[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Fischer Indole Synthesis. V. 2-Carbethoxy-4,7-dimethylindole from Ethyl Pyruvate 2,6-Dimethylphenylhydrazone[1]

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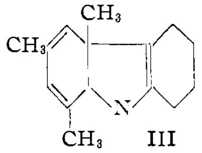
A group of new α-ketoester methyl-substituted phenylhydrazones have been prepared by the Japp–Klingemann reaction and converted by the Fischer reaction to the corresponding methyl-substituted 2-carbethoxyindoles. Among these, ethyl pyruvate 2,6-dimethylphenylhydrazone (I) has been shown to give 2-carbethoxy-4,7-dimethylindole (II) in low yield. Ethyl pyruvate mesitylhydrazone under similar conditions formed crude products that gave a positive Ehrlich test but yielded no pure product. The Japp–Klingemann procedure led to two apparently dimorphic modifications of ethyl pyruvate 2,5-dimethylphenylhydrazone. A mechanism for the conversion of I to II is offered that combines features of recently proposed mechanisms for (a) Fischer reactions of 2,6-dihalogenphenylhydrazones, (b) the *para* Claisen rearrangement and (c) the dienone–phenol rearrangement. Efforts to isolate a maleic anhydride adduct of a proposed dienonimine intermediate have been unsuccessful. No attempt is made to rationalize the formation of 2-carbethoxy-3,7-dimethylindole, the anomalous product of a single Fischer reaction of I.

Previous work has shown that 2,6-dichloro- and 2,6-dibromophenylhydrazones yield 5,7-dihalogenindoles, 7-monohalogenindoles or mixtures of both under various conditions that promote the Fischer indole transformation.[3] Investigation of the Fischer reactions of 2,6-disubstituted phenylhydrazones in which the substituents are of a different nature from halogen appeared to offer promise of affording new information about the mechanism of the reaction. The methyl substituent was selected for the first such investigation because of the contrasting character of the methyl group compared to halogen and because some fragmentary literature reports of Fischer reactions of *o*-methylphenylhydrazones required clarification. This report describes the preparation of some methyl-substituted phenylhydrazones of two α-ketoesters by the Japp–Klingemann reaction and the conversion of ethyl pyruvate 2,6-dimethylphenylhydrazone (I) to 4,7-dimethyl-2-carbethoxyindole (II).

Because the 2,6-dihalogenphenylhydrazones gave indoles in poor yield, it appeared unlikely that 2,6-dimethylphenylhydrazones would undergo clean-cut Fischer reactions; therefore, substantial amounts of 2,6-dimethylphenylhydrazine would probably be required to produce enough pure Fischer reaction products to permit characterization. Literature references to the preparations of 2,6-dimethylphenylhydrazine and of mesitylhydrazine[4] were not encouraging; yields of less than 30% and of 7.5%, respectively, were reported from the corresponding aromatic amines. While the investigation reported in this paper was being carried out, the work of Hunsberger and his associates that resulted in the improvement in the yield of mesitylhydrazine from mesidine by the standard method[5] and their development of the synthesis of monosubstituted hydrazines from sydnones[6] had not yet been published. Furthermore, neither 2,6-xylidine nor mesidine is so easily accessible that large amounts can be sacrificed justifiably in low-yield reactions. The best promise of preparing 2,6-dimethylphenylhydrazones or mesitylhydrazones in useful amounts therefore appeared to reside in the Japp–Klingemann reaction.[7] Accordingly, mesidine and carefully purified 2,6-xylidine were diazotized, and the diazonium salts were coupled in basic solution with ethyl α-methylacetoacetate; ethyl pyruvate mesityl- and 2,6-dimethylphenylhydrazones were isolated in 41 and 54% yields, respectively. These two arylhydrazones were then fused with zinc chloride.

$$\mathrm{ArN_2Cl + Na[CH_3COCH(CH_3)COOEt] \longrightarrow ArNHN{=}C(CH_3)COOEt + CH_3COOH + NaCl}$$

The mesitylhydrazone gave a black, forbidding tar from which a heavy, neutral oil could be isolated in less than 2% yield. The oil gave a positive test with the Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 85% phosphoric acid), indicating that an indole was present, but no pure substance could be isolated from it. The only other report known to us of a Fischer reaction of a mesitylhydrazone is that of Barnes, Pausacker and Badcock,[8] who isolated a picrate of a substance to which they assigned the structure III from a mixture obtained by treating cyclohexanone mesitylhydrazone with glacial acetic acid. The source of their sample of cyclohexanone phenylhydrazone was not disclosed, however, and the product was characterized only by elemental analysis of the product picrate.


III

Ethyl pyruvate 2,6-dimethylphenylhydrazone (I), on fusion with zinc chloride, gave also a dark, intractable tar from which a crystalline indole was eventually separated in less than 1% yield. Although the oils from which this crystalline indole were isolated gave positive Ehrlich tests, the pure indole itself did not. Failure of the Ehrlich test is

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[1] Taken chiefly from a thesis submitted by William O. Henley, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology.

[2] Institute Graduate Fellow, 1953–1954.

(3) (a) R. B. Carlin and E. E. Fisher, THIS JOURNAL, **70**, 3421 (1948); (b) R. B. Carlin, J. G. Wallace and E. E. Fisher, *ibid.*, **74**, 990 (1952); (c) R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).

(4) H. Frantzen, A. Onsager and G. Faerden, *J. prakt. Chem.*, [2] **97**, 336 (1918).

