of the volatile fractions revealed the presence of several low boiling components in addition to 2- and 3-pentanone.[5]

The pentanone fraction was separated by preparative gas chromatography (10-ft. by $^{1}/_{2}$-in. column of butanediol succinate on chromosorb) and was shown to contain about 5% 2-pentanone and 95% 3-pentanone by gas chromatography on a 10-ft. by $^{1}/_{8}$-in. column of 20% triethylene glycol on firebrick. This sample was also analyzed by infrared, which revealed 6% of 2-pentanone in 3-pentanone, and by NMR, which showed 2-pentanone to be present to the extent of 3–5% in the 3-pentanone.

Gas Chromatographic Separation of 2- and 3-Pentanone.—2-Pentanone and 3-pentanone are difficult to separate by gas chromatography on many columns, especially when one component is present in small concentration. The quantitative analyses reported in Table I were taken on the triethylene glycol column mentioned above. When only small amounts are present, the 2-pentanone appears as a shoulder or small peak on the trailing edge of the 3-pentanone peak. For quantitative analysis, samples of known mixtures of 2- and 3-pentanone were run, and the ratio of the 3-pentanone peak height to the 2-pentanone peak height (corrected for the 3-pentanone tail) was plotted against the known concentration of 2-pentanone, giving a linear plot. The unknown samples were run and calculated in the same manner, and the composition was read from the graph. Less than 1% of 2-pentanone could be detected easily, and the error in the measurement at about 10–15% of 2-pentanone is estimated as $< \pm 1\%$ of 2-pentanone. One particular silicone column (but not a number of other silicone columns) also gives a separation of 2- and 3-pentanone, and in this case, in contrast to the triethylene glycol column, the 2-pentanone has the shorter retention time. A poly *m*-phenyl ether column also gives reasonable separation when the percentage of either ketone in the other is large.[6,7]

NMR Analysis.—The NMR spectra were taken at 60 Mc. with a Model V4300D Varian Associates spectrometer. The α-methyl hydrogens (8.11 τ) of 2-pentanone appear as a singlet with no interference from either the methylene (7.61 τ) or methyl (8.96 τ) hydrogens of 3-pentanone, or from the α-methylene (7.62 τ), β-methylene (8.82 τ), or γ-methyl (8.96 τ) hydrogens of 2-pentanone. One can easily detect 0.5% of 2-pentanone in 99.5% 3-pentanone.

Infrared Analyses.—The infrared analyses were run on a Perkin-Elmer Model 21 instrument. Preliminary work using 4% solutions of the ketone in carbon tetrachloride made use of the bands at 8.60 and 8.95 μ. Later work utilized the 13.78-μ region where 2-pentanone shows a medium absorption band and the 3-pentanone spectrum is flat. Using the baseline density method, a straight line was obtained by plotting the absorbance *vs.* the % of 2-pentanone in known solutions. The compositions of the unknown mixtures were read from this graph.

Derivatives of 2-Pentanone.—It was thought to be desirable to furnish chemical proof of the presence of 2-pentanone in addition to the evidence from gas chromatography, infrared, and NMR spectra. Part of the pentanone fraction (4.0 g., containing ~2% 2-pentanone by gas chromatographic analysis) from a large scale reaction (250 g. of 3-pentanone, 36 hr., 75°) was subjected to the iodoform reaction. The iodoform collected amounted to 1.2 g. (nearly three times the theoretical amount from the 2-pentanone present—upon longer standing, even more iodoform is produced). The sodium salts of the acids produced were isolated in the usual fashion, and the *p*-toluidides were made. Fractional crystallization yielded the *p*-toluidides of butyric acid, m.p. 72–74°, reported[8] m.p. 72°, and of propionic acid (presumably from the 2-pentanone) m.p. 120–124°, reported[8] m.p. 124°.

Several 2-pentanone-rich samples of the pentanone fraction recovered from the acid treatment were combined and the 2-pentanone contained was concentrated by treatment with semicarbazide and fractional crystallization of the semicarbazone mixture. The ketone was regenerated from the enriched 2-pentanone semicarbazone by treatment with acid, and the 2-pentanone was further concentrated by gas chromatography using the analytical column. A sample of ~20 μg. of highly enriched 2-pentanone was obtained. The semicarbazone was prepared and subjected to fractional crystallization to the extent possible with the small amount of material present. The purest sample of the semicarbazone of 2-pentanone obtained had a m.p. of 108–109°, reported[9] m.p. 110°, mixed melting point with an authentic sample, 106–109°. (The melting point for the semicarbazone of 3-pentanone[9] is 139°).

