The Exchange Reaction between Carboxylic Acids and *N,N*-Disubstituted Carboxamides[1,2]

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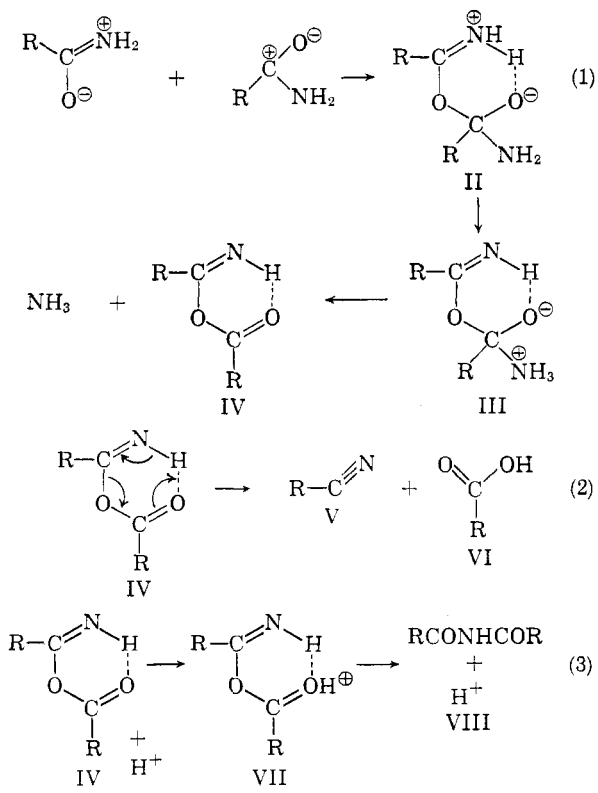
An investigation of the exchange reaction between carboxylic acids and *N,N*-disubstituted carboxamides demonstrated that exchange occurs with benzoic acids containing both electron-donating and electron-withdrawing *para* substituents. The *N*-methylanilino group of *N*-methylacetanilide readily exchanges with the hydroxyl group of these acids when equilibrium is displaced by distilling out the acetic acid formed. Benzoic acids containing dimethylamino, methoxyl, methyl, hydrogen, chloro, and nitro substituents in the *para* position were successfully employed. The mechanistic implications of an exchange reaction between a carboxylic acid and a *N,N*-disubstituted carboxamide are considered.

Exchange reactions between the hydroxyl group of an acid and the amino group of a compound containing a carbamyl or sulfamyl group have been investigated with amides,[5-7] ureas,[8-10] formation of hydantoins and cyclic amides,[11] and *N,N*-disubstituted sulfonamides[12] and sulfamides.[13] Davidson and Karten[14] observed that early stages of pyrolysis of amides to nitriles (V) was accompanied by ammonia evolution, appearance of an imide (VIII) and accumulation of acid. They assumed the primary step to be bimolecular deammination to isoimide (1) which may decompose in part to nitrile and acid (2) while the remainder rearranged reversibly to imide (3).



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The above reaction path was employed by these workers to account for the exchange reaction observed on pyrolysis of an amide in the presence of an unrelated acid as a partial pyrolysis to nitrile and ammonolysis of the unrelated acid.

$$RCONH_2 \rightleftharpoons RCN + RCOOH + NH_3 \quad (4)$$

$$NH_3 + R'COOH \rightleftharpoons R'CONH_2 + H_2O \quad (5)$$

It was suggested that the water formed in this ammonolysis provided another path for the exchange by hydrolysis of the amide, and reaction of the ammonia formed with the unrelated acid.

$$RCONH_2 + H_2O \rightleftharpoons RCOOH + NH_2 \quad (6)$$

$$R'COOH + NH_3 \rightleftharpoons R'CONH_2 + H_2O \quad (7)$$

It was suggested by Davidson and Karten that an amide and unrelated acid might eliminate water to form a mixed isoimide (IX) as an intermediate that rearranged to an imide (X). The latter might then be hydrolyzed to either the original amide and acid or the exchanged pair.

(2) Abstracted from a thesis submitted by R. N. Ring in partial fulfillment of the requirements for the M.A. degree, Brooklyn College, 1961.

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(5) J. Biehringer and W. Borsum, *Ber.*, **39**, 3348 (1906).

(6) J. F. Norris and A. J. Klemka, *J. Am. Chem. Soc.*, **62**, 1432 (1940).