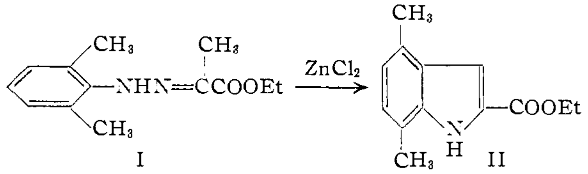
(5) I. M. Hunsberger, E. R. Shaw, J. Fugger, R. Ketcham and D. Lednicer, *J. Org. Chem.*, **21**, 394 (1956).

(6) J. Fugger, J. M. Tien and I. M. Hunsberger, THIS JOURNAL, **77**, 1843 (1955); J. M. Tien and I. M. Hunsberger, *ibid.*, **77**, 6604, 6696 (1955).

(7) F. R. Japp and F. Klingemann, *Ann.*, **247**, 208 (1888).

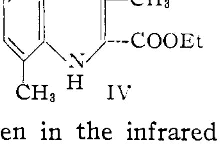
(8) C. S. Barnes, K. H. Pausacker and W. E. Badcock, *J. Chem. Soc.*, 730 (1951).

characteristic of 2-carbethoxyindoles.[9] The composition of the new indole corresponded to that of a dimethylcarbethoxyindole, although a monomethylcarbethoxyindole structure could not be excluded on the basis of the analytical data. The infrared spectrum showed bands at 2.92 and 3.02 μ, characteristic of N–H stretching; therefore, pseudoindole and isoindole structures having C=N linkages could be eliminated from consideration. For the same reason, an N-methylindole structure is excluded. Because migration of both methyl groups during the Fischer reaction seemed improbable, tentative assignment of one methyl group to the 7-position of the new indole could be made with some confidence, and the only apparent problem in the structure determination was then the position of the remaining methyl group. Accordingly, 3,7-, 4,7- and 5,7-dimethyl-2-carbethoxyindoles were synthesized from ethyl α-ketobutyrate *o*-tolylhydrazone and from ethyl pyruvate 2,4- and 2,5-dimethylphenylhydrazones, respectively; and, on the chance that the new indole was 7-methyl-2-carbethoxyindole, the latter was prepared by the Fischer transformation of ethyl pyruvate *o*-tolylhydrazone. The last named arylhydrazone was obtained directly from ethyl pyruvate and *o*-tolylhydrazine; the other three were prepared by Japp–Klingemann reactions between appropriately constituted diazotized aromatic amines and α-alkylacetoacetic esters. The indole from the Fischer reaction of ethyl pyruvate 2,6-dimethylphenylhydrazone proved to be identical by m.p., mixed m.p. and infrared spectral determinations with 4,7-dimethyl-2-carbethoxyindole (II). Therefore, II was the product of the Fischer reaction of I, and one of the methyl groups of I must accordingly have migrated to an adjoining ring carbon atom during the reaction. Thus, the *o*-methyl group of the 2,6-dimethylphenylhydrazone I in this instance behaves differently from *o*-halogen in the 2,6-dihalogenphenylhydrazones, which migrates to a position *meta* to its original location and leads to a 5,7-dihalogenindole.[3a,c]



I II

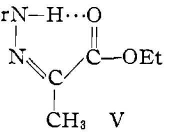
In one experiment, the Fischer reaction of I gave as its only crystalline product an indole that was not II but rather 3,7-dimethyl-2-carbethoxyindole (IV), identified with the synthetic specimen by m.p., mixed m.p. and infrared spectral determinations. Although the reaction was repeated several times, both in the presence and in the absence of diluents, no indications of the presence of the indole IV in any of the reaction mixtures could be detected again, even in the infrared spectra of the crude products. On the other hand, the crude material from which IV was crystallized gave an infrared spectrum that included, in addition to the bands characteristic of IV, some found only in the spectrum of II. Therefore, it is likely that some II accompanied IV in its reaction mixture, but no evidence could be found for the presence of IV in any of the other reaction mixtures, in which II was the sole indole isolated in pure form. We have no explanation to offer for the anomalous formation of IV in a single experiment.



IV

All of the crude products from Fischer reactions of I gave positive Ehrlich tests. Since neither II nor IV responds to this test, it is apparent that traces of one or more indoles other than those identified must have been present. These trace indoles may have been formed by hydrolysis and decarboxylation of II (or possibly IV); 4,7-dimethylindole gives a positive Ehrlich test. The test is positive in the case of 4,7-dimethylindole-2-carboxylic acid only when the test solution is warmed; therefore the trace indoles that give the Ehrlich test cannot consist entirely of this or analogous acids.

The Japp–Klingemann procedure for the preparation of ethyl pyruvate 2,5-dimethylphenylhydrazone led to two isomeric products, m. p.'s 61 and 91°, respectively. Mixtures melted between the two temperatures, and the infrared spectra of the two forms, measured in chloroform solutions, were effectively identical. Ethyl pyruvate 2,5-dimethylphenylhydrazone has been reported previously by Marion and Oldfield,[10] who observed the m. p. 90°, and by Plancher and Carravaggi,[11] who gave the m. p. 50° for the product that they said was "not quite pure." The identity of the infrared spectra of the two forms renders the possibility of geometrical isomerism unlikely: Ramirez and Kirby[12] isolated two forms of α-methoxypropiophenone 2,4-dinitrophenylhydrazone and observed that the infrared bands corresponding to their NH stretching vibrations, measured in chloroform solution, differed by 0.1 μ. They attributed the difference to geometrical isomerism, coupled with intramolecular hydrogen bonding in the case of the *syn* isomer. Ethyl pyruvate 2,5-dimethylphenylhydrazone in a *syn* modification also satisfies the structural requirements for intramolecular hydrogen bonding (V), so that the NH stretching vibrations of the geometrical isomers might also be expected to differ in this case. These considerations make it likely that the two forms are dimorphs and not structural or geometrical isomers.