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[5] The nature and source of these other components will be the subject of a forthcoming communication.

[6] We are indebted to the Wilkins Instrument and Research Co. for suggesting this column.

[7] Since the completion of the major part of this work, Dr. E. Smith, University of Arkansas, Graduate Institute of Technology, has found that a firebrick column coated with 0.5% adiponitrile gives excellent separation of 2- and 3-pentanone. We wish to thank Dr. Smith for this information and for his helpful discussions of the separation problem. Very recently we have found that 0.5% β,β'-oxydipropionitrile on firebrick gives even better results.

[8] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., J. Wiley and Sons, Inc., New York, 1956, p. 276.

[9] Ref. 7, p. 316.

Methylation Studies of the 2-Methylindole–Methyl Isobutyl Ketone Condensation Product[1]

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Condensation of 2-methylindole with methyl isobutyl ketone in ethanolic hydrochloric acid has recently been reported to give a monobasic 2:1 condensation product, isolated in dimorphic forms, m.p. 150–151° and 185–187°, in 11% yield.[2] The monobasic character and the ultraviolet spectrum of the condensation product indicate that both an indoline and an indole nucleus are present, and led to the suggestion of structure Ia, a product of a rather remarkable double bond shift, as a reasonable possibility.[2] We now wish to report methylation studies, analogous to those employed with the monobasic 2:2 cyclizative condensation product of 2-methylindole and acetone,[3] which confirm the presence of both a basic secondary nitrogen and a secondary nitrogen of the indole type in the molecule.

The preparation has been described[2] of an *N*-(in-

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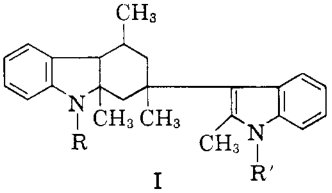
[2] W. E. Noland, M. R. Venkiteswaran, and R. A. Lovald, *J. Org. Chem.*, **26**, 4249 (1961).

[3] W. E. Noland, M. R. Venkiteswaran, and C. G. Richards, *J. Org. Chem.*, **26**, 4241 (1961).

doline)methyl derivative (Ib), m.p. 176–178° after crystallization,[4] in almost quantitative crude yield by action of dimethyl sulfate and potassium carbonate in acetone. By a similar methylation with methyl iodide we have now obtained in 92% crude yield an *N*-(indoline)methyl derivative (Ib), m.p. 260–262°,[4] having an identical infrared spectrum in Nujol. Slow recrystallization of the lower melting form produced the higher melting form, indicating that the two forms are dimorphs. Both forms were methylated on the indole nitrogen by action of sodamide and methyl iodide in liquid ammonia to the same *N,N'*-dimethyl derivative (Id), m.p. 163–164°,[4] in crude yields of 80–94%. Reversal of the methylation sequence by first methylating the monobase Ia with sodamide and methyl iodide in liquid ammonia gave in quantitative crude yield the *N*-(indole)methyl derivative (Ic), m.p. 143–144°,[4] different from the *N*-(indoline)methyl derivative (Ib). Methylation of the *N*-(indole)methyl derivative (Ic) with methyl iodide and potassium carbonate in acetone gave in 87% crude yield the *N,N'*-dimethyl derivative (Id), identical with that obtained by reversal of the sequence of methylation procedures.



I

Ia. R = H, R' = H
Ib. R = CH_3, R' = H
Ic. R = H, R' = CH_3
Id. R = CH_3, R' = CH_3

Both the *N*-(indoline)- and *N*-(indole)monomethyl derivatives (Ib, Ic) have an NH band in their infrared spectra; the *N,N'*-dimethyl derivative (Id) has no NH band. These observations are consistent with a structure such as Ia, suggested as a working hypothesis for the monobasic 2:1 condensation product of 2-methylindole and methyl isobutyl ketone.

Experimental

Melting points were determined on a calibrated Fisher-Johns hot stage.

