Derivatives of Hemimellitic Acid. A Synthesis of Erythrocentaurin[1]

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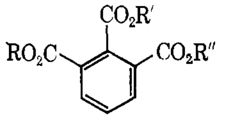
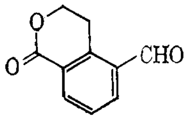
The chemistry of hemimellitic acid has been investigated. Its esters were synthesized and their structures were determined. Its anhydride and anhydride acid chloride were reduced. The homologation and reduction of some carboxyphthalides and the pyrolysis and reduction of others have been studied. Acylation of dimethyl 2-methylisophthalate and its dinitrile has been investigated and the chemistry of the resulting isocoumarin and isocarbostyril has been inspected. The conversion of the isocoumarin derivative into erythrocentaurin is presented.

In the pursuit of two independent problems of structure analysis we were in need of 1,2,3-trisubstituted benzene compounds of the C_6–C_1–C_2–C_1 and C_6–C_2–C_1–C_1 types. Since, in principle, these substances should be derivable from hemimellitic acid (1a) by the homologation of a suitable derivative, we became interested in this process. However, on discovery that little is known about the general chemistry of hemimellitic acid (1a), we expanded our study and now report on the reactions of this interesting aromatic acid and its derivatives as well as on the achievement of one of our initial goals—the synthesis of erythrocentaurin (2).

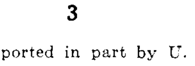


1a, R = R′ = R″ = H
b, R = R′ = R″ = Me
c, R = R″ = H; R′ = Me
d, R = Me; R′ = R″ = H
e, R = R″ = Me; R′ = H
f, R = H; R′ = R″ = Me



2

Hemimellitic Acid (1a).—An early synthesis of hemimellitic acid (1a) and most of the recorded chemistry of the compound are due to the classical studies of Graebe and co-workers.[3] Since the low yield of **1a** by Graebe's method of oxidation of acenaphthene and the further oxidation of the resulting naphthalic acid was discouraging for a large-scale synthesis of the triacid, a new synthesis was developed.[4] The recent successful conversion of a α-pyrone derivative to an aromatic nucleus[5] suggested that copyrolysis of methyl α-pyrone-6-carboxylate (3)[6] and dimethyl acetylenedicarboxylate may produce trimethyl hemimellitate (1b). Indeed, this reaction afforded a 70% yield of the desired product.



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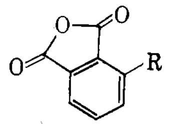
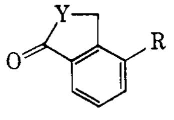
Three of the five possible methyl esters of hemimellitic acid (1a) have been reported by Graebe and coworkers.[3] Diazomethane treatment of hemimellitic anhydride (4a) afforded its ester (4b), which on warming in aqueous acetone yielded an ester diacid different from Graebe's monoester. Pyrolysis of our ester diacid reverted it to the anhydride ester **4b**, while a similar treatment of Graebe's ester yielded hemimellitic anhydride (4a). These facts show Graebe's ester to be 2-carbomethoxyisophthalic acid (1c), as Graebe had proposed, and our ester to be 3-carbomethoxyphthalic acid (1d).



4a, R = CO_2H
b, R = CO_2Me
c, R = COCl
d, R = Me
e, R = CHO

Treatment of 3-carbomethoxyphthalic acid with methanolic hydrogen chloride led to a diester acid, identical with the compound obtained by Graebe[3] on similar treatment of hemimellitic acid, and a small quantity of the triester **1b**.[7]

Methanolysis of 3-carbomethoxyphthalic anhydride (4b) yielded a different diester acid, whose treatment with methanolic hydrogen chloride afforded trimethyl hemimellitate. These data confirm Graebe's assignment of **1e** to his diester acid and indicate **1f** as the structure of our isomer.



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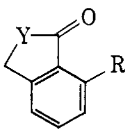

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a, Y = O; R = CO_2H
b, Y = O; R = CH_2OH
c, Y = O; R = CH_2OAc
d, Y = O; R = CHO
e, Y = O; R = $CONH_2$
f, Y = O; R = CN
g, Y = NH; R = CO_2H
h, Y = O; R = CO_2Me
i, Y = O; R = CH_2CO_2Me

Reduction of hemimellitic anhydride (4a) with zinc and acetic acid[8] yielded two phthalides, **5a** and **6a**. The latter structure could be assigned to the lower

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[2] Public Health Service Predoctorate Fellow, 1959–1960.

[3] C. Graebe and M. Leonhardt, *Ann.*, **290**, 217 (1896); C. Graebe and F. Bossel, *Ber.*, **26**, 1797 (1898).

[4] The recent alternate route by J. Gut [*Collection Czech. Chem. Commun.*, **21**, 1648 (1956)] was not investigated.

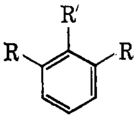
[5] N. P. Shusherina, R. Ya. Levina, and V. M. Shostakovskii, *J. Gen. Chem. USSR*, **29**, 3200 (1959).

[6] A. Lapworth, *J. Chem. Soc.*, **79**, 1265 (1901).

[7] R. Meyer and H. Wesche [*Ber.*, **50**, 452 (1917)] have found some triester to accompany the diester.

[8] *Cf.* the reduction of phthalic anhydride by J. Wislicenus, *ibid.*, **17** 2178 (1884).

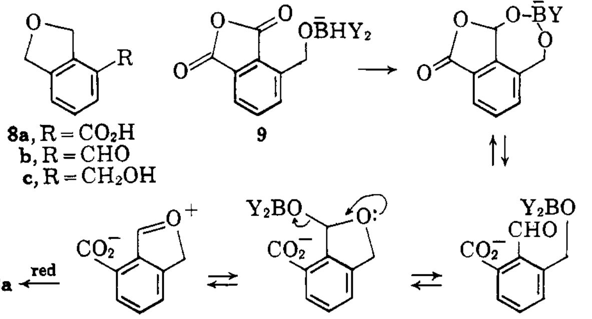
melting isomer on the basis of its conversion to 3-methylphthalic acid with phosphorus and hydriodic acid and the transformation of the reduction product to 3-methylphthalic anhydride (**4d**) on pyrolysis. The higher melting phthalide, thus **5a**, proved unreactive in a similar attempt of reduction.



7a, R = Me; R' = R'' = CO_2H
b, R = R' = R'' = CH_2OH
c, R = R' = R'' = CH_2OAc
d, R = $(CH_2)_2OH$; R' = R'' = CH_2OH
e, R = R'' = CO_2H; R' = $COCO_2H$
f, R = R'' = CO_2H; R' = Me
g, R = R'' = CO_2H; R' = CHO
h, R = NH_2; R' = Me; R'' = CN
i, R = R'' = CN; R' = Me
j, R = R'' = CO_2Me; R' = Me
k, R = R'' = CO_2H; R' = CH_2CO_2H
l, R = R'' = CO_2Me; R' = CH_2CO_2Me
m, R = R'' = CH_2OH; R' = $(CH_2)_2OH$

Alternative syntheses were devised leading specifically to either of the two phthalide systems, in order to avoid the need of separation of isomers in the above reduction scheme. The following route to norerythrocentaurin (**5d**) was designed to serve also as a model for the later synthesis of erythrocentaurin (**2**). Lithium aluminum hydride reduction of hemimellitic anhydride (**4a**) yielded the triol **7b**, the previously reported product of a similar reduction of trimethyl hemimellitate (**1b**),[9] and the phthalide **6b** in minor amount. Acetylation of these substances yielded the triacetate **7c** and the phthalide ester **6c**, respectively. Manganese dioxide oxidation of the triol (**7b**) produced norerythrocentaurin. The structure of the product was established by its synthesis from the phthalide acid **5a**, treatments with thionyl chloride and with sodium borohydride, and manganese dioxide oxidation of the resulting alcohol **5b**. The preferred oxidation of the outside hydroxymethyl groups in triol **7b** revealed itself once again when permanganate oxidation of the triol could be shown to yield **5a**.