V

Discussion

The only previous report of a Fischer reaction of a phenylhydrazone substituted in the 2- and 6-positions by methyl is that of Barnes, Pausacker and

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(9) J. D. Dutcher and A. Kjaer, THIS JOURNAL, **73**, 4140 (1951).

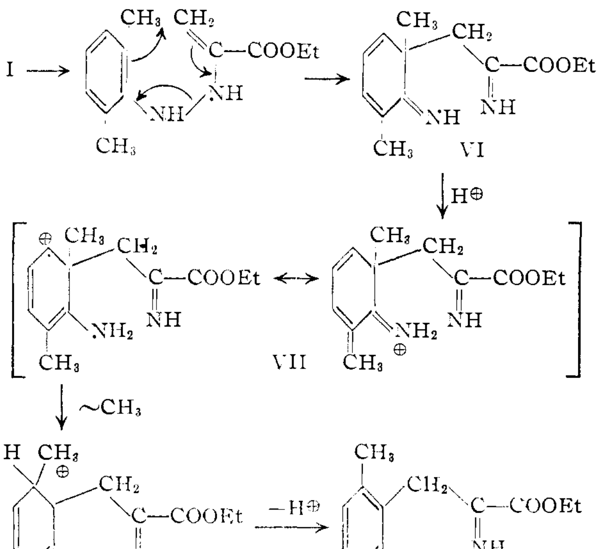
(10) L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947).

(11) G. Plancher and L. Carravaggi, *Atti Reale accad. Lincei*, [5], **14I**, 157 (1905).

(12) F. Ramirez and A. F. Kirby, THIS JOURNAL, **76**, 1057 (1954).

Schubert[8] (see above), who submitted no structure proof for their product. Huisgen[13] showed that cyclohexanone 1-methyl-2-naphthylhydrazone, when heated with nickel chloride in acetic acid solution, gave a 7% yield of the same tetrahydrobenzocarbazole that is formed from cyclohexanone β-naphthylhydrazone; the methyl group was eliminated in the course of the former reaction. Of course, the structural opportunity for the methyl group to migrate to an adjacent, unsubstituted ring carbon atom is not open to Huisgen's 1-methyl-2-naphthylhydrazone as it is to our 2,6-dimethylphenylhydrazone.

Any satisfactory mechanism for the Fischer reaction must be capable of giving an account both of the methyl migration that occurs when I is transformed into II and of the halogen migration or substitution that takes place when 2,6-dihalogenphenylhydrazones form 5,7-dihalogenindoles. A mechanism recently offered[3c] in explanation of the halogen migration or substitution involved a kind of high-energy intermediate similar in structural features to the one postulated in the *para* Claisen rearrangement and supported by substantial experimental evidence.[14] This mechanism now seems adequate to account also for the methyl migration observed in the present investigation. The intermediate VI or its conjugate acid VII are precisely analogous to the expression used to represent the intermediate in the formation of 5,7-dihalogenindoles from the 2,6-dihalogenphenylhydrazones.[3c] Further, the path from VI to VIII constitutes a dienonimine–aniline rearrangement, an exact analog of the simple dienone–phenol rearrangement for which a mechanism was first proposed by Arnold, Buckley and Richter.[15] Thus, the mechanism now suggested for the conversion I to II combines the essential features of certain current views on the mechanism of the Fischer reaction[3c] with some portions of presently accepted mechanisms of the *para* Claisen rearrangement and the dienone–phenol rearrangement.



The analogy of VI and the first intermediate in the *para* Claisen rearrangement suggested that VI, like its analog, might be "trapped" by maleic anhydride, with which it might form a Diels–Alder adduct similar to that isolated by Conroy and Firestone.[14] To that end, Compound I was heated with excess maleic anhydride and zinc chloride both in the presence and in the absence of solvent nitrobenzene. Small quantities of amorphous or semicrystalline materials having acidic properties were isolated after steam distillation of several of the reaction mixtures, but only one of these yielded a pure crystalline solid. This yellow solid, m.p. 110–111°, of which only 10 mg. was obtained in pure form by high vacuum sublimation, gave analytical values corresponding to the formula $C_{12}H_{14}N_2O_3$ and showed an ultraviolet spectrum with one maximum at about 245 mμ and another, much more intense, well above 320 mμ. A maleic anhydride adduct to VI or VII would have the formula $C_{17}H_{21}N_2O_5$ in the unlikely event that the nitrogen linkages could survive hydrolysis during steam distillation; furthermore, no normal adduct would be expected to yield an ultraviolet spectrum such as the one observed. Apparently, then, no substance corresponding to an addition product of maleic anhydride and VI or VII was isolated. Even if the assumption is made that no such adduct was actually formed, however, there is no proof that intermediates VI and VII do not play a part in the transformation of I to II. In this reaction the rate of conversion of VI and VII into the succeeding intermediates leading to II might very well swamp the rate of the diene reaction with maleic anhydride; indeed, the indole II was formed in these reactions that were carried out in the presence of excess maleic anhydride.