***N*-(Indoline)methyl Derivative (Ib).**—Anhydrous potassium carbonate (10 g.) and methyl iodide (4.00 cc., 0.064 mole) were added to a solution of the monobase Ia (m.p. 183–185°, 1.00 g., 0.00290 mole) in dry acetone (75 cc.), and the mixture was refluxed for 20 hr. The acetone was evaporated at room temperature and the residue was treated with water (350 cc.). The insoluble residue was filtered, washed repeatedly with water, and dried, giving a white solid (0.955 g., 0.00266 mole, 92%), m.p. 239–242°, having an infrared spectrum in Nujol essentially identical with that of the analytical sample. Three crystallizations from 5:1 95% ethanol–benzene to constant melting point yielded colorless needles (0.306 g., 29%), m.p. 260–262°; λ_{max} mμ (log ε) in 95% C_2H_5OH: 223 (4.64), 265 (4.24), 282 infl. (3.95), 290 (3.89), 313 (3.53); ν_{NH} 3340 m, $\nu_{C=C}$ 1598 m cm.$^{-1}$ in Nujol. The infrared spectrum in Nujol was identical with the sample of the *N*-(indoline)methyl derivative, m.p. 176–178°, described previously.[2]

Anal. Calcd. for $C_{25}H_{30}N_2$ (358.51): C, 83.75; H, 8.43; N, 7.81. Found: C, 83.49; H, 8.34; N, 7.80.

A sample of the lower melting form, m.p. 175–180°, obtained in 98% crude yield from the dimethyl sulfate methylation procedure,[2] was allowed to crystallize slowly from a concentrated solution in 95% ethanol, giving as a first crop (46%) a sample, m.p. 254–256°. Repetition of the crystallization procedure gave a sample, m.p. 255–256°. A mixed melting point with the sample of m.p. 260–262° from the methyl iodide methylation procedure described above was undepressed, 259–260°. The infrared spectra of all four samples in Nujol were identical.

***N*-(Indole)methyl Derivative (Ic).**—A solution of the monobase Ia (m.p. 183–185°, 0.516 g., 0.00150 mole) in dry tetrahydrofuran (50 cc.) was added, with stirring, to a solution of sodamide (from sodium, 0.69 g., 0.030 g.-atom, with a crystal of ferric nitrate nonahydrate) in liquid ammonia (250 cc.) during a period of 5 min. Stirring was continued for 15 min. and then methyl iodide (2 cc., 0.032 mole), followed by more dry tetrahydrofuran (10 cc.), was added. The mixture was stirred for 2 hr. and then evaporated. Water (200 cc.) was added to the residue and the insoluble brownish solid was filtered and dried, giving a sample (0.550 g., 0.00153 mole, 102%), m.p. 139–143°, having an infrared spectrum in Nujol essentially identical with that of the analytical sample. Three crystallizations from 95% ethanol to constant melting point yielded colorless flakes (0.250 g., 46%), m.p. 143–144°; λ_{max} mμ (log ε) in 95% C_2H_5OH: 229 (4.64), 247 infl. (4.04), 286 (3.97), 293 (3.98); ν_{NH} 3330 mw, $\nu_{C=C}$ 1610 m cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{25}H_{30}N_2$ (358.51): C, 83.75; H, 8.43; N, 7.81. Found: C, 83.58; H, 8.37; N, 8.02.

***N,N'*-Dimethyl Derivative (Id). A. From the *N*-(Indoline)methyl Derivative, Lower Melting Form.**—A solution of the *N*-(indoline)methyl derivative (0.300 g., 0.00836 mole, crude, m.p. 159–162°, from methylation of the monobase Ia in dry acetone with dimethyl sulfate in the presence of anhydrous potassium carbonate,[2] but having an infrared spectrum in Nujol identical with that of the form, m.p. 260–262°) in dry tetrahydrofuran (70 cc.) was added gradually, with stirring, to a solution of sodamide (from sodium, 0.050 g., 0.0022 g.-atom, with a crystal of ferric nitrate nonahydrate) in liquid ammonia (250 cc.) within a period of 10 min. Stirring was continued for 10 min. and then methyl iodide (2.0 cc., 0.032 mole) was added dropwise, followed by more dry tetrahydrofuran (10 cc.). The mixture was stirred for 2 hr. and then evaporated at room temperature. The white solid residue (0.250 g., 0.00670 mole, 80%), m.p. 160–163°, was crystallized from 95% ethanol, yielding white needles (0.245 g., 79%), m.p. 162–164°, giving no depression in mixed melting point with the sample described in part B. The infrared spectrum in Nujol was identical with the corresponding spectra of the samples described in parts B and C.