Sodium borohydride reduction of hemimellitic anhydride chloride (**4c**) in diglyme solution yielded a mixture from which the other phthalide acid (**6a**) and minor quantities of hemimellitic acid (**1b**) and acid **8a** could be isolated. While **1a** was a trivial product of hydrolysis, the dihydroisobenzofuran derivative (**8a**) represents a product of overreduction, a consequence of intramolecular hydride transfer onto the central carbonyl group. Whereas the first reduction intermediate (**4e**) can have its outside carbonyl functions reduced further without interference with the central substituent, one of the possible next intermediates (**9**) may effect tangentially an internal reduction, set up a series of equilibria, and end the reaction sequence by one more reduction (*vide infra*). A most striking second case of an internal reduction was furnished by the sodium borohydride reduction of the acid chloride, prepared by the thionyl chloride treatment of the acid **6a**. While the expected alcohol **6b** was the preponderant product, it was accompanied by the overreduction products **8b** and **8c**. The use of an excess of sodium borohydride led to the triol **7b**.[10] The dihydroisobenzofuran derivatives could be interrelated by manganese dioxide oxidation of the alcohol (**8c**) to the aldehyde (**8b**) and by silver oxide oxidation of the latter to the acid (**8a**). Sodium borohydride reduction of the acid chloride, obtained from the thionyl chloride treatment of the acid **5a**, yielded exclusively the normal alcohol **5b**. In this instance no intramolecular reaction could take place and hence no unusual product resulted.



8a, R = CO_2H
b, R = CHO
c, R = CH_2OH

9

Since phthalide is known to be susceptible to nucleophilic attack by cyanide ion, such a reaction being useful in the synthesis of *o*-carboxyphenylacetonitrile,[11] the potasium cyanide fusion with phthalides of type **5** and **6** was studied. However, the nitrile **5f** (the least sterically hindered compound of type **5**), prepared by treatment of the acid chloride of **5a** with ammonia and the resulting amide **5e**[12] with phosphorus oxychloride, proved inert. A similar reaction with the ester **6h**, prepared by diazomethane treatment of the acid **6b**, produced only its acid **6b**.[13]

Whereas biosynthetic considerations had limited the structure of erythrocentaurin to **2**,[14] the available chemical data did not preclude the isomeric structure **10**.[15] Since the latter represents a C_6–C_2–C_1–C_1 system, which, in principle, should be within synthetic reach by homologation of the acids **5a** or **6a**, a synthesis of the triol **7d**, a degradation product of erythrocentaurin[15] (on the basis of its structure **10**), was undertaken. Arndt–Eistert synthesis transformed the phthalide acids **5a** and **6a** to their homologous methyl esters, **5i** and **6i**, respectively. Repeated lithium aluminum hydride reductions of **6i** led to mixtures still containing carbonyl functions. This result was reminiscent of the aforementioned incomplete reduction of hemimellitic anhydride (*vide supra*). However, a similar reduction of **5i** yielded the desired triol **7d**, which because of its liquid state was characterized as its crystalline tribenzoate. The difference of physical state of the triol (**7d**) and that of the reported product of reduction of erythrocentaurin (m.p. 103°[15]) constituted

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(9) A. Benning and O. Grosskinsky, *Ber.*, **87**, 54 (1954).

(10) Although normally sodium borohydride is not known to reduce esters or lactones, it may do so intramolecularly [*cf.* J. C. Sowden, *J. Am. Chem. Soc.*, **74**, 4377 (1952)].

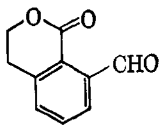
(11) C. C. Price and R. G. Rogers, *Org. Syn.*, **22**, 30 (1942).

(12) An attempted intramolecular displacement also was unsuccessful. The pyrolysis of the phthalide amide **5e**, which might be expected to rearrange to the phthalimidine acid **5g**, yielded an acid product whose lack of crystallinity prevented its characterization.

(13) Cyanide ion may prove to be an excellent demethylating agent; *e.g.*, refluxing of an acetonitrile solution of sodium cyanide and β-naphthyltrimethylammonium iodide affords a quantitative yield of β-dimethylaminonaphthalene (T. L. Reid, unpublished observation).

(14) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474, 6553 (1959).

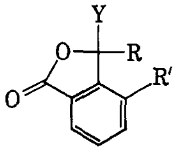
(15) T. Kubota and Y. Tomita, *Chem. Ind.* (London), **230** (1958).



10

our first experimental indication that formula **10** represented the less likely structure of erythrocentaurin.

Graebe's Acid (11a).—The keto triacid **7e**[3,16] is a representative of our desired C_6–C_1–C_2–C_1 system. Hence its chemistry came under scrutiny.

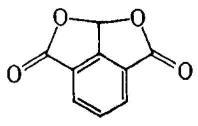


11a, Y = OH; R = R′ = CO_2H
b, Y = OMe; R = R′ = CO_2Me
c, Y = H; R = R′ = CO_2H
d, Y = H; R = R′ = CO_2Me
e, Y = OH; R = H; R′ = CO_2H

Inspection of the infrared spectra of Graebe's acid and its ester [phthalide carbonyl bands at 5.67 μ (Nujol)] indicated the phthalide structures, **11a** and **b**, respectively.[17] In an attempted conversion of the acid by reduction with zinc and acid the phthalide diacid **11c** was produced. Its pyrolytic decarboxylation led to our previously prepared phthalide monoacid **5a**. Attempted catalytic hydrogenation as well as zinc–acetic acid reduction of the diester **11d**, obtained by diazomethane treatment of **11c**, yielded only starting material. While Graebe[16] reported the reduction of his acid (**11a**) with phosphorus and hydriodic acid to yield 2-methylisophthalic acid (**7e**), repetition of this reaction afforded in our hands only starting material and diacid **11c**. Further reduction of the latter with the same reagents left the acid unchanged or, on stronger heating, decarboxylated it to **5a**.

Pyrolysis of Graebe's acid (**11a**) has been reported to yield hemimellitic acid (**1a**), the aldehydo acid **7g** and its dehydration product **12**.[16] While no direct evidence for the structures **7g** and **12** has been brought forth and the aldehyde more recently has been considered to exist mostly in the lactol form **11e**,[17] the fact that exposure of the crude reaction mixture from the pyrolysis of Graebe's acid to nickel–aluminum alloy in base, the ingredients necessary to produce Raney nickel, has led to 2-methylisophthalic acid[18] has lent support to the previous structure assignment of at least the aldehyde (**7g–11e**). On repetition of Graebe's pyrolysis experiment, four substances, one more than had been found heretofore, were isolated in *ca.* 70% over-all yield. They were (in decreasing order of yield) hemimellitic acid (**1a**), the phthalide acid **5a**, the aldehyde **11e**, and the presumed dilactone (**12**).[19]

A mechanistic justification for the pyrolytic formation of hemimellitic acid (**1a**) and the lactol (**11e**) is readily envisaged. Decarbonylation of Graebe's acid, presumably in the glyoxylic acid form **7e**, to **1a** has many precedents,[20] while the decarboxylation to **11e** is in conformity with the pyrolytic conversion of **11c** to **5a** (*vide supra*). However, the appearance of the heretofore unnoticed phthalide acid **5a** as a major product seems unusual. Its low state of oxidation and coproduction with **1a**, a product of high state of oxidation, suggests that a disproportionation led to the formation of **5a**. Two possible reaction paths can be envisaged. One involves the aforementioned decarboxylation of Graebe's acid (**11a**) and a thermal, presumably acid-catalyzed (and thus unusual) Canizzaro reaction of the resulting aldehyde (**7g–11e**). The alternate and more likely path (*vide infra*) involves normal heat-induced lactide formation of the α-hydroxy acid (**11a**), fragmentation of the dehydrated dimer (**13**) into carbon dioxide, hemimellitic anhydride (**4a**), and ketene **14**, hydration of the latter to the phthalide diacid (**11c**), and decarboxylation thereof to **5a**.



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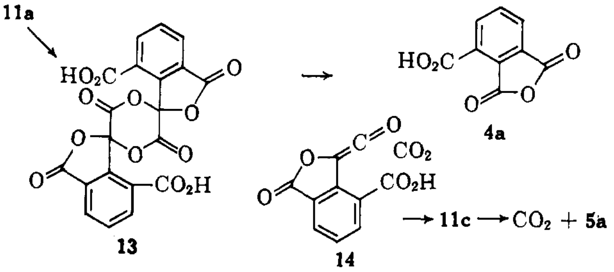

2-Methylisophthalic Acid (7f).—By now our cumulative experience in the chemistry of hemimellitic (**1a**) and Graebe's (**11a**) acids had indicated that the high state of oxidation of the central side chain of these acids and their derivatives and its irreducibility kept us from the erythrocentaurin system (**2**). Hence it was decided to concentrate on the reactions of 2-methylisophthalic acid (**7f**) derivatives. Although the acid was available on degradation of Graebe's acid (**11a**),[18] it and its desired dinitrile (**7i**) and dimethyl ester (**7j**) were prepared on large scale from the cyanotoluidine **7h**.[21] Sandmeyer reaction of its diazonium salt with cuprous cyanide converted the latter to the nitrile **7i**, whose hydrolysis led to the diacid **7f**. Diazomethane treatment of the acid afforded the ester **7j**.