(7) (a) E. T. Roe, J. T. Scanlon, and D. Swern, *ibid.*, **71**, 2215 (1949); (b) S. Sugasawa and H. Shigehura, *J. Pharm. Soc. Japan*, **62**, 532 (1942); (c) R. G. Jarque, M. M. Calvet, and F. M. Archilla, *Anales real soc. espan. fis. y quim.* (Madrid), **54B**, 233 (1958); (d) J. H. MacGregor and F. Ward, *Chem. Ind.* (London), **66**, 344 (1947).

(8) E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, **29**, 1315 (1946).

(9) B. S. Biggs and W. S. Bishop, *Org. Syntheses*, Coll. Vol. III, 769 (1955), note 6.

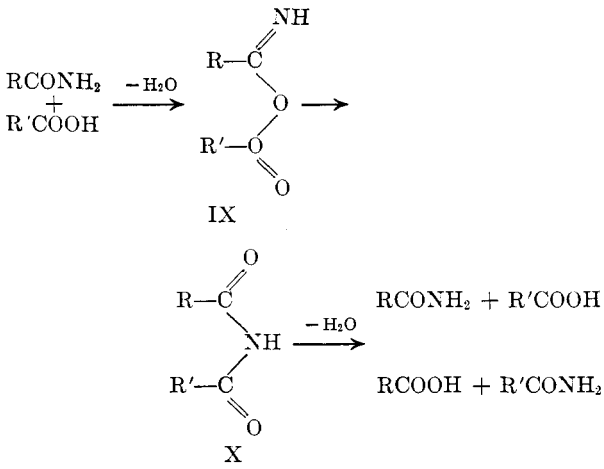
(10) H. R. V. Arnstein and R. Bently, *J. Chem. Soc.*, 3509 (1951).

(11) A. Rahman and M. O. Farouq, *Current Sci.* (India), **21**, 338 (1952).

(12) P. Oxley, N. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, 763 (1946).

(13) (a) A. V. Kirsanov and Y. M. Zolotov, *J. Gen. Chem., U.S.S.R.*, **19**, 2201 (1949); (b) A. V. Kirsanov and N. L. Egorova, *ibid.*, **22**, 1612 (1952); (c) A. V. Kirsanov, *ibid.*, **23**, 223 (1953).

(14) D. Davidson and M. Karten, *J. Am. Chem. Soc.*, **78**, 1066 (1956).



Baumgarten's[15] observation that *N,N*-disubstituted amides resist pyrolysis at temperatures for exchange reactions between acids and amides is not unexpected if such reactions occur only by the mechanisms suggested by Davidson and Karten. They do not, however, explain how exchange between an *N,N*-disubstituted amide and an acid could occur. The first path is ruled out because *N,N*-disubstituted amide pyrolysis does not yield a free amine to form an amide with the unrelated acid. Since this reaction does not generate water, and none is present at the beginning, catalytic hydrolysis to acid and free amine is not possible. Finally, *N,N*-disubstituted carboxamides reacting with carboxylic acids could not produce an isoimide as a free base nor could the isoimidinium salt, $[RC(=NR'_2)OCOR'']^+ [OOCR'']^-$ undergo rearrangement to form an imide.

In the successful exchange reactions of carboxylic acids with *N,N*-disubstituted carboxamides listed in Table I, equilibrium was displaced by distilling off the low-boiling acid and crystallizing out the exchanged amide. Good to fair yields were ob-

$$p\text{-}XC_6H_4COOH + CH_3CON(CH_3)C_6H_5 \longrightarrow CH_3COOH + p\text{-}XC_6H_4CON(CH_3)C_6H$$

tained when *N*-methylacetanilide reacted with benzoic acids having dimethylamino, methoxyl, methyl, hydrogen, chloro, or nitro substituents in the *para* position. With dimethyl diethylene glycol as solvent and chaser for acetic acid, the reaction rate was limited by the rate of distillation rather than by the rate of attainment of equilibrium and resembled the exchange between nitriles and carboxylic acids in this respect.[16] While these exchange reactions occur under the same conditions as unsubstituted carboxamides, they must follow a different reaction path from that suggested by Davidson and Karten for the reasons previously outlined, and it is possible that both substituted and unsubstituted carboxamides react by this alternate mechanistic path. This reasoning may also apply to the mechanism suggested for exchange reactions of carboxylic acids with urea[17] or thiourea[18] that occur under conditions similar to those for exchange of nicotinic acid with tetraethylurea[8] which cannot form a cyanic acid or substituted cyanate intermediate.

