Synthesis and Characterization of Some Toluides of *o*-Phthalic Acid

ROSALIE D. REYNOLDS AND GERALD L. ANDERSON

Northern Illinois University, DeKalb, Illinois

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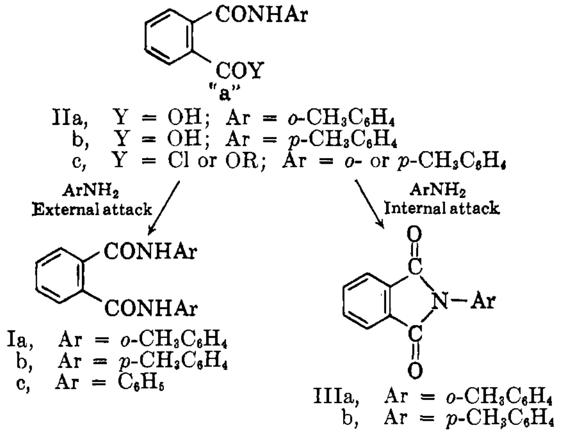
For some time *o*- and *p*-toluides have served as useful derivatives of carboxylic acids, and routine methods for the preparation of these compounds have been developed.[1] Many dicarboxylic acids have been converted to ditoluides[2] even though yields have often been low due to incomplete reaction and consequent contamination by monotoluides and/or concurrent reaction to yield imides. Indeed, in at least one case, that of *o*-phthalic acid, attempts to prepare ditoluides[2d,3] have resulted only in formation of the corresponding imides.

Usual methods for the preparation of ditoluides involve the attack of the appropriate toluidine on either the diacid[2b,3a] or a derivative of the diacid such as a diacyl chloride,[2a,3b] a diester,[2c] or a diazide.[2e] The failure of these methods to yield any of the di-*o*- and di-*p*-toluides of *o*-phthalic acid (Ia and Ib) can be rationalized on the basis of the assumption that the monotoluide II is an intermediate product in all such reactions. Ditoluide formation would require external attack by the appropriate toluidine on carbon "a" of II. However, if the amide nitrogen of II were sufficiently nucleophilic, the N-substituted phthalimide III would be formed by internal attack. The toluidine present would serve as a useful basic catalyst. Tingle and Rolker[4] have shown that only internal attack occurs when the monotoluide–monoacids, IIa and IIb, are allowed to react with the toluidines; *i.e.*, the products produced, in nearly quantitative yields, are the imides, IIIa and b. Since the intermediate monotoluide resulting from use of *o*-phthalic acid derivatives (IIc) would possess a more electrophilic carbon "a" than IIa or b, attack on IIc by any nucleophile should be more facile than the analogous attack on IIa or IIb; hence, the imide, III, should form more easily when IIc is the intermediate, but I would not be an expected product.



Success of syntheses for Ia and Ib appears to be dependent upon using a system in which external attack is heavily favored over internal attack. This prerequisite can be met if the external attacking agent is highly nucleophilic, thus rendering internal attack on carbon "a" of II by the less nucleophilic amide nitrogen ineffectual as a competing reaction. That intermediate nucleophilicity in the external attacking reagent is insufficient to result in ditoluide formation has already been demonstrated. Bodroux,[2d] using Grignard type reagents of the toluidines, $CH_3C_6H_4NHMgI$,[5] and diethyl oxalate, obtained good yields of the ditoluides of oxalic acid. Analogous reactions with diethyl phthalate failed to yield any of Ia or Ib.