B. From the *N*-(Indoline)methyl Derivative, Higher Melting Form.—The *N*-(indoline)methyl derivative (m.p. 260–262°, 0.230 g., 0.00641 mole) was methylated according to the procedure described in part A for the lower melting form. The white solid residue of product (0.224 g., 0.00601 mole, 94%), m.p. 160–162°, and the white needles (0.155 g., 65%), m.p. 163–164°, obtained from it by crystallization from 95% ethanol had identical infrared spectra in Nujol and gave no depression in mixed melting point with the sample described in part C.

C. From the *N*-(Indole)methyl Derivative.—Anhydrous potassium carbonate (5 g.) and methyl iodide (1 cc., 0.016 mole) were added to a solution of the *N*-(indole)methyl derivative (m.p. 143–144°, 0.100 g., 0.000279 mole) in dry acetone (30 cc.) and the mixture was refluxed for 22 hr.

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[4] The melting points given are those of the analytical samples.

The acetone was evaporated and the residue was treated with water (150 cc.). The insoluble crystalline residue was filtered, washed thoroughly with water, and dried, giving white crystals (0.090 g., 0.000242 mole, 87%), m.p. 162–164°, having an infrared spectrum in Nujol identical with that of the analytical sample. Two recrystallizations from 95% ethanol yielded white needles (0.073 g., 70%), m.p. 164°; λ_{max} mμ (log ϵ) in 95% C_2H_5OH: 226 (4.65), 264 (4.22), 285 (3.95), 293 (3.95), 315 infl. (3.54); ν_{NH} none, $\nu_{C=C}$ 1606 cm.$^{-1}$ in Nujol. The infrared spectrum in Nujol was identical with the corresponding spectra of the samples described in parts A and B.

Anal. Calcd. for $C_{26}H_{32}N_2$ (372.53): C, 83.82; H, 8.66; N, 7.52. Found: C, 83.75; H, 8.69; N, 7.73.

The Dinitration of *m*-Toluic Acid

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The nitration of *m*-toluic acid with a mixture of fuming nitric and sulfuric acids was recently carried out by Blatt.[2] He separated the reaction products and isolated approximately equal proportions of 2,6-dinitro-*m*-toluic acid and 4,6-dinitro-*m*-toluic acid.

We have nitrated *m*-toluic acid using Blatt's procedure and have analyzed the reaction products by differential infrared analysis after quantitative conversion to their methyl esters *via* diazomethane. The mixture was found to contain 53 ± 0.5% 2,6-dinitro-*m*-toluic acid, 43 ± 1% 4,6-dinitro-*m*-toluic acid, 2.5 ± 0.5% 2,4-dinitro-*m*-toluic acid, and 1.5 ± 0.5% of the isomeric 5,*x*-dinitro-*m*-toluic acids.

The samples of pure 2,4-, 2,6-, and 4,6-dinitro-*m*-toluic acids, which were used as analytical standards after conversion to their methyl esters, were prepared in the following manner. 4,6-Dinitro-*m*-toluic acid was prepared by the method of Errera and Maltese.[3] 2,4-Dinitro-*m*-toluic acid was prepared by diazotizing 2,4-dinitro-*m*-toluidine,[4] converting this to the nitrile, and then hydrolyzing to 2,4-dinitro-*m*-toluic acid. The same scheme was used to prepare the 2,6-dinitro-*m*-tolunitrile, but hydrolysis of this nitrile could not be carried beyond the amide. Attempts made to convert the amide to its acid involved common methods such as diazotization,[5] the use of potassium hydroxide,[6] 100% phosphoric acid,[7] or aqueous hydrochloric acid[8] at 230°.

