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The Acid-Catalyzed Nitramine Rearrangement. I. The Products of Rearrangement of N-Nitro-N-methylaniline[1]

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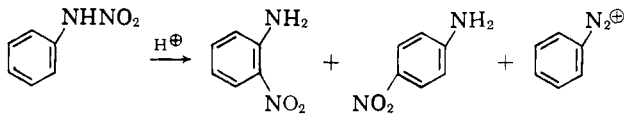
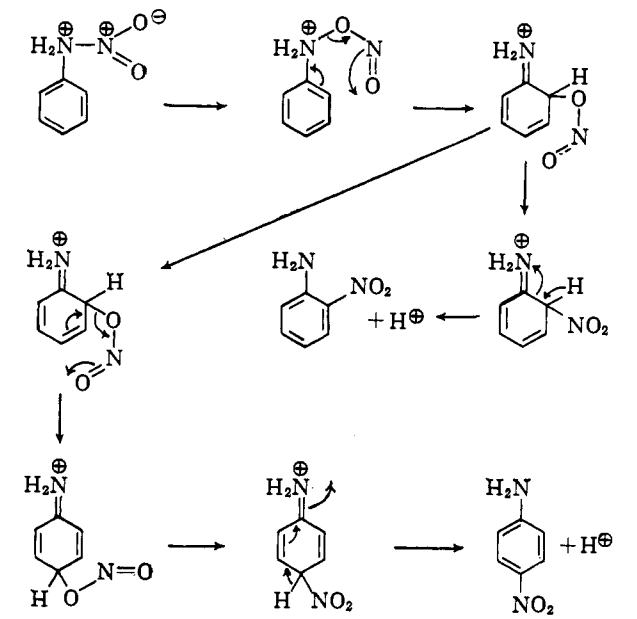
As a first step in an intensive study[2] of the mechanism of the acid-catalyzed nitramine rearrangement, the major products from the isomerization of N-nitro-N-methylaniline in aqueous acid solution were determined. Isotope dilution analysis indicated that the nitramine gave 10% of N-methylaniline, 52% of *o*-nitro-N-methylaniline, and 31% of *p*-nitro-N-methylaniline. No *meta*-isomer was detected. Spectrophotometric examination of the reaction solutions led to essentially the same percentages of *o*- and *p*-nitro-N-methylaniline (49 and 32%, respectively). The solutions were also shown to contain about 13% of nitrous acid. Mechanistic consideration of these results suggests that the rearrangement must occur by cleavage of the nitro–amine bond to give a pair of radicals which either recombine to give intermediates decomposing to *o*- and *p*-nitro-N-methylaniline or else dissociate and undergo reduction to nitrous acid and N-methylaniline.

Introduction

The rearrangement of aromatic nitramines,[3] which is exemplified by the isomerization of N-nitroaniline, has been categorized along with the Claisen and benzidine



rearrangements as an intramolecular aromatic rearrangement. The proposition that the rearrangement proceeded through scission of the nitramine into an aniline and an independent nitrating species (with nitrogen in a +5 oxidation state) was disposed of by the demonstration[4,5] that the relative proportions of *o*-, *m*-, and *p*-isomers from rearrangement and direct nitration under similar conditions were considerably different. The implied intramolecular character of the reaction was assumed to be proved by the observation[6] that the rearrangement of phenylnitramine in the presence of potassium nitrate-N^{15} gave nitroanilines containing no excess N^{15}.



To incorporate these facts, the following mechanism was proposed.[7] Because of several unusual features of this mechanism and of the nitramine rearrangement itself, this isomerization seemed worthy of further study to gain more details of the intimate nature of the process.

A quantitative estimation of the products is a matter of prime importance in any mechanism determination. This constituted the first goal in our studies of the nitramine rearrangement.