It was expected that the ester and especially the nitrile, 2-methylisophthalic acid's sterically least hindered derivative, could be induced to undergo base-catalyzed condensation with esters. While electronically similarly constituted *o*- and *p*-nitrotoluenes have been known for over half a century to be excellent substrates for such a reaction,[22] it is a curious fact that *o*- and *p*-toluic acid derivatives appear never to have been used for this condensation.

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[16] C. Graebe and F. Bossel, *Ann.*, **290**, 206 (1896).

[17] *Cf.* N. P. Buu-Hoï and P. Cagniant, *Compt. rend.*, **212**, 908 (1941).

[18] R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).

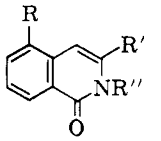
[19] The last two substances were not investigated beyond an inspection of their infrared spectra (see Experimental). The spectrum of the aldehyde tended to confirm a lactol form, while that of the "dilactone (**12**)" indicated a complex substance containing features of phthalide acid **5a**.

[20] *Cf.* W. W. Elliot and D. L. Hammick, *J. Chem. Soc.*, 3402 (1951).

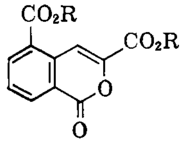
[21] E. Noelting, *Ber.*, **37**, 1015 (1904).

[22] *Cf.* the Reissert indole and oxindole syntheses [A. Reissert, *ibid.*, **30**, 1030 (1897); A. Reissert and J. Scherk, *ibid.*, **31**, 387 (1898)].

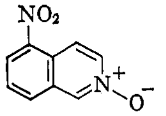
Condensation of 2-methylisophthalonitrile (**7i**) with ethyl formate in the presence of potassium *t*-butoxide, followed by acid treatment, yielded 5-cyanoisocarbostyril (**15a**). This unusual product was probably the consequence of an internal Ritter reaction of the expected 2,6-dicyanophenylacetaldehyde under the influence of the later acid treatment. Condensation of the nitrile **7i** with ethyl oxalate under similar conditions, followed by mild base hydrolysis and diazomethane treatment, gave 2-methyl-3-carbomethoxy-5-cyanoisocarbostyril (**15b**). Apparently the lactam was enough acidic to have been N-methylated by diazomethane. A similar set of reactions with the diester **7j** and ethyl oxalate produced 3,5-dicarboxyisocoumarin (**16a**) and its dimethyl ester (**16b**). It thus appears that relatively simple reactions of 2-methylisophthalic acid derivatives afford a new, fast route to certain aromatic heterocyclic compounds.



15a, R = CN; R′ = R″ = H
b, R = CN; R′ = CO₂Me, R″ = Me
c, R = NO₂; R′ = R″ = H
d, R = NH₂; R′ = R″ = H
e, R = CO₂Me; R′ = R″ = H



16a, R = H
b, R = Me



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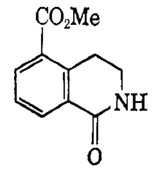
The structure of the isocarbostyril derivative **15a** was established by the following alternate synthesis. Acetic anhydride treatment of 5-nitroisoquinoline oxide (**17**)[23] yielded 5-nitroisocarbostyril (**15c**)[24] whose hydrogenation over palladium-charcoal led to the 5-amino compound **15d**. A Sandmeyer reaction of the latter (with cuprous cyanide) produced 5-cyanoisocarbostyril (**15a**).

Hydrolysis of the cyano compound, followed by diazomethane treatment, gave 5-carbomethoxyisocarbostyril (**15e**). Hydrogenation of the latter over platinum in acetic acid produced its dihydro derivative (**18**) in low yield accompanied by a mixture of over-reduced products. Attempted removal of the nitrogen from **18** by a variety of standard processes failed.[25]

Basic hydrolysis of the isocoumarin **16a**, followed by alkaline hydrogen peroxide treatment, led to *sym*-homohemimellitic acid (**7k**, 2,6-dicarboxyphenylacetic acid). Acetic anhydride treatment of the acid (**7k**) afforded the unusual product **19** which probably arises from an intramolecular condensation of the intermediate mixed anhydride **20b**.[26]



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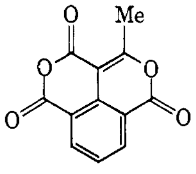

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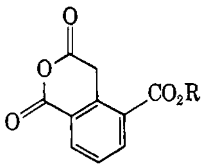

20a, R = H
b, R = Ac

Lithium aluminum hydride reduction of trimethyl *sym*-homohemimellitate (**7l**), obtained by diazomethane treatment of its acid (**7k**), yielded a crystalline triol (**7m**). Manganese dioxide oxidation of the latter afforded the lactone aldehyde **2**, which proved to be identical with erythrocentaurin.[27] This completed our synthesis of the degradation product of swertiamarin, the bitter principle of *Swertia japonica* Makino.[28]

Experimental

Trimethyl Hemimellitate (1b).—A suspension of 23 mg. of 6-carbomethoxy-α-pyrone, prepared by the method of Lapworth,[6] in 100 mg. of dimethyl acetylenedicarboxylate was heated at 210–215°. After 4 hr., a benzene extract of the mixture was chromatographed on silicic acid. Elution with 2:1 benzene-ether afforded 22 mg. of trimethyl hemimellitate, m.p. 99–101°, identified by infrared spectral, melting point, and mixture melting point comparison with authentic material prepared by the method of Graebe.[3]

3-Carbomethoxyphthalic Anhydride (4b).—A solution of 290 mg. of hemimellitic anhydride (**4a**), m.p. 193–195° (lit.[3] m.p. 196°), in tetrahydrofuran was treated with excess diazomethane. Crystallization of the product from acetone yielded 156 mg. of 3-carbomethoxyphthalic anhydride (**4b**). The analytical sample had m.p. 143–145°; infrared spectrum (Nujol): 5.37 and 5.61 (anhydride C═O), and 5.75 μ (ester C═O).

Anal. Calcd. for $C_{10}H_6O_5$: C, 58.26; H, 2.93. Found: C, 58.26; H, 3.00.

3-Carbomethoxyphthalic Acid (1d).—Cooling a solution of 3-carbomethoxyphthalic anhydride (**4b**) in aqueous acetone afforded 3-carbomethoxyphthalic acid (1d), m.p. 194–199° dec.; infrared spectrum (Nujol): 5.75–5.95 μ (acid and ester C═O).

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.58; H, 3.60. Found: C, 53.46; H, 3.53.

Upon heating, **1d** sublimed readily giving 3-carbomethoxyphthalic anhydride (**4b**), identified by comparison with authentic material.

Upon heating, 2-carbomethoxyisophthalic acid, m.p. 204–210° (lit.[3] m.p. 203–205°), sublimed slowly giving hemimellitic anhydride (**4a**), identified by melting point, mixture melting point, and infrared spectral comparison with authentic material.

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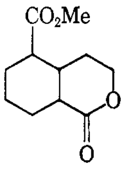
[23] E. Ochiai and M. Ikehara, *J. Pharm. Soc. Japan*, **73**, 666 (1953).

[24] B. Elpern and C. S. Hamilton, *J. Am. Chem. Soc.*, **68**, 1436 (1946).

[25] Acid hydrolysis of the overreduction mixture and nitrous acid and diazomethane treatments afforded the ester lactone i, m.p. 72–73°, in low yield.



i

[26] Pyrolysis of the acid gave the anhydride **20a** in low yield.

[27] The authors are most grateful to Professor Kubota for a comparison sample.

[28] Prior to the completion of the last phases of our work there appeared a preliminary communication on the synthesis of erythrocentaurin by T. Kubota, Y. Tomita, and K. Suzuki [*Tetrahedron Letters*, **No. 6**, 223 (1961)], which, as a consequence, constituted the first proof of its structure. Our work was continued in view of the complete dissimilarity of the two synthetic approaches.

A solution of 3-carbomethoxyphthalic acid (from 205 mg. of hemimellitic acid) in 10 ml. of anhydrous methanol was saturated with dry hydrogen chloride gas. After 24 hr. the solvent was evaporated, and the residue, in ether, was washed with water and aqueous sodium bicarbonate, dried with sodium sulfate, and evaporated to give 13 mg. of trimethyl hemimellitate (**1b**), m.p. 98–101°, identified by melting point, mixture melting point, and infrared spectral comparison with authentic triester.[3]

The aqueous and bicarbonate washings upon acidification and extraction with ethyl acetate afforded 63 mg. of crude dimethyl 2-carboxyisophthalate, identified by melting point, mixture melting point, and infrared spectral comparison with authentic material.[3]

Dimethyl 3-Carboxyphthalate (1f).—Upon cooling a solution of 3-carbomethoxyphthalic anhydride (**4b**) in methanol, crude dimethyl 3-carboxyphthalate (**1f**) was obtained. The analytical sample had m.p. 160–163°; infrared spectrum (Nujol): 5.75–5.83 (ester C=O) and 5.92 μ (acid C=O).

