 g. (0.03 mole) of dimethyl β-methylglutaconate in 1.5 g. (0.03 mole) of sodium methoxide in 250 ml. of methanol to which had been added 25 g. of sodium acetate in 150 ml. of water. The product separated as a tar, which was taken up in benzene and separated into fractions by adsorption on an alumina column followed by elution with benzene–petroleum ether. The fractions thus separated by chromatography were recrystallized to give the products listed in Table VII. The two products melting at 140° and 180° to which structure X has been assigned obtained from *p*-methoxyaniline gave similar infrared absorption in the carbonyl and double bond region with maxima at 5.80, 5.98, 6.22 and 6.68 μ and in the 10–13 μ skeletal region but with three additional bands between 7 and 8 μ in the material melting at 180° which do not appear in the 140° isomer.

1-(*p*-Tolyl)-3-carboxy-4-methyl-6-pyridazone (XIII, Ar = *p*-$CH_3C_6H_4$–). (a) From **1-*p*-Chlorophenyl-1,2,5,6-tetrahydro-2,5,6-triketo-4-methylpyridine 5-*p*-Tolylhydrazone**.—The yellow solution obtained by refluxing 0.3 g. of the starting material and 2.0 g. of sodium hydroxide in 15 ml. of water was cooled, extracted with ether and acidified to precipitate the crude product. Recrystallization from ethyl acetate–ligroin gave 0.1 g. (33%) of the pure product. Some of the derivatives (V, Ar = *p*-ClC_6H_4–; Ar' = 2,5-

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[16] F. Henrich and W. Thomas, *Ber.*, **40**, 4924 (1907).

$(CH_3O)_2C_6H_4$–) required longer periods of hydrolysis to complete this reaction. Others (V, Ar = 2,6-$(CH_3)_2C_6H_3$–; Ar′ = either *o*-$CH_3OC_6H_4$–; *p*-$CH_3OC_6H_4$–; or 2,5-$(CH_3O)_2$-C_6H_3–) were not hydrolyzed after 3.5 to 8 days of refluxing with alkali. Hydrolysis of the product in which Ar′ of V is 2,6-dimethylphenyl gave γ-(2,6-dimethylphenylhydrazono)-β-methylglutaconanilic acid, m.p. 142°.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: N, 11.96. Found: N, 11.77.

(b) From Dimethyl γ-*p*-Tolylhydrazono-β-methylglutaconate (XI, Ar = *p*-$CH_3C_6H_4$–).—A solution was obtained by refluxing 0.1 g. of the starting material with 5% aqueous sodium hydroxide for 15 minutes. The solution was cooled, extracted with ether and acidified to precipitate the product in 65% yield. Recrystallization gave a product with properties identical with those previously recorded.

(c) From the Pyridazone Ester (XII, Ar = *p*-$CH_3C_6H_4$–).—Alkaline hydrolysis gave the same product, m.p. 142°.

1-(*p*-Chlorophenyl)-4-methyl-6-pyridazonecarboxanilide (XVII, Ar = C_6H_5–; Ar′ = *p*-ClC_6H_4–).—A slight excess (1.5 ml.) of thionyl chloride was added to 0.5 g. of the acid (XIII, Ar = *p*-ClC_6H_4–). The acid chloride, prepared with excess thionyl chloride, was dissolved in dry benzene and treated with a solution of 0.37 g. of aniline in benzene. After gentle warming the reaction mixture was washed with water to remove the salt and with dilute acid to remove unreacted base. Evaporation of the solvent deposited the crude product, which was recrystallized from methanol to give 0.55 g. (90%) of the product, m.p. 179°.

Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: N, 12.36. Found: N, 12.45.

4′-Methyl-1-(*p*-chlorophenyl)-4-methyl-6-pyridazonecarboxanilide (XVII, Ar = *p*-$CH_3C_6H_4$–; Ar′ = *p*-ClC_6H_4–).—This was prepared from *p*-toluidine by the procedure given above for the anilide. Recrystallization from methanol gave 85% of the product, m.p. 165°.

Anal. Calcd. for $C_{19}H_{16}ClN_3O_2$: N, 11.87. Found: N, 11.65.

Dimethyl γ-(*p*-Chlorophenylhydrazono)-glutaconate.—Diazotized *p*-chloroaniline was coupled with dimethyl glutaconate in a 1/1 mole ratio following the procedure given above for the similar reaction of dimethyl β-methylglutaconate. The solid precipitate which formed on standing was dissolved in benzene, treated with alumina and evaporated to deposit the crude product. Recrystallization from methanol gave 1.0 g. (18%) of yellow crystals, m.p. 101°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_4$: N, 9.44. Found: N, 9.27.