An alternate reaction path involving acid anhydride as an intermediate was considered because of their reported formation by pyrolysis of carboxylic acids at temperatures not much higher than those needed for exchange reactions.[19] Their observation that anhydrides react with unsubstituted amides to form either amide and acid, or nitrile and acid led Davidson and Skovronek[20] to postulate isoimidinium carboxylate as intermediate. If anhydrides were formed in the exchange reaction, their reaction with disubstituted amides would yield isoimidinium carboxylate, and the water formed could catalyze the exchange reaction. The azlactone test, which was negative in the exchange reaction mixture with unsubstituted amides,[14] was applied and failed to detect anhydride in the reaction mixtures from carboxylic acids and disubstituted amides as well. Formation of anhydride as intermediate therefore appears unlikely, but is not ruled out as a possibility because of evidence from tracer experiments on the intramolecularly catalyzed hydrolysis of phthalmic acid,[21] which showed an intermediate anhydride was present. The inability to obtain direct evidence in these experiments for the existence of an acid anhydride was attributed to the hydrolysis rate which was greater than the rate of formation.

It was previously found that no ammonia was evolved in the exchange reaction of benzoic acid and acetamide,[14] and no amines could be detected in the distillates from exchange reactions with disubstituted amides except for small amounts in the reaction with *p*-dimethylaminobenzoic acid. Decarboxylation in exchange reactions have been observed previously[6,12,22] and occurs readily with benzoic acids having *ortho* or *para* electron-releasing substituents. Inability to detect free amine in these exchange reactions makes unlikely a mechanism for exchange based on direct amination of a carboxylic acid with a free amine.

A suggested mechanism for acid-amide exchange employs initial hydrogen bonding or protonation of the carbonyl oxygen of the amide to increase the electrophilic character and reactivity of the carbonyl. NMR data indicate that amides are

(15) H. E. Baumgarten, F. A. Bower, R. A. Setterquist, and R. E. Allen, *J. Am. Chem. Soc.*, **80**, 4588 (1958).

(16) W. G. Toland and L. L. Ferstandig, *J. Org. Chem.*, **23**, 1350 (1958).

(17) A. Rahman, *Rec. trav. chim.*, **75**, 164 (1956).

(18) A. Rahman, M. A. Medrano, and O. O. Mittal, *ibid.*, **79**, 188 (1960).

(19) D. Davidson and P. Newman, *J. Am. Chem. Soc.*, **74**, 1515 (1952).

(20) D. Davidson and H. Skovronek, *ibid.*, **80**, 376 (1958).

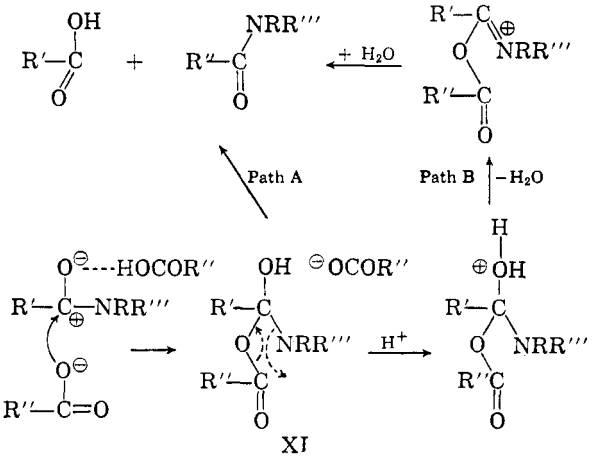
(21) M. L. Bender, Y. L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(22) E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, **29**, 1438 (1946).