The rearrangement of N-nitroaniline produces in addition to ring-substituted nitroanilines, diazonium salts. These salts, which have often been considered to arise by a side reaction mechanistically different from the rearrangement process, are not stable and thus are difficult to determine quantitatively. In order to prevent their formation, N-methyl-N-nitroanilines were chosen for study. These could give rise to diazonium salts only by the improbable loss of the methyl group.

Results

N-Nitro-N-methylaniline-C^{14} was rearranged in 0.5 *N* hydrochloric acid at 40° for a period corresponding to 10 reaction half-lives (99.9% completion). Aliquots of the reaction solution were subjected to isotope dilution analysis. *o*-Nitro-N-methylaniline was isolated directly, *m*- and *p*-nitro-N-methylanilines were obtained as their benzoyl derivatives, and N-methylaniline as the acetanilide. The results are collected in Table I. The isolated N-methyl-N-(*m*-nitrophenyl)-benzamide showed an activity identical with background. It was estimated from the activity of the original nitramine and the weights of radioactive nitramine and inactive diluent used that less than 0.1% of *m*-nitro-N-

TABLE I

REARRANGEMENT PRODUCTS OF N-NITRO-N-METHYLANILINE

	Percentage				
Run	I[a]	II[a]	III[a]	IV[b]	V[b]
$C_6H_5NHCH_3$	.....	9.6 ± 0.1	10.3 ± 0.1	..	..
o-$NO_2C_6H_4NHCH_3$	51.8 ± 0.3	51.7 ± 0.3	51.6 ± 0.2	49.4	48.6
m-$NO_2C_6H_4NHCH_3$	<0.1	<0.1	<0.1	..	..
p-$NO_2C_6H_4NHCH_3$	31.6 ± 0.2	30.9 ± 0.1	30.2 ± 0.3	32.2	31.8
Nitrous acid	.....	.....	.....	13.1	13.3

[a] Isotope dilution analysis; rearrangement conditions: 0.5005 *N* HCl at 40.0 ± 0.5°. [b] Spectrophotometric analysis; rearrangement conditions: 0.503 *N* $HClO_4$ at 40.0 ± 0.5°.

(1) This investigation was supported by a research grant (NSF-G 7345) from the National Science Foundation.

(2) A preliminary report of this work appeared in W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Am. Chem. Soc.*, **83**, 2024 (1961).

(3) For a review of this subject, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 625–628.

(4) A. F. Holleman, J. C. Hartogs, and T. van der Linden, *Ber.*, **44**, 704 (1911).

(5) E. D. Hughes and G. T. Jones, *J. Chem. Soc.*, 2678 (1950).

(6) S. Brownstein, C. A. Bunton, and E. D. Hughes, *ibid.*, 4354 (1958).

(7) S. Brownstein, C. A. Bunton, and E. D. Hughes, *Chem. Ind.* (London), 981 (1956).

methylaniline should have been detectable. Thus, it seems probable that no *m*-isomer was formed.

The amounts of *o*- and *p*-nitro-N-methylaniline in the rearrangement mixture were also determined spectrophotometrically. The reaction mixture was treated with ammonium sulfamate to destroy the nitrous acid and convert the N-nitroso derivatives of the *o*- and *p*-nitro-N-methylanilines to the free amines. Spectrophotometric analysis of the resulting solutions gave the percentages shown in Table I. These results are in quite good agreement with those obtained from isotope dilution analysis.

Since nitrous acid was formed, knowledge of the amount produced would be mechanistically useful information. A diazotization–coupling routine was used. *p*-Nitroaniline was chosen as the nitrous acid scavenger. The *p*-nitrobenzenediazonium salt was coupled with N,N-dimethyl-α-naphthylamine to yield the purple dye 4-(*p*-nitrophenylazo)-N,N-dimethyl-α-naphthylamine which was measured spectrally.

Combination of all these results shows 91–93% of the aromatic portion of the original nitramine was accounted for (as *o*- and *p*-nitro-N-methylaniline and N-methylaniline) and 94–96% of the nitro group was detected (as *o*- and *p*-nitro-N-methylaniline and nitrous acid).