Experimental[16]

Aromatic Amines.—Mesidine hydrochloride was prepared in 95–97% yields by hydrogenation of nitromesitylene[17] in ethanol solution over either Adams catalyst or Raney nickel in a low-pressure apparatus. Following removal of the catalyst from the solution after reaction, the solution was saturated with hydrogen chloride gas and concentrated until hydrochloride precipitation was complete. All of the other methyl-substituted anilines were commercial products.

Ethyl α-methylacetoacetate and ethyl α-ethylacetoacetate were obtained in 71 and 61% yields by following the procedures given by Shirley[18] and by Conrad and Limpach,[19] respectively, with only minor variations. For example, the latter compound was purified by fractionation through a Widmer column, rather than by the original method.[19] Fractionation in both cases could be followed by making use of the colors that develop when the esters in ethanol solution are treated with 2.5% aqueous ferric chloride; ethyl acetoacetate gives a rich red color, and the α-alkyl derivatives produce a violet-blue.[20]

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(13) R. Huisgen, *Ann.*, **559**, 101 (1948).

(14) *Cf.* D. Y. Curtin and H. W. Johnson, THIS JOURNAL, **76**, 2276 (1954); **78**, 2611 (1956); H. Conroy and R. A. Firestone, *ibid.*, **75**, 2530 (1953); **78**, 2290 (1956).

(15) R. T. Arnold, J. S. Buckley and J. Richter, *ibid.*, **69**, 2322 (1947).

(16) Melting points are corrected.

(17) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 449.

(18) D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 158.

(19) H. Conrad and L. Limpach, *Ann.*, **192**, 155 (1878).

(20) E. H. Huntress and S. P. Mulliken, "The Systematic Identification of Organic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 256.

TABLE I

PREPARATION AND PROPERTIES OF SOME α-KETOESTER METHYL SUBSTITUTED PHENYLHYDRAZONES PREPARED BY THE JAPP-KLINGEMANN REACTION

Starting arylamine	α-Substituent on acetoacetic ester	Arylhydrazone Ar-NHN=C (R)COOEt Ar	R	Yield, %	Cryst. from[a]	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Mesidine	Methyl	Mesityl	CH_3	41	E	102–103	$C_{14}H_{20}N_2O_2$	67.71	67.81	8.12	7.95	11.28	11.38
2,6-Xylidine	Methyl	2,6-Xylyl	CH_3	54	M	61–62	$C_{13}H_{18}N_2O_2$	66.64	66.97	7.74	7.55	...	...
2,4-Xylidine	Methyl	2,4-Xylyl	CH_3	34	E	139–140	$C_{13}H_{18}N_2O_2$	66.64	66.64	7.74	7.49	11.96	12.13
2,5-Xylidine	Methyl	2,5-Xylyl	CH_3	26	E	61–62	$C_{13}H_{18}N_2O_2$	66.64	66.98	7.74	7.37	11.96	12.33
2,5-Xylidine	Methyl	2,5-Xylyl	CH_3	7	E	91–92[b]	$C_{13}H_{18}N_2O_2$	66.64	66.64	7.74	7.78	11.96	12.27
o-Toluidine	Ethyl	*o*-Tolyl	Et	29	P	112–113	$C_{13}H_{18}N_2O_2$	66.64	66.81	7.74	7.82	11.96	12.00

[a] E = ethanol, M = methanol, P = petroleum ether (b.p. 65–110°). [b] Reported[10] m.p. 90°.

Methylphenylhydrazones by the Japp–Klingemann Reaction.—In general, the procedures given by Hughes and his collaborators were taken as the model.[21] The aniline homolog (usually 0.15 mole) in 60 ml. of hydrochloric acid and 65 ml. of water (if the amine hydrochloride was used, 52 ml. of hydrochloric acid and 73 ml. of water were used for each 0.15 mole) was stirred vigorously and treated at −5 to 0° with a solution of 10.5 g. of sodium nitrite in 25 ml. of water. The nitrite was introduced through a tube extending nearly to the bottom of the reaction vessel. The diazonium solution was stored at −15 to −20° before use. A solution of the ester was prepared by dissolving 0.15 gram-atom of sodium in a solution of 0.15 mole of ethyl α-alkylacetoacetate in 150 ml. of absolute ethanol at room temperature. This solution was treated in quick succession with 51 ml. of 33% aqueous potassium hydroxide, 300 ml. of ice-water and then, with stirring, with the diazonium solution, which was filtered into the mixture through coarse filter paper. The mixtures were stirred for 15–30 minutes following addition of the diazonium solution; then solid products were collected by filtration, and liquid products were extracted into ether. The washed ether extracts were vacuum distilled, following removal of the ether, and the distillates solidified on cooling. Recrystallization afforded needles that varied in color from yellow to white, except in the case of the higher melting dimorphic modification of ethyl pyruvate 2,5-dimethylhydrazone, which formed yellow-orange platelets. Table I reports the appropriate data on the preparation of the α-ketoester methyl-substituted phenylhydrazones and on the properties of the latter.