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.30; H, 4.37.

The mother liquors afforded a second substance (*ca.* 10% overall yield) which had m.p. 148–153°; infrared spectrum (Nujol): 5.75–5.92 μ (ester and acid C=O). It was identified as dimethyl 2-carboxyisophthalate (**1e**) by comparison with an authentic sample.[3]

Zinc–Acetic Acid Reduction of Hemimellitic Anhydride (4a).—A refluxing solution of hemimellitic anhydride (from 2 g. of acid) in 15 ml. of acetic acid was treated with 3 g. of zinc dust over a 45-min. period. Heating was continued for 1 hr., the mixture was filtered, and the filtrate was evaporated under reduced pressure. A solution of the residue in 50 ml. of dry methanol was saturated with dry hydrogen chloride gas and after standing 24 hr. was taken to dryness under reduced pressure. The residue, in chloroform, was washed three times with water and evaporated under reduced pressure. The solid residue was taken up in 20 ml. of methanol, a solution of 5 g. of sodium bicarbonate in 45 ml. of water was added, and the mixture refluxed for 12 hr. After acidification, the solution was taken to dryness under reduced pressure and the crude products were extracted with tetrahydrofuran from the inorganic solids. Chromatography of the mixture on 30 g. of silicic acid and elution with 3:2 up to 1:1 petroleum ether–ether yielded 4-carboxyphthalide (**5a**), while with 2:3 and 3:7 petroleum ether–ether 7-carboxyphthalide (**6a**) appeared. Yields of crude phthalides were usually 10–15% of each, **6a** predominating slightly. Crystallization from methanol afforded analytical samples having m.p. 170–172° (**6a**) and m.p. 246–247° (**5a**) with crystal changes at *ca.* 180° and *ca.* 220°. Their infrared spectra (Nujol) showed strong bands at 5.69 (phthalide C=O) and 5.93 (acid C=O) (**5a**) and 5.75–6.1 μ (H-bonded phthalide C=O and acid C=O) (**6a**).

Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.40. Found for **5a**: C, 60.80; H, 3.49. Found for **6a**: C, 60.38; H, 3.45.

4-Carbomethoxyphthalide (**5h**) and 7-carbomethoxyphthalide (**6h**) were prepared in the usual fashion from the acids with diazomethane in 1:1 ether–tetrahydrofuran. The analytical samples, crystallized from methanol, had m.p. 179–180° (**5h**) and 106–108° (**6h**); infrared spectra (Nujol): 5.66 (phthalide C=O) and 5.89 (ester C=O) (**5h**), and 5.70 (phthalide C=O) and 5.82 μ (ester C=O) (**6h**).

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found for **5h**: C, 62.37; H, 4.26. Found for **6h**: C, 62.87; H, 4.31.

A sample of ester **6h** was heated and stirred for several hours with an equal weight of powdered potassium cyanide at 180–200°. The cyanide was destroyed with 20% hydrochloric acid and the reaction mixture was evaporated under reduced pressure. The residue afforded only the phthalide acid **6a** upon chromatography.

Phosphorus–Hydriodic Acid Reduction of 7-Carboxyphthalide (6a).—A mixture of 204 mg. of 7-carboxyphthalide and 0.5 ml. of 58% hydriodic acid was heated to 125–150°, and *ca.* 40 mg. of yellow phosphorus added over 4 hr. After 4 hr. more, the colorless solution was decanted from unreacted phosphorus and taken to dryness under reduced pressure. The crude product was crystallized repeatedly form methanol giving 3-methylphthalic acid (**7a**), m.p. 159–161° dec. (lit.[29] m.p. 157°); infrared spectrum (Nujol): 6.00 μ (sh 5.95, acid C=O). Upon heating under reduced pressure, 3-methylphthalic acid underwent rapid sublimation to give 3-methylphthalic anhydride (**4d**), m.p. 116–117° (lit.[30] m.p. 117–118°); infrared spectrum (Nujol): 5.52 and 5.74 μ (anhydride C=O).

Anal. Calcd. for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.87; H, 3.94.

Under the same set of conditions 7-carboxyphthalide failed to give any sign of 2-methylisophthalic acid (**7f**) and was recovered from the reaction mixture.

4-Carboxamidophthalide (5e).—The acid chloride from 54 mg. of **5a** was prepared as in the reduction with sodium borohydride (*vide infra*) and converted to the amide by addition, in tetrahydrofuran, to aqueous ammonium hydroxide. After stirring 5 min., the suspension was concentrated under reduced pressure and filtered. The residue, crystallized from methanol, gave 47 mg. of material in two crops. Recrystallization from methanol yielded 4-carboxamidophthalide (**5e**), m.p. 294–296°; infrared spectrum (Nujol): 2.82 and 3.11 (NH), 5.78 and 5.96 μ (phthalide and amide C=O).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.73; H, 4.15; N, 7.99.

When 47 mg. of the amide **5e** was heated at 110–120° in 3 ml. of phosphorus oxychloride for 18 hr. and worked up by pouring into water to destroy excess phosphorus halides and subsequent extraction with chloroform, a product was obtained which upon crystallization from methanol gave 4-cyanophthalide (**5f**), m.p. 183–184°; infrared spectrum (Nujol): 4.50 (C≡N), 5.67 μ (phthalide C=O). Upon fusion with potassium cyanide and work-up as in the fusion of **6h** with cyanide above, only the original nitrile **5f** was recovered.

1,2,3-Trihydroxymethylbenzene (7b).—A suspension of 2.3 g. of lithium aluminum hydride in 50 ml. of dry tetrahydrofuran was cooled in an ice bath, while a solution of 2.29 g. of hemimellitic anhydride in 50 ml. of dry tetrahydrofuran was added over a 15-min. period with vigorous stirring. The ice bath was removed and the maroon suspension was stirred for 15 hr. It then was cooled with an ice bath and the excess hydride was destroyed by the cautious, dropwise addition of 5 ml. of cold water with stirring. The suspension was filtered through Celite and the filter cake was washed with tetrahydrofuran. The filtrates were evaporated under reduced pressure and the residue, 1.45 g., was dissolved in methanol. Upon concentration and cooling, the triol crystallized. Recrystallization from methanol afforded an analytical sample, m.p. 134–135° (lit.[9] m.p. 134–136°); infrared spectrum (Nujol): 3.15 μ (broad, OH), no C=O bands.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.03; H, 7.15.

A solution of triol **7b** in pyridine and acetic anhydride was heated on the steam bath for 30 min. The solution was evaporated under reduced pressure and the residue repeatedly was taken up in methanol and evaporated under reduced pressure. The residue was crystallized from methanol. Recrystallization gave triacetate **7c**, m.p. 55–56° (lit.[9] m.p. 58°); infrared spectrum (Nujol): 5.80 μ (ester C=O), no OH bands.

The mother liquors from the isolation of **7b** were concentrated to an oil, acetylated by heating with 12 ml. of pyridine and 12 ml. of acetic anhydride, as above, and worked up in the usual manner to give 379 mg. of semicrystalline material. Chromatography on 15 g. of alumina afforded two new crystalline compounds. The first, eluted by 4:1 petroleum ether–ether and crystallized from ether, exhibited m.p. 102–104°, and an infrared spectrum (Nujol): 5.77 μ (sh 5.9) (phthalide and ester C=O). It was subsequently identified as 7-acetoxymethylphthalide (**6c**) by infrared spectral, melting point, and mixture melting point comparison with an authentic sample (*vide infra*). The second compound, eluted by 3:2 petroleum ether–ether and crystallized from ether, exhibited m.p. 112–113°. It was subsequently identified as 7-hydroxymethylphthalide (**6d**) by infrared spectral, melting point, and mixture melting point comparison with authentic material (*vide infra*).

A suspension of 150 mg. of **7b** in 250 ml. of ether was stirred for 26 hr. with 1.5 g. of manganese dioxide. After filtering, the solution was evaporated under reduced pressure and the residue was chromatographed on silicic acid. Elution with benzene afforded 43 mg. of crystalline material identified as 4-formylphthalide (**5d**) (*vide infra*) by infrared spectral, melting point, and mixture melting point comparison with authentic material.