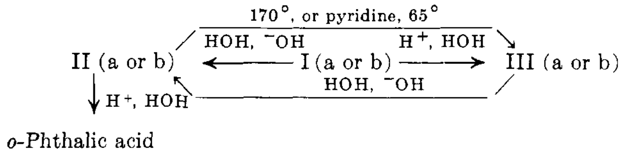
We though it probable that the sodium salts of *o*- and *p*-toluidine would be sufficiently strong nucleophiles to exclude internal attack and allow formation of Ia and Ib. Apparently, sodium salts of amines have been little used although Hjelt[6] prepared the dianilide of succinic acid by heating a mixture of aniline, sodium, and diethyl succinate, a process which presumably involved the sodium salt of aniline. The application of a modification of Hjelt's synthesis to the present problem was successful. The sodium salts of the toluidines were prepared from sodium metal and the amines; reaction of the sodium toluides with diethyl phthalate resulted directly in high yields of Ia and Ib.

Syntheses of Ia and Ib were also carried out by using sodium ethoxide rather than sodium to obtain the intermediate sodium toluides. Undoubtedly the equilibrium in this reaction lies far to the left. However, consumption of the sodium toluide by diethyl phthalate renders the reaction feasible. This situation is a familiar one; it is reminiscent, *e.g.*, of the production and consumption of anions in the Claisen condensation.[7]

$$ArNH_2 + NaOC_2H_5 \rightleftharpoons ArNHNa + C_2H_5OH$$

It seemed desirable to demonstrate that these synthetic methods could be used to produce a known N,N′-diarylamide of *o*-phthalic acid. The dianilide IIc is one of few known compounds of this type.[8] The product obtained using the present methods was shown to be identical with that produced by earlier methods.[1,8a]

Relationships among Ia and Ib, IIa and IIb, and IIIa and IIIb were investigated in order to provide structure proof for the ditoluides. Reactions carried out may be briefly summarized.



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[1] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 198, 200.

[2] (a) C. R. Barnicoat, *J. Chem. Soc.*, 2926 (1927); (b) P. F. Frankland and A. Slator, *ibid.*, **33**, 1349 (1903); (c) A. Reissert and A. More, *Ber.*, **39**, 3301 (1906); (d) M. F. Bodroux, *Compt. rend.*, **142**, 401 (1906); (e) T. Curtius, *J. prakt. Chem.*, [2] **91**, 10 (1915).

[3] (a) E. Froehlich, *Ber.*, **17**, 2679 (1884); (b) M. Kuhara, *Am. Chem. J.*, **9**, 52 (1887); M. Kuhara and S. Komatsu, *Chem. Zentr. I*, 1509 (1911).

[4] J. R. Tingle and H. F. Rolker, *J. Am. Chem. Soc.*, **30**, 1882 (1908).

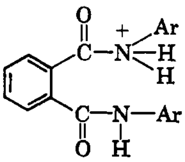
[5] In view of recent work concerning the structure of Grignard reagents [E. C. Ashby and W. E. Becker, *ibid.*, **85**, 118 (1963)] this structure may require modification.

[6] E. Hjelt, "Jahresbericht über die Fortschritte der Chemie," F. Vieweg and Son, Braunschweig, Germany, 1887, p. 1536.

[7] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 334, and references therein.

[8] (a) M. Rogow, *Ber.*, **30**, 1442 (1897); (b) F. L. Dunlap and F. W. Cummers, *J. Am. Chem. Soc.*, **25**, 612 (1903).

Base-catalyzed hydrolysis of Ia or Ib with 20% aqueous sodium hydroxide at reflux resulted in formation of the known compounds,[4] IIa or IIb, as expected; the monotoluide–monoacids were obtained first as sodium salts which were stable under the reaction conditions. Hydrolysis of Ia or Ib in the presence of 5 *N* hydrochloric acid yielded the corresponding known imides,[4] IIIa and IIIb. Formation of the imides under the conditions used probably involved the protonated amides IV.[9] These reactions are being further investigated. We have confirmed the earlier work[4] concerning the interconversions of IIa and IIb and IIIa and IIIb and have established that *o*-phthalic acid is the product of acid-catalyzed hydrolysis of IIa or IIb.