Isomeric Modifications of Ethyl Pyruvate 2,5-Dimethylphenylhydrazone.—The reaction mixture contained a solid which was collected by filtration. After recrystallization from ethanol, the substance had the m.p. 91–92°. The filtrate from the crystalline product was extracted with ether, and the ether extracts, after washing and drying, gave a residue when the ether was removed that was vacuum distilled. The distillate crystallized after standing in a refrigerator; it had m.p. 61–62° after recrystallization from ethanol. Mixtures melted over the entire range 61–90°. Table I contains the analytical data. The infrared absorption bands were located as follows (in microns): 2.07w, 3.35m, 3.42m, 3.50s, 5.95i, 6.18m, 6.30i, 6.43i, 6.60m, 6.83m, 6.91s, 7.17s, 7.24m, 7.30m, 7.65i, 7.90i, 8.65i, 9.01i, 9.13s, 9.75m, 9.96m, 10.60w, 11.10s, 11.40w, 11.70w. The spectrum of the higher-melting isomer showed a shoulder at 5.85 and a very weak band at 5.50 that did not appear on that of the lower-melting form, but in view of the complete agreement of the remaining parts of the two spectra, these slight differences were considered insignificant.

2-Carbethoxy-7-methylindole.—An intimate mixture of 10 g. of ethyl pyruvate *o*-tolylhydrazone[10] and 13 g. of powdered anhydrous zinc chloride was heated until the melt temperature reached 150°, when a vigorous reaction began and copious quantities of white fumes were evolved. As this reaction started, two water-cooled Graham condensers were connected to the reaction vessel in series in reflux position. The reaction mixture boiled, and its temperature reached 220°. Heating of the mixture was stopped, and when the mixture had cooled and the evolution of fumes had ceased, the white solid material that had collected in the condensers was washed out with ether. Removal of most of the ether left a solid, which, after recrystallizations once from ether–petroleum ether, b.p. 65–110°, and twice from methanol, formed 200 mg. of white needles, m.p. 131°, as reported.[10] This compound gave a negative Ehrlich test. Because additional amounts of this indole were not required for comparison purposes, no effort was made to obtain additional amounts from the reaction mixture itself. The infrared absorption spectrum included the following bands: 2.91w, 3.01w, 3.30s, 3.38w, 5.80s, 5.90i, 7.20s, 7.28m, 7.56i, 7.62i, 7.96m, 8.00m, 8.16i, 8.34i, 8.44m, 8.62w, 9.00w, 9.12w, 9.78w, 12.10m, 12.81m.

2-Carbethoxy-5,7-dimethylindole.—An intimate mixture of 21 g. of ethyl pyruvate 2,4-dimethylphenylhydrazone and 31 g. of powdered anhydrous zinc chloride was heated until the melt temperature reached 110°, when the same kind of vigorous reaction described in the preceding paragraph occurred and the same procedures for controlling it were employed. The maximum temperature reached by the reaction mixture in this case was 160°. About 100 mg. of white crystalline solid was washed with ether from the Graham condensers. After one recrystallization from ether–petroleum ether (b.p. 65–110°) and two from absolute ethanol, the substance formed white needles, m.p. 139–140°, depressed 30° by admixture with the starting arylhydrazone of the same m.p. The reaction mixture, when subjected to the same separation procedure to be described presently in connection with the preparation of II from I, gave an additional 2.7 g. (15%) of product of the same m.p. It gave no Ehrlich test.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.20; H, 6.95; N, 6.66; infrared absorption bands as follows: 2.92w, 3.02w, 3.44w, 5.80w, 5.90i, 7.20s, 7.30m, 7.53i, 7.66m, 7.99i, 8.16i, 8.32i, 8.74w, 8.96w, 9.07w, 9.76m, 10.30s, 11.76i, 12.24w, 12.96w, 13.43i.

2-Carbethoxy-4,7-dimethylindole (II) from Ethyl Pyruvate 2,5-Dimethylphenylhydrazone.—A solution[10] of 5 g. of the hydrazone and 5 ml. of concentrated sulfuric acid in 55 ml. of absolute ethanol was boiled for 6 hr., then cooled and diluted with 100 ml. of water. The mixture was extracted with ether until the extracts were colorless. The dried (Drierite) ether solution was concentrated until crystals began to form. After refrigeration of the mixture, it was filtered, and the solid was recrystallized once from ether–petroleum ether (b.p. 65–110°) and twice from methanol, from which it formed 1.2 g. (25%) of white needles, m.p. 140–141°, reported[10] 142°. The Ehrlich test was negative. Infrared bands are as follows: 2.93w, 3.01w, 3.45w, 5.90i, 7.20s, 7.30w, 7.51m, 7.60w, 7.68m, 8.10i, 8.35i, 8.44i, 8.68w, 8.92w, 9.16w, 9.78w, 10.28w, 11.58w, 12.12m, 12.40m, 12.90w, 13.40m, 14.98w.

4,7-Dimethylindole-2-carboxylic Acid.—Two-hour saponification of 0.333 g. of II with 0.5 g. of potassium hydroxide in 0.5 ml. of water and 20 ml. of ethanol, followed by acidification with concentrated hydrochloric acid, extraction with ether and removal of the solvent gave about 150 mg. of an amorphous solid that gave a positive test when heated with Ehrlich reagent. A recrystallization from ethanol and a sublimation at 1 μ gave white crystalline material, m.p. 198°. Another vacuum sublimation failed to raise the m.p. In another similar experiment, in which sodium hydroxide was the base, a 46% yield of a product was obtained which had the m.p. 201–203°, after recrystallization from aqueous ethanol. The m.p. 208° has been re-

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(21) G. K. Hughes, F. Lions and E. Ritchie, *Proc. Royal Soc. N. S. Wales*, **72**, 209 (1939); *C. A.*, **33**, 6837 (1939), and preceding papers.

ported.[10] Re-esterification of about 100 mg. of this acid gave about 40 mg. of colorless needles, m.p. 140–141°, after recrystallization from *n*-heptane.