TABLE I
EXCHANGE REACTIONS OF SUBSTITUTED BENZOIC ACIDS WITH *N*-METHYLACETANILIDE

para Substituent of Benzoic Acid	Mole Ratio Amide/Acid	Reaction Temp.	Reaction Time (hr.)	Yield of Acetic Acid (%)	Yield of Exchanged Amide (%)
$(CH_3)_2N$—	2.0	244–264	3.0	68.0	60.0
CH_3O—	1.0	212–310	15.0	58.8	26.1 (57% crude)
CH_3—	2.0	247–286	2.0	91.0	68.2
H—	2.0	255–288	7.5	65.0	64.0 (80% crude)
Cl—	2.0	234–280	3.0	78.6	56.1 (74% crude)
NO_2—	2.0	208–213[a]	4.5	67.2	29.4

[a] Reaction carried out at reduced pressure.



protonated predominantly on the oxygen, and hydrogen bonding to oxygen is also favored.[23] Nucleophilic attack by carboxylate anion on the electrophilic carbonyl carbon of the amide provides an intermediate which undergoes intramolecular acylation through a four-membered ring transition state as the more likely reaction path A. This postulated intermediate is similar to that proposed for intramolecular hydrolysis of phthalamic acid[21] and for the transformation of maleamic acid to isomaleimides.[24] In water this intermediate would be expected to undergo hydrolysis, but in anhydrous media, exchange of amino and hydroxyl groups appears plausible.

The formation of the intermediate (XI) is probably an example of electrophilic-nucleophilic catalysis similar to that in hydrolysis of *N*-butylacetamide in nearly neutral buffered solutions of acetic acid, for which the proposed rate-determining step was attack of acetate anion on protonated amide.[25]

Rearrangement of the intermediate is proposed as an intramolecular four center reaction.[26] Intramolecular acyl migrations through a four-membered ring transition state reported in the literature include reaction of a nitrile with a carboxylic acid to give an imide or exchange products,[16] reaction of an anhydride with an amide to form an imide,[20] carbodiimides with carboxylic acids to yield acylureas,[27] ketimines with carboxylic acids to produce amides,[28] isocyanate with carboxylic acid to give amide and carbon dioxide,[29] isothionate and thiol acid to give amide and carbon disulfide,[30] and pyrolysis of amides previously described. The above differ from the exchange reaction mechanism proposed in that the acetylated nitrogen was initially in an imino group as part of an isoimide or similar structure. Such an isoimide intermediate seems unnecessary in the exchange reaction of carboxylic acids with carboxamides because this reaction path B would require two additional steps, dehydration and hydration after rearrangement, and would not enchance the reactivity at the sites of reaction.

Experimental[31]

***p*-Dimethylaminobenzoic Acid.**—A solution of 68.0 g. (0.40 mole) of silver nitrate in 100 ml. of water was added slowly, over a period of 1 hr., to a well stirred mixture of 96.0 g. (2.4 moles) of sodium hydroxide and 49.2 g. (0.33 mole) of *p*-dimethylaminobenzaldehyde in 500 ml. of water at 50–60°. After 24 hr. the mixture was again heated to 50° and the silver oxide was removed by filtration. The filtrate was cooled and filtered again to remove 2.29 g. of *p*-dimethylaminobenzaldehyde (4.7%) which had separated, m.p. 70.0–71.5. (lit., m.p. 73–74°[32]). The filtrate was acidified with sulfur dioxide, and the white solid which separated was removed by filtration and air-dried, giving 37.6 g. (68%) of *p*-dimethylaminobenzoic acid, m.p. 235.0–238.0°. Recrystallization from ethanol raised the melting point to 245.0–245.5° dec.[33]

Authentic Amides.—*N*-Methylbenzanilide, m.p. 59.0–60.0° (hexane-ether) (lit., m.p. 63.0°,[34] 58–59°,[35] 63.5–

(23) G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, **82**, 4478 (1960).

(24) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

(25) (a) K. G. Wyness, *J. Chem. Soc.*, 2934 (1958); (b) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(26) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1956, p. 453.

(27) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

(28) C. L. Stevens and M. E. Munk, *ibid.*, **80**, 4065 (1958).

(29) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1936); S. Goldschmidt and M. Wick, *Ann.*, **575**, 217 (1952).

(30) J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956).

(31) All melting points were determined using a Fisher-Johns apparatus and are corrected; boiling points are uncorrected. Analyses were made by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(32) W. D. Kumler, *J. Am. Chem. Soc.*, **68**, 1189 (1946).

(33) Literature melting points vary from 234 to 240° E. Bischoff, *Ber.*, **22**, 341 (1889); W. Michler, *ibid.*, **9**, 400 (1876); J. Houben and A. Schottmuller, *ibid.*, **42**, 3736 (1909).

(34) O. Hess, *ibid.*, **18**, 685 (1885).