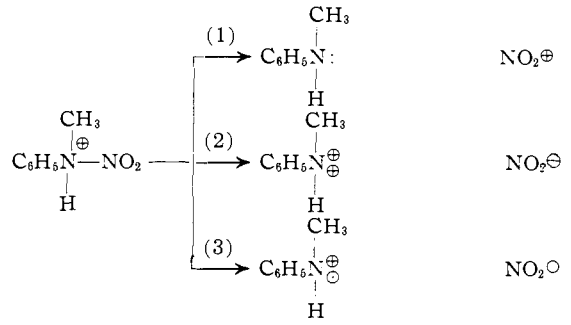
Discussion

Two features of the nitramine rearrangement product distribution impose rather severe restrictions upon any mechanistic proposal for this reaction. These are the production of *p*-nitro-N-methylaniline and the formation of reasonably sizable and comparable amounts of nitrous acid and N-methylaniline.

The relationship between the amounts of nitrous acid and N-methylaniline produced has important implications. The denitrated nitramine cannot arise from a simple hydrolytic cleavage of the nitramine—this would produce no nitrous acid. Since only a portion of the total nitrous acid (13%) could arise from the nitramine unaccounted for in the product analysis (7–9%), it follows that both nitrous acid and denitrated nitramine must come from the same nitramine molecule. This is possible only if a reduction occurs. Although there are no obvious reducing agents in the medium, easily oxidizable substances such as the product amines may function in this way. This oxidation of a part of the product may explain the lack of quantitative recovery of the products.

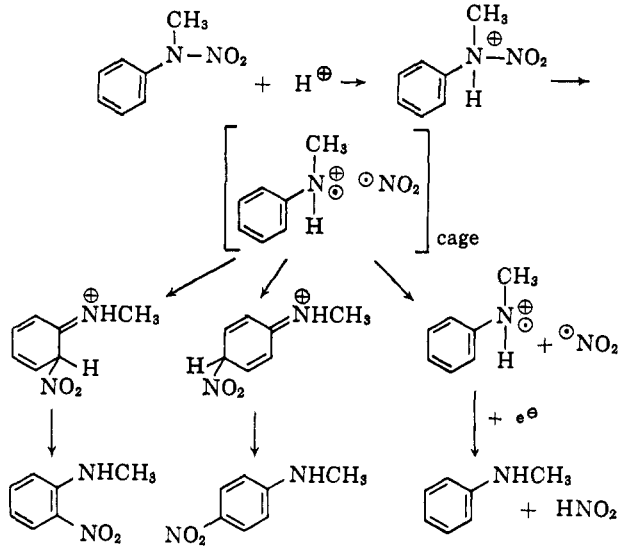
The formation of *p*-nitroaniline or one of its derivatives by rearrangement of a nitramine has great significance in the formulation of a mechanism for the process. Any mechanisn which does not involve the breaking of the nitro–amine bond prior to the formation of a new bond to the nitro group encounters logical difficulties. Direct transfer of the nitro group from the amino nitrogen to the *p*-position of the ring is ruled out by the large distances (4.0–4.5 Å.) which would have to be spanned in the transition state. Likewise, any stepwise transfer of the nitro group first to the *o*- and then to the *p*-position (see Introduction) is mechanistically unsound because of the likelihood that the necessary intermediates will undergo reactions other than those leading to products (*e.g.*, hydrolysis of the nitrite, proton loss from cyclohexadieneimine intermediates, etc.).

The origin of the *p*-isomer can be most easily interpreted if the severance of the N–N bond precedes any process in which the nitro group is rebonded to the aromatic fragment. The nitramine bond in the protonated nitramine could break in several ways to give a pair of particles.