Permanganate Oxidation of Triol (7b).—A solution of 74 mg. of **7b** in 20 ml. of acetone was treated with 525 mg. of potassium permanganate in *ca.* 10 ml. of water. After standing for 32 hr.,

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(29) V. Jurgens, *Ber.*, **40**, 4409 (1907).

(30) F. Mayer and O. Stark, *ibid.*, **64**, 2003 (1931).

the excess permanganate was destroyed with methanol, the suspension was filtered, and the filter cake was washed with acetone. The filtrates were evaporated under reduced pressure. Chromatography of the residue, 68 mg., on 1.8 g. of silicic acid and elution with 4:1 to 7:3 petroleum ether–ether gave 51 mg. of crude 4-carboxyphthalide (**4b**) identified by infrared spectral, melting point, and mixture melting point comparison with authentic material.

Sodium Borohydride Reductions of Acid Chlorides.—Reductions with sodium borohydride were all carried out in dry diglyme. Although attempts to dry diglyme with $LiAlH_4$ have been reported[31] to lead to explosions, we experienced no difficulties using the following precautions. Fresh diethyleneglycol dimethyl ether (Eastman) was stirred with lithium aluminum hydride for several hours. The material was then distilled behind a safety shield *under reduced pressure while being vigorously stirred* magnetically. A carefully controlled *oil bath* supplied the heat and *no more than 80%* of the solution was distilled.

In most cases a stock solution of *ca.* 1.5 *M* sodium borohydride in diglyme was employed. It was standardized by the method of Lyttle, *et al.*,[32] and stored over sodium wire. The acid chlorides were prepared by refluxing the acids in thionyl chloride for several hours, evaporating the solution under reduced pressure, and removing traces of thionyl chloride by dissolving the residues in dry benzene and evaporating under reduced pressure several times. Occasionally dry air was also passed over the acid chlorides for a few minutes.

The acid chloride of hemimellitic anhydride was prepared from 1.57 g. of hemimellitic anhydride and 25 ml. of thionyl chloride. The crystalline chloride was dissolved in 25 ml. of dry diglyme, heated to 120°, and stirred vigorously, while 5.6 ml. of a 1.54 *M* diglyme solution of sodium borohydride and 25 ml. of dry diglyme was added over a 3-min. period. Heating and stirring were continued for 3 min. more, and the reaction was terminated by the rapid addition of 10 ml. of water. The clear yellowish solution was evaporated under reduced pressure and the residue was dried by the repeated evaporation of benzene under reduced pressure. The residue was extracted with dry tetrahydrofuran; the extract was evaporated under reduced pressure to a thick suspension of crystals in oil. Separation of the mixture by centrifugation and washing of the solid several times with cold methanol gave 460 mg. of 7-carboxyphthalide (**6a**), m.p. 168–172°, identified by infrared spectral, melting point, and mixture melting point comparison with authentic material. Concentration of the mother liquors afforded an additional 222 mg. of **6a**.

Chromatography of 1 g. of mother liquors from several runs on 25 g. of silicic acid and elution with 4:1 to 7:3 petroleum ether–ether afforded a new compound, contaminated with hemimellitic acid. Continued elution with a 7:3 to 3:2 solvent mixture led to recovery of additional hemimellitic acid, while a 3:2 to 1:1 mixture yielded a small amount of 7-carboxyphthalide (**6a**). The new material was crystallized repeatedly from acetone and afforded an analytical sample with m.p. 207–209°; infrared spectrum (Nujol): 5.94 μ (acid C=O). A sharp but weak peak was present at 5.79 μ which could not be accounted for.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.94; H, 4.96.

On the basis of this evidence and its relation to compounds obtained during reduction of the acid chloride of **6a**, the compound was assigned structure **8a**,

On one occasion the acid chloride from 150 mg. of hemimellitic anhydride in 1 ml. of diglyme was treated at room temperature with 4 ml. of 1.57 *M* sodium borohydride in dry diglyme. Upon work-up, *ca.* 16 mg. of solid was obtained which upon crystallization from acetone gave 1,2,3-trihydroxymethylbenzene (**7b**), m.p. 134–135°, identified by infrared, melting point, and mixture melting point comparison with authentic material (*vide supra*).

The acid chloride of 7-carboxyphthalide was prepared from 544 mg. of acid and 5 ml. of thionyl chloride. The crystalline chloride was treated in the same manner as was hemimellitic anhydride acid chloride (*vide supra*) and the reaction was worked up in the same manner except that in this case the aqueous diglyme solution was made basic with sodium bicarbonate prior to evaporation to dryness. Evaporation of the tetrahydrofuran extract under reduced pressure afforded 432 mg. of oily crystals. Repeated crystallization from methanol afforded an analytical sample of 7-hydroxymethylphthalide (**6b**), m.p. 111–113°; infrared spectrum (Nujol): 2.92 (OH) and 5.80 μ (phthalide C=O).

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.57; H, 4.86.

Acetylation of **6b** with acetic anhydride and pyridine led to an acetate identical by infrared spectral, melting point, and mixture melting point comparison with the lower melting solid isolated from the acetylated mother liquors of triol **7b**.

The mother liquors from the isolation of **6b** were chromatographed on alumina. Elution with 4:1 petroleum ether–ether produced a new crystalline compound, while 4:1 to 2:3 petroleum ether–ether eluted a viscous oil. Continued elution with 2:3 petroleum ether–ether afforded an additional quantity of 7-hydroxymethylphthalide (**6b**).

Infrared examination of the fractions showed a strong OH peak at 2.95 μ and variable weak peaks in the 5.5–6.0-μ region presumed to be due to contaminants. It could be shown that the material was a low-melting solid with m.p. >28°, but no serious attempt was made to crystallize it. Exposure to air for several weeks caused the development of complex bands in the carbonyl region.

A small sample of the oil was stirred overnight in ether with a tenfold weight of active manganese dioxide. After filtration, the ether was concentrated and cooled. The resulting crystalline material was shown by infrared spectral, melting point, and mixture melting point comparison to be identical with the first crystalline compound eluted from the column prior to the oil.

Repeated crystallization of the crystalline chromatography product from ether afforded material with m.p. 115–117° and an infrared spectrum (Nujol) with a carbonyl peak at 5.96 μ. Treatment of a sample with Tollens reagent led to formation of a fine black precipitate. The reaction mixture was acidified with hydrochloric acid and centrifuged. The precipitate was washed with tetrahydrofuran, the washings were combined with the aqueous supernatant liquid, and the solution was evaporated under reduced pressure. Crystallization of the semisolid residue from acetone gave material with m.p. *ca.* 205°. Insufficient material was available for recrystallization, but the infrared spectrum (Nujol) was identical with that of the acid, m.p. 207–209°, obtained as a side product in the reduction of hemimellitic anhydride acid chloride above. Upon admixture with this material the mixture melting point was *ca.* 206°.

The acid chloride of **5a** was prepared in the standard way from 129 mg. of 4-carboxyphthalide. The crystalline chloride in 10 ml. of dry diglyme was stirred at 108° while a centrifuged solution of 45 mg. of sodium borohydride in 10 ml. of dry diglyme was added. After heating for 2 hr., the reaction mixture was treated with 5 ml. of water and evaporated under reduced pressure. The residue was extracted several times with tetrahydrofuran and the extract was chromatographed on 3 g. of silicic acid. Elution with 4:1 petroleum ether–ether afforded *ca.* 58 mg. of a crystalline compound. Repeated crystallization from ether gave an analytical sample of 4-hydroxymethylphthalide (**5b**), m.p. 109.5–110.5°; infrared spectrum (Nujol): 2.89 (OH) and 5.76 μ (phthalide C=O).

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.37; H, 4.84.

Further elution with 3:2 petroleum ether–ether afforded *ca.* 40 mg. of 4-carboxyphthalide (**5a**), identified by infrared spectral, melting point, and mixture melting point comparison with authentic material.

Manganese Dioxide Oxidation of 4-Hydroxymethylphthalide (5b).—A mixture of 17 mg. of **5b** and 133 mg. of active manganese dioxide in 15 ml. of ether was stirred and refluxed for 13.5 hr. The manganese dioxide was removed by filtration and washed several times with ether. Evaporation of the solvent afforded 15 mg. of crude 4-formylphthalide (**5d**). Repeated crystallization from ether afforded an analytical sample with m.p. 166–168°; infrared spectrum (Nujol): 5.68 (phthalide C=O) and 5.96 μ (aldehyde C=O).

Anal. Calcd. for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 67.05; H, 3.92.

The infrared spectrum was also identical with that of a compound obtained by manganese dioxide oxidation of **7b**.