(35) W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

64.5°[36]), *N*-methylanisanilide, m.p. 78.5–79.5° (ether) (lit.,[37] m.p. 74°), *N*-methyl-*p*-dimethylaminobenzanilide, m.p. 150.0–153.5° (benzene–hexane), and *N*-methyl-*p*-toluanilide, m.p. 69.5–71.0° (ether) lit.,[37] m.p. 70°) were prepared from the corresponding acids by the method of Kuehn and McElvain.[38]

N-Methyl-*p*-nitrobenzanilide was prepared by the reaction of *p*-nitrobenzoyl chloride and *N*-methylaniline in 1,2-dimethoxyethane in the presence of pyridine. Recrystallization from hexane yielded light yellow crystals, m.p. 110.0–111.0° (lit., m.p. 103–106°,[39] 110–120).[40]

N-Methyl-*p*-chlorobenzanilide was similarly prepared by the reaction of *p*-chlorobenzoyl chloride and *N*-methylaniline. Recrystallization from ether and then petroleum ether yielded white crystals, m.p. 51.0–52.0°.

Exchange Reactions.—The exchange reactions were carried out by gently refluxing a mixture of acid and amide in a Claisen flask. The side arm of the flask was connected to a Y-tube, one branch of which was connected to a safety bottle charged with mineral oil and the other was connected to a delivery tube, which passed into an Erlenmeyer flask containing a neutral aqueous solution and phenolphthalein indicator. The end of the delivery tube was placed just below the surface of the solution. One thermometer extended into the bulb of the Claisen reaction flask and another was in the usual position in the side tube. Heating was regulated so that the mixture refluxed in the lower part of the side tube. The acetic acid formed was allowed to distil into water, and both the extent of reaction and an indication of the rate were determined by continuous titration of the low-boiling acid (acetic) with standard sodium hydroxide solution as it distilled from the reaction mixture. It was originally planned to obtain rate data that could be correlated with structure but the considerable temperature variation as the reaction proceeded, the significant quantity of acid held up in the system, and other factors rendered the data obtained, unsuitable for kinetic studies. The amide was generally used in excess to aid in driving the reaction and to reduce the temperature of the refluxing mixture. Reaction temperatures varied from 210–310°, the temperature increasing as the reaction proceeded. When the reaction was complete (2–15 hr.), the heat was removed and the mixture worked up. The exchanged amides were purified by careful fractional crystallization, sometimes preceded by distillation. In several cases, considerable difficulty was encountered in causing the crude exchanged amide to solidify. This was finally accomplished by seeding the chilled liquid with a trace of the authentic material. Difficulties in the crystallization of solid amides have been reported previously.[41]

Preliminary Experiments.—Benzoic acid was used in attempted exchange reactions with *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide and in some reactions a small amount of sulfuric acid was used as catalyst. The acids formed could not be effectively separated by distillation because of the high-boiling azeotropes formed by dimethylformamide and formic acid, and by dimethylacetamide and acetic acid.[42] Inasmuch as any exchanged amides formed were present in only small amount and their isolation from a large quantity of unexchanged amide was not easily accomplished, these experiments were discontinued. Although a small amount of acetic acid was produced in a preliminary experiment with *p*-nitrobenzoic acid and dimethylacetamide, the large amount of tarry substances formed made isolation of any exchanged amide impossible.

Exchange between Benzoic Acid and *N*-Methylacetanilide.—A mixture of 2.44 g. (0.02 mole) of benzoic acid and 5.68 g. (0.04 mole) of *N*-methylacetanilide was refluxed for 7.5 hr. During this period the reflux temperature rose from 255 to 288° and 0.0129 mole (65%) of acetic acid distilled over. The residue was dissolved in ether which was extracted with dilute sodium hydroxide. The aqueous phase was washed with ether, and the combined ether extracts were dried and evaporated to dryness. Recrystallization from hexane yielded 0.61 g. of crude *N*-methylacetanilide, m.p. 93–97° (lit., m.p. 102°).[43] The ether solution was stripped of solvent leaving 6.0 g. of liquid residue. All attempts to crystallize this material were unsuccessful. Distillation yielded the following fractions: (1) 1.36 g., b.p. 75–80° (1 mm.); (2) 0.37 g., b.p. 130–138° (1 mm.); (2) 3.00 g., b.p. 139–140° (1 mm.); and (4) 0.98 g. of residue. Fraction 1 solidified in the receiver, m.p. 93.5–98.5°. This increased the recovery of *N*-methylacetanilide to 1.97 g. (34%). Fractions 2 and 3 were very difficult to crystallize but crystals were finally obtained by seeding the chilled liquid with authentic *N*-methylbenzanilide. The solid obtained (79.8% crude yield) was then recrystallized from a mixture of hexane and a little ether. By this method 2.70 g. (64.0%) of *N*-methylbenzanilide, m.p. 58.0–60.0°, was obtained as white prisms. After repeated purifications, a sample melted at 59.0–60.0°. The identity of this product was established by its undepressed mixed melting point with an authentic sample of *N*-methylbenzanilide, m.p. 58.5–59.5°.