Recombination of any pair of these would lead to the observed products. Two pieces of evidence rule out the possibility 1 of a cleavage into nitronium ion and aniline or one of its derivatives. These are the demonstrations that the rearrangment products are not at all similar to those obtained from reaction of nitronium ion with aniline in acid, and the finding that there is no N^{15} in the *o*- and *p*-nitroanilines formed when N-nitroaniline is rearranged in a medium containing $KN^{15}O_3$. However, these findings do not exclude the other two modes of bond scission.

CHART I



52%,[a] 49%[b] 31%,[a] 32%[b] 10%,[a] 13%[b]

[a] Isotope dilution analysis. [b] Spectrophotometric analysis.

Some support for the alternative types of bond breaking is afforded by the present investigation. The nitrous acid detected could arise from either nitrite ion or from reaction of two nitrogen dioxide molecules with water. Unfortunately the amount of nitrous acid found (13%) is intermediate between the quantities expected from mechanism 2 (17–19%) and mechanism 3 (9–10%). Thus, a clear-cut decision between the two mechanisms cannot be made on this basis. However, mechanism 3 is to be preferred because it is more likely that NO_2 will be reduced to NO_2^- under the conditions of the reaction than that NO_2^- will be oxidized to NO_3^-. The reducing agents may be the same as those which convert the aromatic portion of the product to N-methylaniline.

If simple unconcerted nitro–amine bond breaking is involved, actual dissociation of the nitro and anilino moieties need not precede nitroaniline formation. These particles will undergo a large number of mutual collisions before escaping from the solvent cage and from each other. During one of these collisions they could recombine to yield intermediates capable of decomposing to the nitroanilines. The fragments held

TABLE II

NITROANILINE DERIVATIVES

	N-*p*-Toluenesulfonyl			N-Methyl-N-*p*-toluenesulfonyl				N-Methyl		
Isomer	Yield, %	M.p., °C.	Lit. m.p., °C.	Yield, %	Solvent	M.p., °C.	Lit. m.p., °C.	Yield, %	M.p., °C.	Lit. m.p., °C.
ortho	95	113.7–114.7	112–114[a]	88	EtOH	132.2–133.8	130–132[a]	94	33.8–35.2	34–35[a]
meta	97	136.7–138.1	137–138[b]	92	EtOH	105.8–108.2	111[c]	95	66.4–67.0	65–66[d]
para	96	187.7–188.5	189–190[e]	92	HOAc	175.1–177.1	175–176[f]	91	152.7–153.4	150–151[g]

[a] E. H. Usherwood and M. A. Whiteley, *J. Chem. Soc.*, **123**, 1084 (1923). [b] G. T. Morgan and F. M. G. Micklethwait, *ibid.*, **89**, 1289 (1906). [c] G. T. Morgan and F. M. G. Micklethwait, *ibid.*, **101**, 143 (1912). [d] E. Noelting and T. H. Stricker, *Ber.*, **19**, 546 (1886). [e] G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **87**, 1302 (1905). [f] F. Bell and P. H. Robinson, *ibid.*, 1129 (1927). [g] E. Bamberger, *Ber.*, **27**, 359 (1894).

within the cage might exhibit some attraction for each other which would further impede their dissociation. Thus, the dication and anion in mechanism 2 would interact electrostatically and perhaps electronically. The radical pair in mechanism 3 might be involved in a complex of some type.[8] In any case, any forces between the nitro and anilino fragments must be quite weak since some dissociation must occur if nitrous acid and N-methylaniline are to be formed.

In conclusion, the available data favor a tentative mechanism of the type in Chart I for the acid-catalyzed nitramine rearrangement.

Experimental

N-Nitro-N-methylanilineC^{14}, m.p. 36.6–37.6° (lit.[9] m.p. 38.5–39.5°), was prepared from uniformly labeled aniline-C^{14} by a procedure[10] described previously.