We then decided to nitrate 2-nitro-*m*-toluic acid[9] in sulfuric acid solvent and then separate the 2,6-dinitro-*m*-toluic acid from the 2,4-dinitro isomer by a selective esterification technique.[10] We found that this nitration product contained 96.2 ± 0.5% 2,6-dinitro-*m*-toluic acid and 3.8 ± 0.5% 2,4-dinitro-*m*-toluic acid and that the former precipitated during the reaction in nearly pure form. Conversion of this acid to its corresponding amide gave a product which was identical with 2,6-dinitro-*m*-toluamide made by hydrolysis of the nitrile.

Physical properties of the heretofore unreported 2,4- and 2,6-dinitro-*m*-toluyl chlorides, amides, and nitriles are described in the Experimental.

Experimental[11]

Analytical Equipment.—The infrared analyses were obtained with a Beckman double-beam IR-7 prism-grating spectrophotometer. The samples were run 5% (weight per volume) in chloroform in 0.1-mm. cells. Samples were compared differentially against carefully prepared standard mixtures of the three isomers and, for additional accuracy, pen-expansion techniques were employed. The presence of the three isomers was unequivocally verified and the accuracy of the determinations checked by repeated sampling.

Nitration of *m*-Toluic Acid.—The method of Blatt[2] was repeated exactly.

2-Nitro-*m*-toluic Acid.—*m*-Toluic acid was nitrated by the procedure of Müller.[9] Filtration of the precipitate from nitric acid (*d* 1.5) and subsequent recrystallization from xylene gave the compound in 41.4% yield (m.p. 222.5–223.5°).

2,6-Dinitro-*m*-toluic Acid.—Nitrating acid was prepared by adding 23.2 g. (0.332 mole) of fuming nitric acid (*d* 1.5) to 200 ml. of concd. sulfuric acid. Forty grams (0.221 mole) of 2-nitro-*m*-toluic acid was quickly added to the nitrating mixture. During the addition the temperature of the reaction mixture rose from 36° to 52°, solution took place, and a new solid precipitated from the solution. After stirring an additional hour at 52°, the mixture was cooled to 20° and the solid filtered off. The latter was washed with sulfuric acid and then ice water. Yield of product melting at 178.5–179.5° was 30.2 g. (60.4%). Recrystallization from toluene gave 95% recovery of 2,6-dinitro-*m*-toluic acid melting at 178.7–179.5°. Blatt[2] reports 182–183°.

Anal. Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67; N, 12.40. Found: C, 42.52; H, 2.59; N, 12.37.

The filtrate from the nitration was diluted with ice water. This precipitated 11.6 g. (23.2%) of a second fraction which proved to be a mixture of 2,4, and 2,6-dinitro-*m*-toluic acids melting at 156–176°. A composite mixture of the two fractions was found to contain 96.2 ± 0.5% of 2,6-dinitro-*m*-toluic acid and 3.8 ± 0.5% 2,4-dinitro-*m*-toluic acid by infrared analysis.

2,6-Dinitro-*m*-toluyl chloride was prepared by refluxing 6.3 g. (0.0278 mole) of 2,6-dinitro-*m*-toluic acid in 30 ml. of thionyl chloride for 1 hr. After the excess thionyl chloride was removed by reduced pressure distillation, 6.8 g. (99.9%) the crude acid chloride soldified. A small portion was removed and recrystallized from a 3:1 hexane–toluene mixture. The purified product, obtained as long pale yellow needles, melted at 87.7–88.9°.

Anal. Calcd. for $C_8H_5ClN_2O_5$: C, 39.30; H, 2.06; Cl,

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(1) Present address: Department of Chemistry, Harvard University, Cambridge, Mass.

(2) A. H. Blatt, *J. Org. Chem.*, **25**, 2030 (1960).

(3) G. Errera and R. Maltese, *Gazz. chim. ital.*, **33**, II, 277 (1903).

(4) J. W. Cook and O. L. Brady, *J. Chem. Soc.*, **117**, 750 (1920).

(5) N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

(6) A. Claus and R. Wallbaum, *J. prakt. chem.*, **56**, 48 (1897).

(7) G. Berger and S. C. J. Olivier, *Rec. trav. chim.*, **46**, 600 (1927).

(8) A. Claus and C. Beysen, *Ann.*, **266**, 223 (1891).

(9) E. Müller, *Chem Ber.*, **42**, 423 (1909).

(10) V. Meyer and J. J. Sudborough, *Chem. Ber.*, **27**, 3146 (1894).

(11) All melting points are corrected values.