IV

Solid state infrared spectra of Ia, Ib, Ic, and IIa have been examined. Certain absorption peaks important to structure determination are given in Table I; all peaks occur in expected regions.[10]

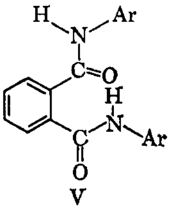
TABLE I

ABSORPTION MAXIMA (cm.$^{-1}$)

Assignment	Ia	Ib	Ic	IIa
Bonded NH	3210 (vs) 3190 (m)	3200 (vs) 3240 (vs)	3190 (vs) 3200 (vs) 3240 (vs)	3240 (s)
Carboxyl CO				1670 (vs)
Amide I CO	1635 (vs)[a]	1635 (vs)[a]	1635 (vs)[a]	1626 (vs)
CH out-of-plane deformation	739–750 (vs)[b]	739 (m) 815 (vs)	752 (vs) 760 (vs)	739 (vs)

[a] Wave number given is that of sharp, strong peak; shoulders also occur in this region. [b] At least two peaks occur in this area, one at 750 and one at 745 cm.$^{-1}$; the latter is broad and is probably a doublet.

The presence of more than one bonded NH band, as well as the suggestion of multiplicity in the carbonyl region, in the spectra of Ia, Ib, and Ic may be attributed to the existence of rotational isomers.[10] Since IIa shows NH absorption at 3240 cm.$^{-1}$ which is almost certainly due to chelation, and since this band is missing in the spectrum of Ia but present in the spectra of Ib and Ic, the *trans–trans*-rotational isomer, V, may quite possibly be an important conformer for Ib and Ic. That chelation is important in Ib is also indicated by its melting point which is *ca.* 27° lower than that of Ia.



V

Further evidence for the structure of Ia was obtained by integration of its n.m.r. spectrum. Six methyl hydrogen atoms accounted for a sharp peak at 2.25 δ. Twelve aromatic hydrogen atoms gave rise to multiple peaks centered at 7.10 and 7.65 δ; the former aromatic multiplet had an area corresponding to eight hydrogen atoms, the latter an area corresponding to four hydrogen atoms. Two exchangeable hydrogen atoms attached to nitrogen resulted in a peak at 8.22 δ. Exchangeability of these hydrogen atoms was shown by running spectra in both deuteriochloroform and deuterium oxide.

Experimental[11]

Materials.—Aniline, *o*-toluidine, *p*-toluidine, and diethyl phthalate were obtained from Eastman Kodak Company and purified by standard methods. The amines were repurified immediately prior to use.

Di-*o*-toluide of *o*-Phthalic Acid (Ia). Method A.—*o*-Toluidine (32.1 g., 0.3 mole) was heated with sodium (4.60 g., 0.2 g.-atom) at 150° in an atmosphere of nitrogen for 1 hr. To the cooled reaction mixture were added absolute ethanol (10 ml.) and diethyl phthalate (22.2 g., 0.1 mole). The mixture was stirred at 75° for 1 hr. and filtered while hot. Cooling to room temperature resulted in deposition of a white crystalline solid which was recrystallized from ethanol to yield 25.0 g. (73%) of Ia, m.p., 209.0–209.5°.

Method B.—*o*-Toluidine (2.68 g., 0.020 mole) was added dropwise to a stirred solution of sodium ethoxide (0.46 g., 0.020 g.-atom of sodium in 10 ml. of absolute ethanol) protected from atmospheric moisture; over a period of 5 min. the temperature was raised sufficiently to bring about reflux. Diethyl phthalate (2.22 g., 0.01 mole) was added in one portion after the mixture had refluxed for 10 min. Heating and stirring were continued for 30 hr. after which the reaction mixture was filtered while hot and concentrated on a rotary evaporator to approximately half volume. Cooling resulted in deposition of Ia which, when recrystallized from ethanol, melted at 209.0–209.5° and weighed 2.7 g. (78%).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.72; H, 5.59; N, 8.14.