N-(*x*-Nitrophenyl)-*p*-toluenesulfonamide.—To a solution of 69 g. (0.5 mole) of *x*-nitroaniline in 158 g. (2.0 moles) of pyridine was added 143 g. (0.75 mole) of *p*-toluenesulfonyl chloride. The resulting mixture was allowed to stand 6 hr. at 25° and then treated with 10 cc. of water. After heating on the steam bath for 30 min., it was stirred into a solution of 200 cc. of concentrated hydrochloric acid in 2 l. of ice-water. The precipitated solid was collected by filtration, washed with water, and crystallized from a mixture of ethanol and acetic acid. The yields and physical data are summarized in Table II.

N-Methyl-N-(*x*-nitrophenyl)-*p*-toluenesulfonamide.—A solution of 147 g. (0.5 mole) of N-(*x*-nitrophenyl)-*p*-toluenesulfonamide in 1250 cc. of dioxane was mixed with a solution of 100 g. (2.5 moles) of sodium hydroxide in 400 cc. of water, and then 231 cc. (2.5 moles) of dimethyl sulfate was added. The resulting mixture was stirred for 15 hr. at 25° and poured into 2 l. of ice-water. The solid was filtered off and dissolved in 1500 cc. of chloroform. The chloroform solution was washed with two 250-cc. portions of 5% sodium hydroxide solution and two 250-cc. portions of water. The chloroform was evaporated and the residue was crystallized. The results are reported in Table II.

***x*-Nitro-N-methylaniline.**—A mixture of 122 g. (0.4 mole) of N-methyl-N-(*x*-nitrophenyl)-*p*-toluenesulfonamide, 125 cc. of glacial acetic acid, and 125 cc. of concentrated sulfuric acid was heated on the steam bath until solution was complete and then for an additional 15 min. The cooled solution was stirred into 3 l. of ice-cold 10% sodium hydroxide solution.

In the cases of the *m*- and *p*-nitro-N-methylanilines, the solid was filtered off, washed with water, and crystallized from ethanol or aqueous ethanol.

The *o*-nitro-N-methylaniline was obtained by extraction of the basic solution with three 250-cc. portions of ether. The combined ether solutions were washed with water, dried over magnesium sulfate, and evaporated. The residue was distilled (b.p. 110–130° at 4.0 mm.) to give an orange oil which readily solidified. The solid was crystallized from ethanol at 0°.

Yield data and physical properties of these compounds will be found in Table II.

Isotope Dilution Analysis of the Rearrangement Products of N-Nitro-N-methylaniline.—The following example is illustrative of the general procedure used.

Rearrangement of N-Nitro-N-methylaniline-C^{14}.—A solution of 120.25 mg. of N-nitro-N-methylaniline-C^{14} in 2.00 cc. of purified dioxane was diluted to exactly 500.0 cc. (volumetric flask) with 0.5005 *N* hydrochloric acid at 40°. The reaction mixture was maintained at 40.0 ± 0.5° for 2 hr. and then cooled to room temperature. The contents of the flask were again brought to 500.0 cc. with water and aliquots of the solution were removed and treated as follows.

Isolation of *o*-Nitro-N-methylaniline.—A 20.00-cc. aliquot of the above reaction mixture was added to a solution of 497.50 mg. of *o*-nitro-N-methylaniline in 25 cc. of ether and 10 cc. of 5% sodium hydroxide solution in a separatory funnel. The mixture was shaken vigorously for 10 min. The ether layer was separated and the aqueous phase was extracted twice with 15-cc. portions of ether. The combined ether solutions were dried over magnesium sulfate and then evaporated. The residue was crystallized repeatedly from petroleum ether, b.p. 30–60°, at 0° until there was no further change in activity. The *o*-nitro-N-methylaniline-C^{14} was obtained as brilliant orange prisms, m.p. 33.6–35.0° (lit.[11] m.p. 34–35°).