4,7-Dimethylindole.—When a solution of 0.2733 g. of 4,7-dimethylindole-2-carboxylic acid in 10 ml. of quinoline was treated with 0.1 g. of copper chromite catalyst and then heated to 160°, gas evolution began. The temperature was gradually raised to 215°, when no more gas bubbles were evolved. The cooled mixture was dissolved in ether, and the ether solution was extracted with dilute hydrochloric acid, with dilute aqueous sodium hydroxide and then with water. Ether was removed from the dried (sodium sulfate) solution, and the dark brown, solid residue gave 0.120 g. of light yellow needles, m.p. 88–92°, after sublimation at 105° (1 mm.). Recrystallization from ether–petroleum ether (b.p. 65–110°) gave colorless needles, m.p. 98–100°, reported[10] 102°.

2-Carbethoxy-3,7-dimethylindole.—A solution of 3 g. of ethyl α-ketobutyrate *o*-tolylhydrazone and 3 ml. of concentrated sulfuric acid in 30 ml. of absolute ethanol, when subjected to the same procedure used to prepare the 4,7-isomer, afforded 1.6 g. (59%) of a solid, m.p. 147–148°, after recrystallization from ethanol. It gave no Ehrlich test.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.77; H, 6.84; N, 6.65; infrared spectrum bands: 2.90w, 3.00w, 3.30s, 3.37w, 3.45s, 5.80m, 5.88i, 7.09w, 7.27w, 7.57i, 7.65m, 8.15i, 8.30s, 8.62w, 8.85w, 9.15w, 9.28w, 9.47w, 9.80w, 12.81m, 13.42.

Fusion of Ethyl Pyruvate Mesitylhydrazone with Zinc Chloride.—An intimate mixture of 33.5 g. of ethyl pyruvate mesitylhydrazone and 199 g. of powdered anhydrous zinc chloride was heated to 180°, when a vigorous reaction occurred, and copious fumes were evolved. A sample of the mixture at this point gave a positive Ehrlich test. The mixture was heated at 270° until evolution of fumes ceased (1 hr.); then the cooled mixture was digested with 2.5% hydrochloric acid. The mixture was extracted with portions of chloroform totaling 2.5 l., and the extracts were concentrated to 30 ml. and poured into 300 ml. of petroleum ether (b.p. 65–110°). The precipitated material was first extracted with petroleum ether (b.p. 65–110°) for 30 hr. in a Soxhlet apparatus, and the solvent was removed from the extract solution. Sublimation of the residual oil (2 ml.) at 135–140° (1 μ) gave a small quantity of pasty yellow material that could not be crystallized. Resublimation of the sublimate gave a few mg. of a yellowish oil that could not be crystallized from methanol, ethanol or petroleum ether. The solid remaining in the Soxhlet thimble following petroleum ether extraction was then extracted for 24 hr. with benzene, and the extract solution was allowed to trickle through a 24-cm. column of alumina. Elution of the alumina with methanol and removal of the solvent produced only a small amount of an oil that could not be crystallized and that gave no Ehrlich test. The benzene solution yielded about 1 ml. of an oil when the benzene was removed. Distillation at 80° (<1 μ) gave 0.5 ml. of a yellowish oil that gave a positive Ehrlich test. Treatment of an ether solution with picric acid in ether–methanol gave a deep red color, but no picrate could be crystallized.

The chloroform–petroleum ether filtrate yielded a residual oil when the solvents were removed. The oil was divided arbitrarily into three fractions by distillation at 90–120° (<1 μ). The first fraction (0.1133 g.) was boiled for 1 hr. in a solution of 0.5 g. of potassium hydroxide and 0.5 ml. of water in 7 ml. of ethanol, the solution was acidified with hydrochloric acid and the acid solution was extracted with ether. The residual oil from the evaporation of the ether was sublimed (<1 μ) to yield a grayish amorphous substance which, after recrystallization from petroleum ether (b.p. 65–110°), gave a solid of m.p. 165–169° in amounts too small to permit analysis or further processing.

Unsuccessful efforts were made to prepare a picrate and a picrolonate, respectively, from the second and third distillation fractions.

2-Carbethoxy-4,7-dimethylindole (II) from Pyruvic Acid 2,6-Dimethylphenylhydrazone (I) and the Isolation of 2-Carbethoxy-3,7-dimethylindole (IV) from One Such Reaction Mixture.—To make sure that the 2,6-xylidine from which the hydrazone I was prepared was free of homologs and isomers, it was formylated in accordance with the method of Busch[22] to 2,6-dimethylformanilide, m.p. 164°, as reported,[22] after recrystallization from ethanol. The formanilide derivative was saponified in ethanolic potassium hydroxide, and the product was distilled through a Widmer column, b.p. 88–90° (2 mm.), $n^{19}\mathrm{D}$ 1.5608, reported[23] $n^{20}\mathrm{D}$ 1.5610. This material was converted to the hydrazone I. The latter was freshly distilled, and a 30 to 36-g. sample was melted and poured onto an equal weight of powdered, anhydrous zinc chloride. Heating the mixture caused the reaction to occur in accordance with either one of two patterns; no control could be exerted over which pattern a particular mixture was to follow. In the first pattern, the melt temperature was increased to 170°, when the usual vigorous reaction occurred, as was manifest from the copious evolution of fumes and swift rise in temperature. Two Graham condensers were attached in series to the mixture at this point. The mixture boiled when its temperature reached 220°; then the temperature declined. The cooled mixture gave a positive Ehrlich test. The second reaction behavior pattern was characterized by the onset of fume evolution and a spontaneous temperature increase when the melt temperature reached 130°. In these cases, the mixture boiled at 160°, and then the internal temperature declined. Again, a sample gave a positive Ehrlich test.