Di-*p*-toluide of *o*-Phthalic Acid (Ib).—Methods used for the preparation of Ib were completely analogous to those described for Ia. Reaction mixtures were treated with water after hot filtration and cooling in order to facilitate precipitation of Ib. Recrystallization from benzene yielded colorless needles, m.p. 181–182° (55% yield *via* method A, 65% *via* method B).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.70; H, 5.76; N, 7.99.

Dianilide of *o*-Phthalic Acid (Ic).—Application of method A or method B to the synthesis of Ic yielded a white crystalline solid which, after recrystallization from ethanol, melted at 230–231° (lit.[8a] 231–232°). Yields ranged from 60–70%. Ic produced in this manner was shown by undepressed mixture melting point and identical infrared spectrum to be identical with Ic resulting from earlier methods of synthesis.[1,8a]

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86. Found: C, 75.91; H, 5.00; N, 8.97.

Monotoluides of *o*-Phthalic Acid (IIa and IIb). Base-Catalyzed Hydrolysis of Ia and Ib.—Treatment of either Ia or Ib (3.44 g., 0.01 mole) with 20% aqueous sodium hydroxide at reflux for 3 hr. followed by acidification with 8 *N* hydrochloric acid resulted in formation of IIa or IIb. Both monotoluide–monoacids were recrystallized from ethanol to yield, in each case, 2.2 g. (86%) of purified material. IIa melted at 168.5–169.5° (lit.[4] 166–167°) and had a neutralization equivalent of 255 ± 2 (calcd. 255); IIb melted at 160.0–160.5° (lit.[4] 160°).

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(9) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 205.

(11) Melting points were taken on a Büchi melting point apparatus calibrated against standard substances. Infrared spectra were determined in potassium bromide pellets (1–2 mg. of sample/400 mg. of KBr) on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were determined by Varian Applications Laboratory, Palo Alto, Calif., using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Elemental analyses were performed by Clark Microanalytical Laboratories, Urbana, Ill., or by the authors.

When heated above their melting points or with pyridine at 65°, both IIa and IIb were converted to the corresponding imides, as previously reported.[4]

N-Tolyl Phthalimides (IIIa and IIIb). Acid-Catalyzed Hydrolysis of Ia and Ib.—Hydrolysis of either Ia or Ib (3.44 g., 0.01 mole) with 5 *N* hydrochloric acid (10 ml., 0.05 mole) at reflux for 3 hr. resulted in high yields (2.0 g., 84%, from Ia; 1.9 g., 80%, from Ib) of the corresponding phthalimides, IIIa and IIIb. IIIa had a melting point of 182.5–183.0° (lit.[3] 182°), undepressed by admixture with an authentic sample prepared by a usual method[3a]; IIIb melted at 201–202° (lit.[4] 201–202°).

As previously reported,[4] IIIa and IIIb were converted to IIa and IIb, respectively, when heated on a steam cone for 1 hr. with 10% sodium hydroxide.

Acid-Catalyzed Hydrolysis of IIa and IIb.—Hydrolysis of IIa or IIb (2.55 g., 0.01 mole) with excess 5 *N* hydrochloric acid on a steam bath for 15 min. resulted in formation of *o*-phthalic acid (1.4 g., 84% in both cases). The product was identified by its infrared spectrum which was identical with that of an authentic sample.

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F^{19} Nuclear Magnetic Resonance Spectra of Some Benzotrifluorides

CARL L. BUMGARDNER

Gorgas Laboratory, Rohm and Haas Company,
Redstone Arsenal Research Division, Huntsville, Alabama

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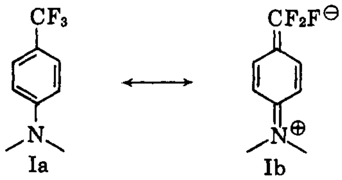
The electronic effect of the trifluoromethyl group attached to an aromatic ring and the dipole moment of *p*-dimethylaminobenzotrifluoride have been discussed in terms of resonance forms Ia,b.[1] If forms such as Ib are important, this effect might be reflected in the F^{19} n.m.r. spectrum. Taft, *et al.*,[2] have interpreted the F^{19} chemical shifts in various substituted fluorobenzenes as evidence for contributing forms IIa,b.