Isolation of N-(*m*-Nitrophenyl)-N-methylbenzamide-C^{14}.—A 250.00-cc. aliquot of the reaction mixture was added to 25 cc. of 25% sodium hydroxide solution and a solution of 494.65 mg. of *m*-nitro-N-methylaniline in 50 cc. of ether contained in a separatory funnel. The mixture was shaken vigorously for 10 min. The organic layer was separated and the aqueous solution was washed two times with 50-cc. portions of ether. The combined ether solutions were dried over magnesium sulfate and then evaporated. The residue was dissolved in 10 cc. of dry pyridine. The resulting solution was treated with 1.2 cc. of benzoyl chloride and refluxed for 10 min. The excess acid chloride was destroyed by refluxing for another 10 min. after the addition of 1.0 cc. of water. The reaction mixture was poured into 20 cc. of water and the product was extracted with 20 cc. of ether. The ether solution was washed with two 5-cc. portions of 10% sodium bicarbonate solution and two 5-cc. portions of 5% hydrochloric acid. It was then dried over calcium chloride. The dry ether solution was chromatographed on a 2 × 20 cm. column of Woelm activity grade I neutral alumina using ether as eluent. The residue obtained from evaporation of the eluate was crystallized to constant activity from ethanol. The benzamide of *m*-nitro-N-methylaniline-C^{14} formed almost colorless prisms, m.p. 102.9–103.8° (lit.[12] m.p. 104–105°).

Isolation of N-(*p*-Nitrophenyl)-N-methylbenzamide-C^{14}.—A 150.00-cc. aliquot of the reaction mixture was added to a separatory funnel containing 15 cc. of 25% sodium hydroxide solution and a solution of 496.65 mg. of *p*-nitro-N-methylaniline in 75 cc. of ether. The mixture was shaken for 10 min. and the ether layer was then separated. The water layer was extracted twice with 50-cc. portions of ether. The combined ether solutions were dried over magnesium sulfate and evaporated. The residue was dissolved in pyridine and treated with benzoyl chloride exactly as described above for the *m*-isomer. The chromatographed benzoyl derivative was crystallized several times from ethanol to obtain material of constant activity. The benzamide of *p*-nitro-N-methylaniline-C^{14} was a slightly yellowish crystalline compound, m.p. 110.1–111.2° (lit.[12] m.p. 111–112°).

Isolation of N-Methylacetanilide-C^{14}.—A 75.00-cc. aliquot of the rearrangement product was added to a separatory funnel containing 30 cc. of 5% sodium hydroxide solution and a solution of 516.35 mg. of redistilled N-methylaniline in 25 cc. of ether. The mixture was shaken thoroughly for 10 min. after which the ether layer was separated and the aqueous fraction was extracted two times with 25-cc. portions of ether. The combined ether solutions were dried over magnesium sulfate and carefully evaporated. To the residue was added 1.0 cc. of acetic anhydride and the mixture was heated on the steam bath for 5 min. During this heating period, the reaction mixture was subjected to water-pump aspiration. The solid residue was repeatedly crystallized from cyclohexane. The N-methylacetanilide-C^{14} was obtained as colorless needles, m.p. 100.0–101.2° (lit.[13] m.p. 101–102°).

Determination of Activities and Calculation of Percentages of Products.—After several crystallizations, the substances to be analyzed were thoroughly dried and their activities were determined. This was done by burning samples to carbon dioxide, collecting the carbon dioxide in an ionization chamber, and measuring the "rate of drift" by means of a Cary Model 31 vibrating

(8) K. H. Hausser and J. N. Murrell, *J. Chem. Phys.*, **27**, 500 (1957).

(9) E. Bamberger, *Ber.*, **27**, 359 (1894).

(10) Method D in W. N. White, E. F. Wolfarth, J. R. Klink, J. Kindig, C. Hathaway, and D. Lazdins, *J. Org. Chem.*, **26**, 4124 (1961).

(11) E. H. Usherwood and M. A. Whiteley, *J. Chem. Soc.*, **123**, 1084 (1923).

(12) R. Meldola and E. H. R. Salmon, *ibid.*, **53**, 774 (1888).