Regardless of the reaction pattern, the tarry mixture was digested with 2.5% aqueous hydrochloric acid, and the acid solution was decanted from the resulting tar, which was allowed to stand for 4–8 hr. with 500 ml. of ether. The ether-insoluble, charcoal-like solid was extracted with ether for 24–48 hr. in a Soxhlet apparatus; two 500-ml. batches of ether were used in this extraction. The three 500-ml. ether extracts were then combined and concentrated to about 500 ml. This ether solution was extracted with five 100-ml. portions of 5% aqueous sodium hydroxide, with five 100-ml. portions of 5% aqueous hydrochloric acid and finally with five 100-ml. portions of water. Acidification of the basic extract produced a small quantity of amorphous material which did not give a positive test when warmed with the Ehrlich reagent, as a 2-carboxyindole should.[9] Removal of the solvent from the dried (Drierite) ether solution left an oil, which was distilled at a bath temperature of 80–110° (<1 μ). The distillate was dissolved in 1:3 ether–petroleum ether (b.p. 65–110°), and after refrigeration this solution deposited about 200 mg. of a crystalline solid from which short white needles, m.p. 139–140°, could be obtained by repeated recrystallizations from methanol. A mixture of this substance with an indole sample produced from ethyl pyruvate 2,5-dimethylphenylhydrazone (above) gave no m.p. depression, but a 20° m.p. depression was observed in the case of a mixture with 2-carbethoxy-7-methylindole (m.p. 131°), and a mixture with 2-carbethoxy-5,7-dimethylindole, m.p. 139–140°, showed a 30° depression.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.04; H, 6.62; N, 6.91.

Because of the scarcity of analytically pure material, the sample submitted for determination of the infrared spectrum was impure, m.p. 126–127°. Nevertheless, it gave all of the same bands found in the spectrum of authentic II (see above). Two bands not found in the latter spectrum were present in that of the 126–127° material: an intense one at 8.24 μ and a weak shoulder at 13.20 μ on the medium band at 13.40 μ. These may have been caused by the presence of some unchanged I, which was present in all of these reaction mixtures. In any case, the spectrum of the 126–127° material was quite different, especially in the 12–14 μ region, from those of the other indoles than II.

One (and only one) reaction mixture gave a high vacuum distillate from whose ether–petroleum ether solution an indole, m.p. 147–148°, alone or when mixed with authentic IV, was obtained after repeated recrystallizations from methanol and/or ethanol. The infrared spectrum of a pure specimen was indistinguishable from that of authentic IV. An infrared spectrum of some of the crude product, m.p. *ca.* 120°, however, showed some bands, notably at 7.18s, 8.10i and 12.40m, that are characteristic of the 4,7-isomer; therefore some of the latter may have been formed along with IV in this mixture. However, no indication of IV in the infrared spectra of crude products of any other mixture from this reaction was ever observed.

Refrigeration of the mother liquors from separation of II (or IV) caused the separation of long white needles which,

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(22) M. Busch, *Ber.*, **32**, 1012 (1899).

(23) "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, O., 1946, p. 1102.

after recrystallization from methanol, had the m.p. 61–62°, alone or when mixed with authentic hydrazone I.

Reaction of Ethyl Pyruvate 2,6-Dimethylphenylhydrazone (I) with Zinc Chloride in the Presence of Excess Maleic Anhydride.—A mixture of 38 g. of freshly distilled I, 57 g. of powdered anhydrous zinc chloride, 240 g. of maleic anhydride and 400 ml. of nitrobenzene was beaten with a Hershberg stirrer while it was heated at 135° for 0.5 hr. Steam distillation of the reaction mixture removed the nitrobenzene and left 22 g. of a black, water-insoluble residue which was extracted with ether in a Soxhlet apparatus until only 4.9 g. of black, ether-insoluble material remained. The ether extract was shaken with 180 ml. of 10% aqueous sodium hydroxide, and when the alkaline solution was acidified, 3.29 g. of a tan, amorphous powder separated. Sublimation of this powder at 140° (1 μ) produced about 50 mg. of a pale yellow solid. A solution of this material in ether–petroleum ether deposited 10 mg. of a yellow, crystalline solid, m.p. 110–111°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.14; H, 6.02; N, 12.32.

Following the extraction with sodium hydroxide, the ether solution was shaken with 180 ml. of 10% aqueous hydrochloric acid and then with water. The dried (Drierite) ether solution yielded 4.5 g. of a brown powder when the ether was removed. Sublimation of this powder at 110–120° (10 μ) gave 2.2 g. of a solid, m.p. 119–131°. Recrystallization from *n*-heptane following charcoal treatment afforded 1.25 g. of pale yellow crystals, m.p. 130–135°. Saponification of this sample of II with sodium hydroxide in accordance with directions previously described gave a sample of the corresponding carboxylic acid, m.p. 198–200°. Re-esterification with ethanol containing sulfuric acid yielded a new sample of II, m.p. 136–137°. The infrared absorption spectrum showed the sample of m.p. 130–135° to be II, with very little contamination.