Ia Ib

IIa IIb

To see if n.m.r. spectroscopy could be used to detect interactions exemplified by form Ib (negative hyperconjugation), we examined the benzotrifluorides collected in Table I.

Table I shows clearly that n.m.r. spectroscopy does distinguish between the *p*-aminobenzotrifluorides and all other compounds listed. In the same solvent there is little change in the spectra until the *p*-aminobenzotrifluorides are encountered. In methanol, for example, the ϕ^* values of *p*-nitrobenzotrifluoride and *m*-dimethylaminobenzotrifluoride differ by only 0.6 unit, whereas those of *m*-dimethylaminobenzotrifluoride and *p*-aminobenzotrifluoride differ by 1.4 units. The difference between *m*-dimethylaminobenzotrifluoride and *p*-dimethylaminobenzotrifluoride is even greater (1.8 units). A similar trend is shown by the values obtained in cyclohexane.

TABLE I

F^{19} N.M.R. SPECTRA OF BENZOTRIFLUORIDES

	Cyclohexane[a] ϕ^{*b}	Methanol[a] ϕ^{*b}
Benzotrifluoride	64.1	62.7
m-Nitrobenzotrifluoride	64.2	63.1
p-Nitrobenzotrifluoride	64.5	63.2
m-Aminobenzotrifluoride	63.9	62.9
m-Dimethylaminobenzotrifluoride	63.7	62.6
p-Aminobenzotrifluoride	62.2	61.2
p-Dimethylaminobenzotrifluoride	62.0	60.8

[a] Approximately 5% solutions by volume. [b] B. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

Resonance exemplified by Ia,b, which has been invoked to account for the high dipole moment of *p*-dimethylaminobenzotrifluoride,[1] also may be responsible for the unusual F^{19} n.m.r. spectra displayed by *p*-amino and *p*-dimethylaminobenzotrifluoride. Interestingly, Gutowsky, *et al.*,[3] who have compared the F^{19} n.m.r. spectra of several substituted benzotrifluorides and fluorobenzenes, observed that substituents affect the aromatic fluorine and trifluoromethyl fluorine resonances in an opposite manner.

Experimental

The *para* substituted benzotrifluorides in Table I and *m*-dimethylaminobenzotrifluoride were prepared according to directions given in ref. 1. The remaining compounds were purchased from Columbia Organic Chemicals Company, Columbia, South Carolina, or from Aldrich Chemical Company, Milwaukee, Wisconsin. N.m.r. spectra were obtained with a Varian Associates, Model V-3000-B, high resolution spectrometer using a 40-Mc. probe at 28°. Samples were measured with trichlorofluoromethane as internal standard by counting sideband frequencies. The CF$_3$ peaks were sharp and symmetrical in all cases.

Acknowledgment.—This research was carried out under Army Ordnance Contract Da-01-021 ORD-11878. We are grateful to Mr. Kirt Keller for technical assistance and to Mrs. Carolyn Haney for n.m.r. spectra.

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[1] J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).

[2] R. W. Taft, Jr., R. E. Glick, I. C. Lewis, I. Fox, and S. Ehrenson, *ibid.*, **82**, 756 (1960).

[3] H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *ibid.*, **74**, 4809 (1952).

Proton Nuclear Magnetic Resonance Analysis of Some Acylmetallocenes

M. D. RAUSCH AND V. MARK

Monsanto Chemical Company, Research and Engineering Division,
St. Louis, Missouri

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A gradual deshielding of the cyclopentadienyl ring protons in the metallocene series proceeding from ferrocene to ruthenocene to osmocene has been noted by