(13) P. Hepp, *Ber.*, **10**, 327 (1877).

reed electrometer and a Cary multi-range recorder. This procedure has been described in detail by Neville[14] and by Raaen and Ropp.[15]

Spectrophotometric Analysis of the Rearrangement Products of N-Nitro-N-methylaniline.—*o*- and *p*-nitro-N-methylaniline were determined directly and nitrous acid was estimated by conversion to a diazonium salt and the coupling of the latter with N,N-dimethyl-α-naphthylamine. To carry out these analyses the following solutions were used.

Solutions.—N-nitro-N-methylaniline (81.5 mg. in 50.00 cc. of purified dioxane), *o*-nitro-N-methylaniline (48.6 mg. in 25.00 cc. of purified dioxane), *p*-nitro-N-methylaniline (24.1 mg. in 25.00 cc. of purified dioxane), N-methylaniline (18.6 mg. in 25.00 cc. of purified dioxane), sodium nitrite (16.5 mg. in 25.00 cc. of water), perchloric acid (5.03 *N*), ammonium sulfamate (5.0 g. in 100 cc. of water), acetate buffer (to a solution of 15.0 g. of sodium acetate trihydrate in 50.0 cc. of water was added 50.0 cc. of glacial acetic acid), nitrous acid reagent (to a solution of 0.2 g. of *p*-nitroaniline and 0.2 g. of N,N-dimethyl-α-naphthylamine in 45.0 cc. of glacial acetic acid was added 5.0 cc. of 60% perchloric acid).

Determination of *o*- and *p*-Nitro-N-methylaniline.—Two-cc. aliquots of purified dioxane and of the *o*-, *p*- and N-nitro-N-methylaniline solutions were separately treated according to the following procedure.

A 2.00-cc. aliquot of dioxane or one of the nitro-N-methylaniline solutions was added to a thermostated (40.0 ± 0.5°) solution of 5.00 cc. of 5.03 *N* perchloric acid and about 40 cc. of water in a 50.0-cc. volumetric flask. The contents of the flask were made up to volume with water at 40° and the mixture was shaken and thermostated at 40.0 ± 0.5° for 60 min. A 5.00-cc. aliquot of the resulting solution was added to 5.00 cc. of 5% ammonium sulfamate solution in a 25.0-cc. volumetric flask. The flask was then heated on a steam bath for 30 min. and cooled. Acetate buffer was added to bring the volume to 25.0 cc. and the mixture was shaken. The final solution from the dioxane run was used as a spectral blank. The solutions made up from the *o*- and *p*-nitro-N-methylaniline solutions were employed as standards for evaluating the extinction coefficients of these compounds so that the ultimate solution obtained from N-nitro-N-methylaniline could be analyzed for these components using Beer's law. The absorptions of these final solutions were determined at 390, 410, 430, 450, and 470 mμ using a Beckman DU spectrophotometer.

The method of least squares was used to compute the concentrations of *o*- and *p*-nitro-N-methylaniline that best reproduced the optical densities at the five wave lengths.

Nitrous Acid Determination.—The procedure described below was carried out simultaneously on three different original mixtures to obtain blanks, standards, and unknowns.

To a solution of 5.00 cc. of 5.03 *N* perchloric acid and about 40 cc. of water at 40.0 ± 0.5° in a 50.0-cc. volumetric flask were added accurately measured aliquots of the standard solutions (*vide infra*). The solution was brought to the mark with water at 40°, shaken, and thermostated at 40.0 ± 0.5° for 60 min.

One 5.00-cc. aliquot of this reaction mixture was treated as described above under "Determination of *o*- and *p*-Nitro-N-methyl-aniline" (*i.e.*, it was added to 5.00 cc. of 5% ammonium sulfamate solution, heated at 100° for 30 min., and diluted to 25.0 cc. with acetate buffer) with the exception that the absorption of the final solution was determined at 500, 520, 540, and 560 mμ.