Exchange between Anisic Acid and *N*-Methylacetanilide.—A mixture of 7.61 g. (0.05 mole) of anisic acid and 7.46 g. (0.05 mole) of *N*-methylacetanilide was refluxed for 15 hr. During this time, the reflux temperature rose from 212° to 310° and then fell to 283° and 0.0294 mole (58.8%) of acetic acid distilled out of the mixture. The liquid residue was dissolved in ether, extracted with 1 *N* sodium hydroxide, dried over anhydrous sodium sulfate, and the ether stripped off to leave a liquid residue. All attempts to purify this mixture by crystallization were unsuccessful. Distillation yielded the following fractions: (1) 1.93 g., b.p. 133–140° (20 mm.); (2) 0.62 g., b.p. 140° (12 mm.); (3) 1.01 g., b.p. 185–188° (3 mm); (4) 5.83 g., b.p. 188–190° (3 mm.); and (5) 1.28 g. of residue. Fractions 1 and 2 solidified in the receivers and melted at 92.5–101° when recrystallized from ether and 2.55 g. (34.2%) of *N*-methylacetanilide were recovered. Fractions 3 and 4 consisted of 6.84 g. (57.0%) of crude *N*-methylanisanilide. By seeding these fractions a solid, b.p. 49–68°, was obtained. Recrystallization from ether yielded 3.13 g. (26.1%) of *N*-methylanisanilide, m.p. 77.5–79.5°. The identity of this material was confirmed by its undepressed mixed melting point with a sample of authentic *N*-methylanisanilide, m.p. 78.5–79.5°.

Exchange between *p*-Nitrobenzoic Acid and *N*-Methylacetanilide.—Attempts to carry out the exchange reaction at atmospheric pressure resulted in extensive decomposition and a resinous product. It was previously reported that extensive decomposition also occurred at 160° and higher temperature in the reaction between *p*-nitrophenylacetic acid and *p*-nitrophenylacetonitrile.[44] A mixture of 8.36 g. (0.05 mole) of *p*-nitrobenzoic acid and 14.92 g. (0.10 mole) of *N*-methylacetanilide was refluxed in a vacuum distillation set up with the receiver cooled in an ice–salt bath. The pressure of the system was constantly adjusted to maintain a reflux temperature of 210°. The mixture was refluxed under these conditions for 1.5 hr. with no signs of decomposition. During this time period 0.0151 mole of acetic acid (30.2%) was collected as distillate. The mixture was refluxed for an additional 3 hr. under the same conditions and 0.0185 mole of acetic acid (37.0%) distilled to make the total

(36) I. A. Kaye, H. C. Klein, and W. J. Burlant, *J. Am. Chem. Soc.*, **75**, 745 (1953).

(37) F. Weygand and R. Mitgau, *Ber.*, **88**, 301 (1955).

(38) M. Kuehn and S. M. McElvain, *J. Am. Chem. Soc.*, **53**, 1173 (1931).

(39) J. Forest, S. H. Tucker, and M. Whalley, *J. Chem. Soc.*, 303 (1951).

(40) S. I. Luré, *Zhur. Obshcheĭ Khim.* (J. Gen. Chem.), **18**, 1517 (1948).

(41) E. F. Pratt and J. Lasky, *J. Am. Chem. Soc.*, **78**, 4310 (1956).

(42) O. E. Ruhoff and E. E. Reid, *ibid.*, **59**, 401 (1937).

(43) P. Hepp, *Ber.*, **10**, 329 (1877).