Arndt-Eistert Reactions with 5a and 6a.—The acid chlorides of 4- and 7-carboxyphthalides were prepared by the procedure used above.

A solution of the acid chloride from 64.1 mg. of 7-carboxyphthalide and 2 ml. of thionyl chloride in 3 ml. of dry tetrahydrofuran was added dropwise to an excess diazomethane in *ca.* 6 ml.

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[31] R. M. Adams, *Chem. Eng. News*, **31**, 2334 (1953).

[32] D. A. Lyttle, *et al.*, *Anal. Chem.*, **24**, 1843 (1952).

of dry, ice-cold 1:1 ether–tetrahydrofuran. The yellow solution was evaporated under reduced pressure and the solution of the residue in 3 ml. of absolute methanol was stirred and refluxed while a slurry of silver oxide, from 50 mg. of silver nitrate in absolute methanol, was added in four portions at 15-min. intervals. After refluxing overnight, cooling and filtering, the solution was concentrated under reduced pressure. Cooling and further concentration gave 48 mg. of crude methyl 7-phthalidylacetate (**6i**). Crystallization from ether afforded an analytical sample, m.p. 94–96°; infrared spectrum (Nujol): 5.73 (phthalide C═O) and 5.82 μ (ester C═O).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.82; H, 4.96.

The acid chloride from 92 mg. of 4-carboxyphthalide was treated as above except that refluxing after addition of silver oxide was maintained for only 1 hr. The crude product was chromatographed on 3 g. of alumina and 25-ml. fractions were collected. Elution with 9:1 to 4:1 petroleum ether–ether led to 4-carbomethoxyphthalide, while the later 4:1 eluates contained the major portion of the product whose crystallization from methanol gave 49 mg. of methyl 4-phthalidylacetate (**5i**). Recrystallization from methanol afforded an analytical sample, m.p. 94–95°; infrared spectrum (Nujol): 5.72 (phthalide C═O) and 5.82 μ (ester C═O).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.96; H, 5.24.

Reduction of Methyl 4-Phthalidylacetate (5i).—A solution of 332 mg. of **5i** in 10 ml. of dry tetrahydrofuran was reduced with 350 mg. of lithium aluminum hydride and worked up as in the reduction of hemimellitic anhydride to 1,2,3-trihydroxymethylbenzene (*vide supra*), to give 242 mg. of oily material which would not crystallize, and which exhibited no significant infrared absorption in the carbonyl region. The material was dissolved in 5 ml. of pyridine and treated with 1 ml. of freshly distilled benzoyl chloride. It then was heated on the steam bath for 10 min., poured into 25 ml. of water, and again heated on the steam bath for 10 min. The product obtained from work-up in the usual manner was badly contaminated with benzoic anhydride. This was conveniently destroyed by heating in aqueous pyridine for 45 min. on the steam bath. Work-up in the usual manner gave *ca.* 0.5 g. of oil which lacked the characteristic of 5.65-μ anhydride peak. Chromatography on 15 g. of alumina and elution with 4:1 petroleum ether–ether led to 0.4 g. of an oil which slowly crystallized. Repeated crystallization from acetone afforded an analytical sample of the tribenzoate of **7d** m.p. 97–99°; infrared spectrum (Nujol): 5.82 μ (ester C═O).

Anal. Calcd. for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.52; H, 5.40.

Reduction of 6-Carboxyphthalonic Acid (7e).—A mixture of 22 mg. of mercuric chloride and 322 mg. of zinc dust was stirred with 5 ml. of water and 1 ml. of 3 *M* hydrochloric acid for 15 min. The amalgamated zinc was washed several times with water. A solution of 151 mg. of 6-carboxyphthalonic acid, prepared by Graebe's method,[3] and 0.5 ml. of concentrated hydrochloric acid were added with stirring. The slowly foaming mixture was stirred for 60 min. and centrifuged. The precipitate was washed several times with water, dissolved in acetone, and centrifuged for the removal of unreacted metal. Evaporation of the acetone under reduced pressure yielded 131 mg. of crude 3,4-dicarboxyphthalide (**11c**). Repeated crystallization from water afforded an analytical sample which upon heating decomposed at 210–215° with the evolution of gas and resolidification to a material melting at 233–236°. The diacid showed a complex absorption pattern in 5.6–5.9-μ carbonyl region of its infrared spectrum (Nujol).

Anal. Calcd. for $C_{10}H_6O_6$: C, 54.06; H, 2.72. Found: C, 53.83; H, 2.88.

In contrast with Graebe's results, heating 98 mg. of 6-carboxyphthalonic acid with hydriodic acid and phosphorus at *ca.* 160° for 7 hr. afforded 62 mg. of 3,4-dicarboxyphthalide (**11c**) as the only crystalline product. The sirupy mother liquor failed to afford additional solids, and was not examined further.

Prolonged exposure of 3,4-dicarboxyphthalide to zinc amalgam and hydrochloric acid or to nickel–aluminum alloy and base failed to effect further reduction. Heating with phosphorus and hydriodic acid at 90° for 15 hr. and then at 110° for 8 hr. was equally ineffective. The same reagents at 120–130° for 24 hr. followed by *ca.* 160° for 20 hr. led to a 35% yield of 4-carboxyphthalide (**5a**) and a mixture which decomposed upon heating in a manner reminiscent of the original diacid.

Treatment of 3,4-dicarboxyphthalide in tetrahydrofuran with excess diazomethane in ether–tetrahydrofuran, followed by evaporation of the solution under reduced pressure gave crude crystalline 3,4-dicarbomethoxyphthalide (**11d**). Crystallization from methanol afforded an analytical sample, m.p. 113–116°; infrared spectrum (Nujol): 5.63 (phthalide C═O) 5.70 and 5.80 μ (ester C═O).

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found: C, 57.76; H, 4.21.

An ethyl acetate solution of the diester was exposed to hydrogen and 10% palladium–charcoal at atmospheric presssure for 40 hr. as well as to Raney nickel and hydrogen at 3 atm. for 268 hr. In both cases 85% of the diester was recovered.

A sample of 3,4-dicarboxyphthalide was heated at 225–250° until gas evolution ceased. After cooling, the residue was crystallized from methanol to give a compound identified as 4-carboxyphthalide by infrared spectral, melting point, and mixture melting point comparison with an authentic sample.

Pyrolysis of 6-Carboxyphthalonic Acid (7e).—An oil bath was preheated to >250° and a sublimation apparatus, charged with 1.06 g. of **7e** and open to the atmosphere, was introduced. The temperature was maintained at *ca.* 250° for 5–10 min., at the end of which time the reaction had subsided. Extraction of the unsublimed residue with 7 ml. of warm water in four portions and washing with acetone gave 81 mg. of light yellow powder, soluble in base, m.p. >360°, presumed to be Graebe's "dilactone" (**12**). The sublimate and the aqueous and acetone washings were combined and evaporated under reduced pressure and the resulting residue was chromatographed on 30 g. of silicic acid. Elution with 1:1 petroleum ether–ether afforded several solids which proved to be (in the order of their appearance) 4-carboxyphthalide a mixture of unidentified solids, m.p. *ca.* 220°, Graebe's aldehyde (**11e**), and hemimellitic acid. After purification of the solids by crystallization, all the mother liquors and intermediate oil fractions were combined and rechromatographed as above. Combination of the appropriate fractions gave 120 mg. of 4-carboxyphthalide, 225 mg. of hemimellitic acid, 90 mg. of Graebe's aldehyde, 40 mg. of unidentified solids, and 264 mg. of oils.

Identification of 4-carboxyphthalide and hemimellitic acid was by infrared spectral, melting point, and mixture melting point comparisons.

The aldehyde was recrystallized from ether–acetone to give material with m.p. 163–167° (lit.[16] m.p. 175–178°) and an infrared spectrum (Nujol): 3.0, 3.83, and 5.87 μ (strongly H-bonded). It was not examined further.

The "dilactone" exhibited an infrared spectrum (Nujol): 3.75–4.0 (H-bonded carboxyl OH), 5.65 (phthalide C═O), 5.79 and 5.98 μ. The insolubility of the material in ordinary organic solvents hindered its purification. Although crystallization from dimethyl sulfoxide afforded crystalline material, its spectrum suggested that its structure had been modified in the process. No further characterization was attempted.