Another 5.00-cc. aliquot was added to 5.00 cc. of nitrous acid reagent in a 25.0-cc. volumetric flask. This mixture was kept for 24 hr. at 25° and was then diluted to the mark with acetate buffer. The spectrum of the resulting solution was determined at 500, 520, 540, and 560 mμ.

For the blanks a 2.00-cc. aliquot of purified dioxane was carried through the procedure outlined above. The sulfamate-treated solution was used as a spectral blank for all the other solutions and the nitrous acid reagent-treated portion (designated B) was used to determine the absorption characteristics of the reagent.

The standards were prepared by adding 1.00 cc. each of the *o*- and *p*-nitro-N-methylaniline, N-methylaniline, and sodium nitrite solutions to the warm perchloric acid solution (the nitrite was added last). This mixture approximates that resulting from rearrangement. The final solution containing sulfamate was called S′ and that containing nitrous acid reagent, S.

The rearrangement was carried out using a 2.00-cc. portion of the N-nitro-N-methylaniline solution. The solution subjected to nitrous acid reagent was termed R and that treated with sulfamate solution as R′.

The concentration of the nitrous acid formed in the rearrangement was found from the expression

$$C = M(D_R - D_{R'} - D_B)/50(D_S - D_{S'} - D_B)$$

where M is the concentration of $NaNO_2$ in the original standard and the D's are the optical densities of the solutions referred to above. Since all solutions were examined at four wave lengths, four separate values of C resulted from each determination. The average deviation of these values from the mean was always less than 1%.

(14) O. K. Neville, *J. Am. Chem. Soc.*, **70**, 3501 (1948).

(15) V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

[CONTRIBUTION FROM MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N. J.]

Synthesis and Structure of Steroidal Pregn-4-eno- and 5α-Pregnano[3,2-*c*]pyrazoles. A Novel Class of Potent Anti-Inflammatory Steroids[1,2]

BY RALPH HIRSCHMANN, PAUL BUCHSCHACHER, N. G. STEINBERG, J. H. FRIED, R. ELLIS, G. J. KENT, AND MAX TISHLER

RECEIVED SEPTEMBER 23, 1963

The preparation of several [3,2-*c*]pyrazoles related to cortisol, to 16α-methylcortisol, and to 4,5α-dihydrocortisol is described. The novel observation that a carbonyl function at C-3 is not required for anti-inflammatory activity is discussed. The 2′-phenyl and especially the 2′-*p*-fluorophenyl[3,2-*c*]pyrazole functions have the greatest enhancing effect on anti-inflammatory activity known to date. The [3,2-*c*]pyrazole function, unlike the 2α-methyl substituent, does not enhance mineralocorticoid activity. The structure assignment for the isomeric 1′- and 2′-alkyl- and arylpyrazoles is discussed. In the 4,5α-dihydro series the ratio of the isomeric pyrazoles obtained was markedly dependent on the reaction temperature.

Since the synthesis of cortisone by Sarett[3,4] and the discovery of the dramatic success of that compound in the treatment of rheumatoid arthritis by Hench and Kendall,[5] much has been learned about structural changes which enhance the activity of the anti-inflammatory steroids.[6] In 1959, Clinton and his co-workers[7] and more recently de Ruggieri, *et al.*,[8] reported that androst-4-eno- and androstano-[3,2-*c*]pyrazoles are potent anabolic agents. These results were consistent with other reports that an oxygen at C-3 is not required for anabolic-androgenic[9] or pro-

(1) For preliminary announcements concerning this class of compounds see: R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963).

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(3) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(4) L. H. Sarett, *ibid.*, **71**, 2443 (1949).

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(6) For recent reviews see: L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959; L. H. Sarett, A. A. Patchett and S. L. Steelman, "Fortschritte der Arzneimittelforschung," Vol. 5, E. Jucker, Ed., Birkhäuser Verlag, Basel and Stuttgart, 1963.

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(8) P. de Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. chim. ital.*, **92**, 768 (1962).