(44) R. H. Wiley and W. B. Guerrant, *J. Am. Chem Soc.*, **71**, 981 (1949).

distillate 0.0336 mole of acetic acid (67.2%). The residue was treated with about 50 ml. of ethyl acetate and 0.69 g. of crude high-melting solid (235°) was filtered off. The ethyl acetate extract was successively washed with hot water, aqueous 1 *M* sodium carbonate, and water, and then dried over anhydrous sodium sulfate. A 6.6% recovery (0.55 g.) of *p*-nitrobenzoic acid was obtained by acidification of the combined aqueous wash solutions. Evaporation of the ethyl acetate left a residue (16.23 g.) which was extracted with 1 l. of hot hexane. An insoluble viscous residue (5.77 g.) remained, which could not be purified. When chilled, the hexane extract yielded 6.75 g. of yellow crystals, m.p. 60–105°. Recrystallization from hexane yielded 3.03 g. (23.6%) of *N*-methyl-*p*-nitrobenzanilide as small light yellow leaflets, m.p. 110.0–111.0°. The hexane filtrates were evaporated to dryness, the residue recrystallized twice from hexane, and the crystals obtained were thoroughly washed with hot water to yield 0.73 g. (5.7%) of product, m.p. 108.5–111.5°. Evaporation of the aqueous filtrate yielded 2.20 g. (14.7% recovery) of *N*-methylacetanilide, m.p. 99.5–102.5°. A total yield of 3.76 g. (29.4%) of *N*-methyl- *p*-nitrobenzanilide was obtained. The identity of this product was confirmed by its undepressed mixed melting point with a sample of authentic *N*-methyl- *p*-nitrobenzanilide, m.p. 110.0–111.0°.

Exchange between *p*-Chlorobenzoic Acid and *N*-Methylacetanilide.—A mixture of 7.83 g. (0.05 mole) of *p*-chlorobenzoic acid and 11.92 g. (0.10 mole) of *N*-methylacetanilide was refluxed for 3 hr. During this period the reflux temperature rose from 234 to 280° and 0.0393 mole of acetic acid (78.6%) were distilled from the reaction mixture. The residue was dissolved in ether and washed with 1 *M* sodium carbonate until no acid could be recovered by acidification of the aqueous wash solution. A total of 0.91 g. of *p*-chlorobenzoic acid (11.6%) was obtained by filtration of the wash solutions. The ether solution was washed with water, dried over anhydrous sodium sulfate, and stripped of solvent. The residue was dissolved in a large volume of hexane and allowed to cool very slowly to yield 4.09 g. (27.3% recovery) of *N*-methylacetanilide, m.p. 93.0–99.5°. Crystals were obtained with great difficulty since the material usually separated as an oil. A second crop of 3.35 g. (22.4% recovery) m.p. 89–99°, was obtained by concentrating the filtrate and chilling for several days. The filtrate was evaporated to dryness to yield 9.1 g. (74.2% crude yield) of *N*-methyl- *p*-chlorobenzanilide, m.p. 27.0–29.5°. Three recrystallizations from petroleum ether yielded 4.12 g. of purified product, m.p. 50.5–52.5° (33.5% yield), and 2.78 g. additional, m.p. 36.0–40.0° (22.7% yield), as a second crop. The identity of the purified product was confirmed by its undepressed mixed melting point with a sample of authentic *N*-methyl-*p*-chlorobenzanilide, m.p. 51.0–52.0°, and by nitrogen analysis.

Anal. Calcd. for $C_{14}H_{12}ClNO$: N, 5.70. Found N, 6.08.

Exchange between *p*-Dimethylaminobenzoic Acid and *N*-Methylacetanilide.—A mixture of 8.26 g. (0.05 mole) of *p*-dimethylaminobenzoic acid and 14.92 g. (0.10 mole) of *N*-methylacetanilide was refluxed for 3 hr. The reflux temperature rose from 244° to 264° during this time and 0.0340 mole of acetic acid (68.0%) was distilled from the reaction mixture. At the end of this period, the aqueous solution in the receiver became cloudy and the odor of an aniline derivative was detected. The solid residue was dissolved in benzene and ether, and the solution washed with 1 *M* sodium carbonate until no acid could be obtained by acidification of the wash water. A 4.5% recovery of *p*-dimethylaminobenzoic acid (0.37 g.) was obtained in this manner. The organic phase was washed with water and then with several portions of dilute hydrochloric acid. The solvent was distilled from the organic phase, leaving 7.82 g. of solid residue, m.p. 99.0–99.5° (52.3% recovery of *N*-methylacetanilide). The acid wash was made basic with 1 *N* sodium hydroxide and 7.71 g. (60.0%) of yellow solid *N*-methyl- *p*-dimethylaminobenzanilide separated, m.p. 149.5–151.5°. Crystals, m.p. 150.5–151.5°, were obtained by recrystallization from petroleum ether. The identity of this material was established by its undepressed mixed melting point with a sample of authentic *N*-methyl-*p*-dimethylaminobenzanilide, m.p. 150–153.5°, and by a nitrogen analysis.