2-Methylisophthalonitrile (7i).—A solution of 4.0 g. of 2-amino-6-cyanotoluene, prepared by the method of Noelting,[21] in 10 ml. of concentrated sulfuric acid was treated at 0° with a solution of 5 g. of sodium nitrite in 25 ml. of water. The excess reagent was destroyed by addition of a saturated solution of sodium acetate followed by urea, and the solution was added dropwise with stirring to a solution of cuprous cyanide prepared from 20.0 g. of copper sulfate. After heating on the steam bath for 2 hr., the solution was cooled and extracted with ether. The extract was washed with 10% sodium hydroxide and dried over potassium carbonate. Evaporation of the solvent, treatment of a benzene solution of the residue with Norit, filtration of the solution through alumina, and evaporation yielded 2.8 g. of solid. Sublimation at 125–130° (2 mm.) gave 2-methylisophthalonitrile (**7i**), m.p. 135–136°; infrared spetcrum (chloroform): 4.50 μ (C≡N).

Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.12; H, 4.40; N, 19.51.

Dimethyl 2-Methylisophthalate (7j).—A solution of 3.8 g. of **7i** in 50 ml. of 50% ethanolic potassium hydroxide was refluxed until ammonia ceased to be evolved (48 hr.). Concentration under reduced pressure and acidification with dilute hydrochloric acid and filtration of the resultant suspension led to a solid which on washing with water and crystallization from methanol gave 2-methylisophthalic acid (**7f**), m.p. 245–248° (lit. m.p. 228–230°,[16] 236–238°[18]), sintering at 226–228°. A solution of the acid in 20 ml. of methanol was treated with excess ethereal diazomethane and then evaporated under reduced pressure. Crystallization of the residue from hexane yielded 2.2 g. of dimethyl 2-methylisophthalate (**7j**), m.p. 53–56°; infrared spectrum (Nujol): 5.78 μ (ester C=O).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.46; H, 5.84.

5-Nitroisocarbostyril (**15c**).—A solution of 4.3 g. of 5-nitroisoquinoline N-oxide (**17**)[23] in 50 ml. of acetic anhydride was heated on the steam bath for 8 hr. and then evaporated under reduced pressure. A mixture of the crystalline residue and 10% sodium carbonate was heated on the steam bath for 30 min. and then filtered. Crystallization of the product from methanol gave 3.2 g. of **15c**, m.p. 251–252° (softening at 227°) (lit.[24] m.p. 250°); infrared spectrum (Nujol): 5.95, 6.16, and 6.23 (C=O and C=C) and 6.59 μ (NO_2).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.86; H, 3.18; N, 14.73. Found: C, 56.59; H, 3.26; N, 14.65.

5-Cyanoisocarbostyril (**15a**) **A.**—A solution of 0.4 g. of **7i** in 10 ml. of ethyl formate was added to a solution of 0.6 g. of potassium in dry *t*-butyl alcohol at 0–5° and the temperature was maintained for 8 hr. Addition of ether produced a solid which was filtered and dissolved in water. The solution was acidified with acetic acid, saturated with sodium chloride, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated under reduced pressure, and the residue was chromatographed on silicic acid. Elution with 2:1 chloroform–ethyl acetate afforded 98 mg. of colorless crystals. Crystallization from ethyl acetate and then from methanol gave 5-cyanoisocarbostyril (**15a**), point of sublimation 265°, m.p. 275° dec.; infrared (Nujol): 4.48 (C≡N) 5.92, 6.01 (sh), 6.13 and 6.26 μ (C=O and C=C); ultraviolet (95% ethanol): λ_{max} 226, 240 (sh), 248, 276, 284, 312 (sh,) 325, and 338 (sh) mμ (log ϵ 4.27, 4.06, 4.02, 4.01, 4.00, 3.63, 3.72, and 3.57, respectively).

B.—A mixture of 3.2 g. of **15c**, 8 ml. of hydrochloric acid, 2.0 g. of 10% palladium–charcoal, and 120 ml. of 90% ethanol was shaken in a hydrogen atmosphere of 3–5 lb. until hydrogen uptake had ceased. The suspension was filtered and the solids were extracted with hot water. Upon concentration and cooling, the extracts afforded 2.1 g. of crystals. Crystallization from methanol–water gave 5-aminoisocarbostyril hydrochloride, m.p. 273–276° dec. (blackening at 267°).

Anal. Calcd. for $C_9H_9ClN_2O$: N, 14.21. Found: N, 14.18.

Treatment of the salt with ammonium hydroxide and recrystallization of the product from methanol yielded the free base **15d**, m.p. 264–266° dec. A suspension of 2.1 g. of the latter in ice water was diazotized and treated with cuprous cyanide as in the conversion of 2-amino-6-cyanotoluene to **7i** (*vide supra*). After stirring the cyanide solution for 12 hr., the precipitate was filtered, washed with water, and extracted for 2 days with methanol in a Soxhlet apparatus. Evaporation of the extract and crystallization of the residue twice from methanol and once from ethyl acetate gave 1.05 g. of 5-cyanoisocarbostyril, m.p. 275–276° (point of sublimation 265°). Infrared spectral and mixture melting point comparison showed the material to be identical with that obtained from the condensation of ethyl formate with **7i** (*vide supra*).

Anal. Calcd. for $C_{10}H_6N_2O$: N, 16.46. Found: N, 16.64.

2-Methyl-3-carbomethoxy-5-cyanoisocarbostyril (**15b**).—A solution of 142 mg. of **7i** in 0.6 ml. of diethyl oxalate was added to dry potassium *t*-butoxide, from 78 mg. of potassium, and the mixture was stirred for 6 hr. Addition of sodium bicarbonate and stirring for 1 hr. yielded a suspension. It was filtered and the solid residue was treated with 20 ml. of 10% ptoassium hydroxide for 6 hr. Acidification and crystallization of the resulting solid from methanol yielded 3-carboxy-5-cyanoisocarbostyril, m.p. 350–353° dec. (prior sintering); infrared spectrum (Nujol): 4.5 (C≡N), 5.8 and 6.0–6.2 μ (ester C=O).

The acid was dissolved in methanol and treated with excess ethereal diazomethane, and the solution was evaporated under reduced pressure. A benzene solution of the residue was passed through a short alumina column. Evaporation of the solvent afforded colorless needles. Crystallization from benzene–hexane and then from methanol gave 115 mg. of 2-methyl-3-carbomethoxy-5-cyanoisocarbostyril (**15b**), m.p. 132–133°; infrared (Nujol): 4.50 (C≡N), 5.82 (ester C=O), 5.99, 6.08 (sh), 6.21, and 6.30 μ (amide C=O and C=C); ultraviolet: λ_{max} 256 and 322 mμ (log ϵ 3.98 and 4.02); proton magnetic resonance (deuteriochloroform solution with TMS as internal standard): 3-proton singlet at δ 4.00 (ester Me) and 3-proton singlet at 3.75 (N–Me).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.17; H, 4.19; N, 11.33.

The assignment of the p.m.r. signals of the methyl groups of this compound was corroborated by interpretation of the p.m.r. spectrum of the ethyl ester analog of **15b**, prepared by saponification of **15b** and esterification of the intermediate acid with ethanolic hydrochloric acid; 3-proton triplet at δ 1.48 (J = 7 c.p.s., ethyl Me), 3-proton singlet at 3.75 (N–Me), and 2-proton quartet at 4.48 (J = 7 c.p.s., ethyl CH_2).

Dimethyl 3,5-Isocoumarindicarboxylate (**16b**).—A solution of 2.0 g. of dimethyl 2-methylisophthalate in 8.0 ml. of diethyl oxalate was stirred for 4 hr. at room temperature with dry potassium *t*-butoxide, prepared from 0.8 g. of potassium. The mixture was poured into ice water causing an oily solid to separate which solidified fully after stirring for an hour. The suspension was filtered and the solid was stirred with 50 ml. of 10% sodium hydroxide for 6 hr. The solution was acidified and after 12 hr. the resulting solid was collected. Crystallization from methanol gave 3,5-dicarboxyisocoumarin (**16a**), m.p. >350°.

A suspension of **16a** in methanol was treated with an excess of ethereal diazomethane and the solution was evaporated under reduced pressure. Crystallization of the product from ethyl acetate yielded 1.2 g. of **16b**, m.p. 164–165°; infrared (Nujol): 5.8 μ (broad, ester and isocoumarin C=O); ultraviolet: λ_{max} (95% ethanol) 243, 292, and 335 (sh) mμ (log ϵ 4.12, 3.98, and 3.32, respectively).

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.54; H, 3.82. Found: C, 59.60; H, 3.98.