Infrared absorption spectra were measured by means of a Perkin–Elmer infrared spectrophotometer model 21, equipped with sodium chloride optics. The spectra of the isomeric samples of ethylpyruvate 2,5-dimethylphenylhydrazones were measured in 3% solutions in chloroform; all others were measured in 2% solutions in carbon disulfide. The legend used throughout this section: i = intense (>70% absorption), m = medium (40–70% absorption), w = weak (<40% absorption), s = shoulder (band not resolved).

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PITTSBURGH 13, PENNSYLVANIA

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Condensation of Bisurethans and the Formation of New Polymers

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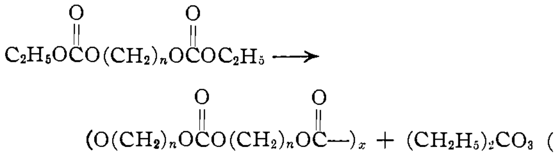
Bisurethans of the type $C_2H_5O\overset{O}{\overset{\|}{C}}—\overset{H}{N}—(CH_2)_n—\overset{H}{N}—\overset{O}{\overset{\|}{C}}OC_2H_5$ condense with themselves at elevated temperatures in the presence of an alkaline catalyst to yield polymers possessing urea units and dimerized and trimerized isocyanate units. When $n = 3$, trimethyleneurea is formed, along with the polymer. Structures have been assigned to these condensation products.

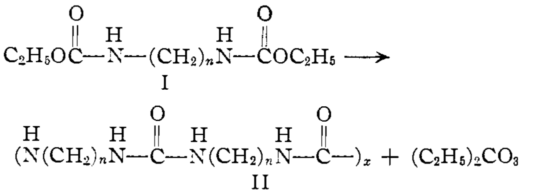
The condensations of bisurethans with bifunctional compounds, such as glycols, dimercaptans and amino-alcohols, have been the subject matter of numerous patents.[1] However, a study of the self-condensation of bisurethans had not been reported until after the present work was completed.[2] Since an extended study of the condensation of biscarbonates has been made in these Laboratories,[3] it seemed of value to investigate the analogous bisurethans.

The biscarbonates have been shown to condense to yield polycarbonates, with the elimination of diethyl carbonate, according to the reaction



$$C_2H_5O\overset{O}{\overset{\|}{C}}O(CH_2)_nO\overset{O}{\overset{\|}{C}}OC_2H_5 \longrightarrow (O(CH_2)_nO\overset{O}{\overset{\|}{C}}O(CH_2)_nO\overset{O}{\overset{\|}{C}}—)_x + (CH_2H_5)_2CO_3 \quad (1)$$

Therefore, one might expect the bisurethans to yield polyureas as



$$\underset{\text{I}}{C_2H_5O\overset{O}{\overset{\|}{C}}—\overset{H}{N}—(CH_2)_n\overset{H}{N}—\overset{O}{\overset{\|}{C}}OC_2H_5} \longrightarrow \underset{\text{II}}{(\overset{H}{N}(CH_2)_n\overset{H}{N}—\overset{O}{\overset{\|}{C}}—\overset{H}{N}(CH_2)_n\overset{H}{N}—\overset{O}{\overset{\|}{C}}—)_x} + (C_2H_5)_2CO_3 \quad (2)$$

Indeed, this does take place, but it is accompanied by a more predominant reaction. The purpose of this paper is to discuss the results of a study where compounds of type (I), where n = 2, 3, 4, 6 and 10, were condensed with themselves at elevated temperatures in the presence of alkaline catalysts.

Experimental

Bisurethans.—The bisurethans (N,N′-bis-carbethoxy-1,*n*-diamines) were prepared by the reaction of the appropriate diamine with ethyl chlorocarbonate in the presence of sodium hydroxide. One mole of the diamine in 250 ml. of water was added to 250 ml. of benzene. A solution of 2 moles of sodium hydroxide in 300 ml. of water was cooled to 10°. The diamine was allowed to react stepwise with 2 moles of ethyl chlorocarbonate as follows: The amine solution was stirred and kept at 10° by external cooling while one mole of ethyl chlorocarbonate was added slowly with stirring. Then 1 mole, *i.e.*, one-half of the sodium hydroxide solution, was added. Next, one-half mole of ethyl chlorocarbonate was added slowly, followed by one-half mole of sodium hydroxide. This stepwise process was continued until all of the reagents had been added. The reaction mixture was stirred for an additional hour. The white crystalline product was separated and recrystallized from ethanol. The products are listed in Table I.

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(1) U. S. Patents 2,343,808, P. Schlack, March 7, 1944; 2,568,885, H. Dreyfus, Sept. 25, 1951; 2,623,867, H. Dreyfus, Dec. 30, 1952. British Patent 620,116, H. Dreyfus, Nov. 21, 1949. Belgium Patent 449,106, Zellwolle- und Kunstseide Ring G.m.b.H., Mar., 1943; 449,368, Thüringer Zellwolle A.B., Mar., 1943.

(2) E. Dyer and H. Scott, THIS JOURNAL, **79**, 672 (1957).

(3) Williams, D. D. Reynolds, Dunham and Tinker, *J. Org. Chem.*, in press.