Dimethyl α-(*p*-Chlorophenylazo)-γ-(*p*-chlorophenylhydrazono)-glutaconate.—This compound was obtained using two moles of diazonium salt per mole of ester. Recrystallization from benzene–petroleum ether gave 1.5 g. (13%) of red-brown crystals which melted at 135°, resolidified and remelted at about 188°.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_4O_4$: N, 12.87. Found: N, 12.64.

1-(*p*-Chlorophenyl)-3-carbomethoxy-5-(*p*-chlorophenylazo)-6-pyridazone.—The precipitate formed on warming a solution of 0.5 g. of the preceding compound in 50 ml. of methanol for 15 minutes was recrystallized from methanol to give 0.35 g. (75%) of orange-brown crystals, m.p. 209°.

Anal. Calcd. for $C_{18}H_{13}Cl_2N_4O_3$: N, 13.90. Found: N, 13.95.

Infrared absorption data were obtained using a Baird double beam recording infrared spectrophotometer equipped with a beam condensing unit on samples prepared as potassium bromide pellets. All measurements were calibrated against the 3.419 μ band in polystyrene.

LOUISVILLE, KENTUCKY

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, CAIRO UNIVERSITY AND AIN SHAMS UNIVERSITY]

Experiments with 2-Methyl-1,4-α-naphthopyrone and Related Substances

BY ALEXANDER SCHÖNBERG, ABD EL KADER FATEEN AND ABD EL MAGED AMINE SAMMOUR

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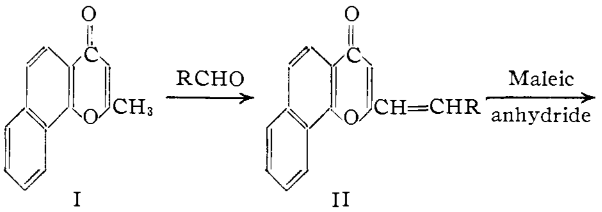
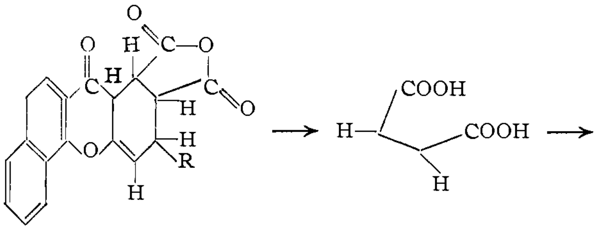
2-Methyl-1,4-α-naphthopyrone (I) was condensed with various aromatic aldehydes. The 2-styryl derivatives IIf and IIg were allowed to react with maleic anhydride, yielding the Diels–Alder products III which are derivatives of xanthone. The action of hydroxylamine on I led to (Va or Vb, R = VI); with hydrazine hydrate and phenylhydrazine the pyrazole derivatives (VIIa or VIIb) and (VIIIa or VIIIb) were obtained. 2-Styryl-1,4-α-naphthopyrone was hydrolyzed to give cinnamic acid and 1-hydroxy-2-acetonaphthalene and allowed to react with phenylhydrazine to give VIIIa or VIIIb (R = VI, R′ = $C_6H_5CH{=}CH$-).

Schönberg, Mustafa and Aziz[1] have found that some 2-styrylchromones which are easily obtainable by the condensation of 2-methylchromones with aromatic aldehydes may enter into the Diels–Alder reaction with maleic anhydride.

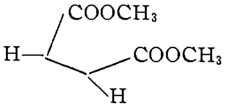
We have condensed 2-methyl-1,4-α-naphthopyrone (I) with *o*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, 3,4-diethoxybenzaldehyde, cinnamaldehyde and piperonal and obtained the corresponding new 2-styryl derivatives (IIa-e). IIf and IIg, two known substances, have been tested toward maleic anhydride.



I II

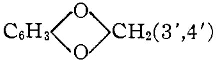


III IIIa



IIIb

a, R = $C_6H_4Cl(o)$
b, R = $C_6H_4NO_2(p)$
c, R = $C_6H_3(OC_2H_5)_2(3',4')$
d, R = CH:CH–C_6H_5

e, R = 

$C_6H_3\langle O_2 \rangle CH_2(3',4')$

f, R = C_6H_5
g, R = $C_6H_4OCH_3(p)$

2-Styryl-1,4-α-naphthopyrone (IIf)[2] reacts easily with maleic anhydride in boiling xylene, yielding

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[1] A Schönberg, A. Mustafa and G. Aziz, THIS JOURNAL, **76**, 4576 (1954).

[2] Ujager Singh Chemma, Khushhal Chand Gulati and Krishnusami Venkataraman, *J. Chem. Soc.*, 925 (1932).