Anal. Calcd. for $C_{16}H_{18}N_2O$: N, 11.02. Found: N, 11.14.

Exchange between *p*-Toluic Acid and *N*-Methylacetanilide.—A mixture of 6.80 g. (0.05 mole) of *p*-toluic acid and 14.92 g. (0.10 mole) of *N*-methylacetanilide was refluxed for 2 hr. The reflux temperature rose from 247 to 286° during this period and 0.0455 mole of acetic acid (91.0%) was distilled from the reaction mixture. The residue was dissolved in ether and washed with 1 *M* sodium carbonate. A 2.94% recovery (0.20 g.) of *p*-toluic acid was obtained by acidification of the basic wash solution. The organic phase was washed with water, dried over anhydrous sodium sulfate, and the solvent distilled under reduced pressure. The residue was dissolved in hot petroleum ether, which was then cooled slowly and seeded with a crystal of *N*-methylacetanilide. Crystals of crude *N*-methylacetanilide (4.35 g., 29.1%) m.p. 89.5–97.0°, were obtained after several days. Recrystallization from ether gave 3.32 g., m.p. 101.0–102.0°. A second crop of crystals was obtained by concentrating the petroleum ether filtrate and chilling for 2 days. Thus 5.98 g. (47.1%) of *N*-methyl-*p*-toluanilide was obtained as white crystals, m.p. 66.0–69.0°. Fractional crystallization of the material remaining the filtrate followed by washing the resulting impure solid with hot water, left 2.68 g. (21.1%) *N*-methyl- *p*-toluanilide, m.p. 67.5–69.5°. Evaporation of the water yielded 2.61 g. (17.5% recovery) of *N*-methylacetanilide, m.p. 91.0–97.5°. A total of 6.96 g., of *N*-methylacetanilide was recovered (46.6%) and 8.66 g. (68.2%) of *N*-methyl-*p*-toluanilide was isolated. Recrystallization of the latter from petroleum ether gave white crystals, m.p. 69.5–71.0°. The identity of this product was established by its undepressed mixed melting point with a sample of authentic *N*-methyl-*p*-toluanilide, m.p. 69.5–71.0°.

Attempt to Detect Anhydrides.—A mixture of 0.83 g. (0.005 mole) of *p*-dimethylaminobenzoic acid and 1.49 g. (0.010 mole) of *N*-methylacetanilide was refluxed for 38 min. in the distillation set-up described previously. The reflux temperature rose from 246 to 262° during this period and titration of the distillate indicated that 5.0% of the theoretical quantity of acetic acid had distilled over. The residue was then rapidly cooled and tested for the presence of anhydride, using a 3% solution of 2-(*p*-nitrobenzamido)phenylacetic acid [α-(*p*-nitrobenzoyl)amino-α-toluic acid] in pyridine.[45] No anhydride could be detected.

Exchange Reaction at Constant Temperature.—A mixture of 1.49 g. (0.01 mole) of *N*-methylacetanilide and 1.36 g. (0.01 mole) of *p*-toluic acid was heated in the distillation set-up described previously, but modified by the use of an addition funnel which could drop liquid directly into the reaction flask. Dimethyl diethylene glycol was slowly added at a rate such that the temperature of the refluxing mixture was maintained between 200–210° and the vapor temperature varied from 160–167°. Acid was observed in the distillate almost as soon (reaction temperature 170°) as the solvent began to distill. Once the desired temperature range was reached, the acetic acid distilled over at a practically constant rate of 8×10^{-5} mole (0.8%) per min. After about 110 min. of total heating time, 80% of the acetic acid had been collected in the distillate.

(45) D. Davidson and P. Newman, *J. Am. Chem. Soc.*, **74**, 1515 (1952).