5-Carbomethoxyisocarbostyril (**15e**).—A solution of 1 g. of **15a** in 20 ml. of 20% ethanolic potassium hydroxide was refluxed under nitrogen until ammonia evolution had ceased (36 hr.). The solution was acidified with hydrochloric acid and evaporated under reduced pressure. Extraction of the dry cake with methanol and concentration of the combined extract gave 0.72 g. of solid. After crystallization from methanol, the solid, m.p. >300°, was treated in methanol with excess ethereal diazomethane, and the solution then was evaporated under reduced pressure. Crystallization of the residue from methanol yielded 0.63 g. of 5-carbomethoxyisocarbostyril (**15e**), m.p. 207–208°; infrared spectrum (Nujol): 2.92 (NH), 5.84 (ester C=O), and 6.04, 6.12 (sh), and 6.29 μ (C=O and C=C).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.03; H, 4.56; N, 6.95.

Hydrogenation of 5-Carbomethoxyisocarbostyril (**15e**).—A solution of 0.5 g. of **15e** in 10 ml. of acetic acid was shaken with 10.2 g. of Adams' catalyst under a hydrogen atmosphere (5 lb.) for 10 hr. The suspension was filtered and the solution was evaporated. Silicic acid chromatography of the residue and chloroform elution gave a solid whose crystallization from benzene–hexane led to 108 mg. of **18**, m.p. 126–127°; infrared spectrum (Nujol): 5.78 (ester C=O), 6.09 μ (broad, lactam C=O).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.54; H, 5.45.

sym-**Homohemimellitic Acid** (**7k**).—A solution of 1.17 g. of **16a** and 2.4 g. of potassium hydroxide in 25 ml. of water was treated with 7 ml. of 30% hydrogen peroxide and stirred for 3 hr. The solution was saturated with salt and acidified, and the resulting crystalline precipitate was filtered, washed with saturated salt solution, and dried over phosphorus pentoxide in a vacuum desiccator. Crystallization of the solid, 0.68 g., from ethyl acetate afforded **7k**, m.p. 205–206° (lit.[28] m.p. 214–215°). A methanol solution of the acid was treated with excess ethereal diazomethane, and the solution was evaporated. Crystallization of the residue from hexane afforded the trimethyl ester **7l**, m.p. 98–99° (lit.[28] m.p. 108–109°).

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.53; H, 5.13.

Sublimation of 140 mg. of the triacid **7k** at 180–185° (2 mm.) and crystallization of the sublimate from anhydrous ether gave 23 mg. of anhydride **20a**, m.p. 205–206°, after recrystallization m.p. 208–210°; infrared spectrum (Nujol): 5.58 and 5.71 (anhydride C=O), and 5.90 μ (carbonyl C=O).

A solution of 75 mg. of **7k** in 1 ml. of acetic anhydride was refluxed for 1 hr., cooled, and the crystalline precipitate was filtered. Crystallization from anhydrous ether gave 62 mg. of the isocoumarin anhydride **19**, m.p. 192–193°; infrared (Nujol): 5.62, 5.70, and 5.78 μ (anhydride and isocoumarin C=O); ultraviolet: λ_{max} (dioxane) 246, 296, and 334.5 mμ (log ϵ 4.29, 3.98, and 3.84, respectively).

Anal. Calcd. $C_{12}H_6O_5$: C, 62.62; H, 2.63. Found: C, 62.77; H, 2.79.

β-(2,6-Bishydroxymethylphenyl)ethanol (7m).—A solution of 1.1 g. of **7m** in 50 ml. of dry tetrahydrofuran was added dropwise with vigorous stirring to a suspension of 1.1 g. of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran. The mixture then was refluxed for 14 hr. and the excess hydride was destroyed by the addition of magnesium sulfate hydrate. The mixture was filtered, the residue was washed with tetrahydofuran, and the combined filtrates were evaporated under reduced pressure. Crystallization of the residue from ethyl acetate gave 0.61 g. of triol **7m**, m.p. 95–96°. Recrystallization gave the raised m.p. 98–99° (lit.[15] m.p. 105° for monohydrate); infrared spectrum (Nujol): 3.0–3.2 μ (broad, OH), no C=O absorption.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.75; H, 7.71.

Erythrocentaurin (2).—A mixture of 210 mg. of triol **7m** and 2.1 g. of active manganese dioxide in 240 ml. of ether was stirred vigorously for 18 hr., filtered, and evaporated under reduced pressure. Crystallization of the residue, 145 mg., from ether yielded erythrocentaurin (**2**), m.p. 138–139°; infrared spectrum (KBr): 5.83 and 5.92 μ (lactone and aldehyde C=O). Infrared spectral, melting point, and mixture melting point comparison showed the material to be identical with the natural product.[27]

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.37; H, 4.70.

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1,2,4-Triazoles. VIII. *s*-Triazolo[2,3-*a*]pyrazine Derivatives[1a]

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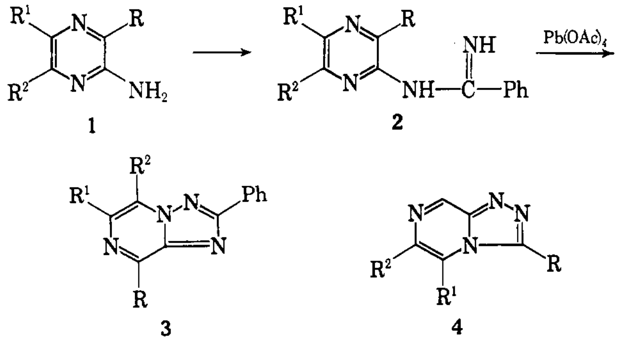
Cyclization of N-2-pyrazinylbenzamidines (**2**) with lead tetraacetate led to 2-phenyl-*s*-triazolo[2,3-*a*]pyrazine derivatives (**3**). Aliphatic cyanides would not form amidines with the 2-aminopyrazines (**1**) used, this being the limiting factor in the reaction scheme. Ultraviolet spectral data for the *s*-triazolo[4,3-*a*]pyrazines (**4**) and the *s*-triazolo[2,3-*a*]pyrazine systems are reported and compared with those of similar systems.

Of the two possible ways of effecting fusion of an *s*-triazole nucleus with a pyrazine nucleus, one, the *s*-triazolo[4,3-*a*]pyrazine system, has been reported on in an earlier communication.[2] We now wish to describe the synthesis of several examples of the isomeric *s*-triazolo[2,3-*a*]pyrazine system. The synthesis of this nucleus can be achieved most efficiently by starting with a preformed pyrazine ring and bringing about a ring closure to form the *s*-triazole nucleus, rather than the reverse procedure of forming the pyrazine nucleus by a suitable cyclization reaction.

An adaptation of the method[3] used to obtain derivatives of the *s*-triazolo[2,3-*a*]pyridine ring system was used in this study. Suitably substituted 2-aminopyrazines[4] (**1**) such as the 3,6-dimethyl, 5,6-dimethyl, and 5,6-diphenyl derivatives were condensed with benzonitrile in the presence of aluminum chloride to form the appropriate N-2-pyrazinylbenzamidine (**2**), which with lead tetraacetate underwent oxidative ring closure to the corresponding 2-phenyl-*s*-triazolo[2,3-*a*]pyrazine (**3**). It was found that amidine formation occurred only with the aryl cyanides and in no case was the yield greater than 56%. Even with alkyl cyanides such as trichloroacetonitrile, where the cyano group has greatly increased electrophilic character, the only product isolated was that formed by self-condensation of the nitrile, namely 2,4,6-tri(trichloromethyl)-*s*-triazine.[5] As various substituted 2-aminopyridines have been converted into the corresponding N-2-pyridylamidines in good yield with alkyl cyanides and aluminum chloride,[3b] one can attribute the lack of amidine formation with alkyl cyanides in the pyrazine series to the lower basicity of the 2-aminopyrazine derivatives. Thus, 2-aminopyridine with a pK_a value of 6.86 and aniline, pK_a 4.58, are much stronger bases[6] than 2-aminopyrazine, pK_a 3.14, and there are numerous examples in the literature, largely from the work of Oxley and Short,[7] that substantiate this reasoning. It is interesting that the amidine derived from 2-amino-5,6-diphenylpyrazine (**1**, R = H; $R^1 = R^2$ = Ph) was formed in best yield (56%), whereas that derived from 2-amino-3,6-dimethylpyrazine (**1**, R = R^2 = CH_3; R^1 = H) was formed in only 18% yield. This can be attributed to the greater stability of the amidine derived from the former amine under the alkaline conditions used in the isolation procedure, as 2-amino-5,6-diphenylpyrazine would be expected to be a slightly weaker base than the dimethyl compounds. This decomposition of the amidines under reaction work-up conditions was more noticeable in the pyridine series where low temperatures were required to suppress the hydrolysis.[3b]



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