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

Condensations by Sodium. XXXI. The Effect of Salts and Other Substances on the Alkylation of Toluene, a Modified Wurtz Reaction[1]

BY AVERY A. MORTON AND ARMAND E. BRACHMAN

The reaction of amyl chloride with sodium at 20° gives decane and disproportionation products. If carried out in toluene as a solvent, the sodium shifts to toluene and the decane is largely replaced by *n*-hexylbenzene. The intermediate organosodium reagents, amylsodium and benzylsodium, are insoluble in the medium. Other insoluble salts which may be added to the reaction mixture usually increase the yield of *n*-hexylbenzene and affect also the yields of other products. Of the metal halide salts, cesium chloride is more effective than the others. Of the alkoxide salts, the secondary ones have greater influence than the primary or tertiary and the potassium alkoxide more than the sodium. By proper choice the yield of *n*-hexylbenzene can be more than doubled. An explanation is suggested which accords with the insoluble character of the reagent.

In earlier papers the polymerization of butadiene by allylsodium was found to be influenced remarkably by the presence of sodium isopropoxide[2] and sodium chloride.[3] The velocity was increased enormously while the intrinsic viscosity, surprisingly enough, was also increased; and the proportion of 1,4-addition resembled the emulsion or free radical process rather than the usual sodium type. These extraordinary changes in both degree and kind have led to the present study of the effect of supposedly inert salts on a Wurtz reaction, specifically, amyl chloride with sodium which goes by way of amylsodium[4,5] according to equations (1) and (2).

$$C_5H_{11}Cl + 2Na \longrightarrow C_5H_{11}Na + NaCl \quad (1)$$

$$C_5H_{11}Na + C_5H_{11}Cl \longrightarrow C_5H_{11}\text{-}C_5H_{11} + NaCl \quad (2)$$

As in all reactions of this type, this coupling was low, around 29% decane, the remaining part disproportionating to pentane and pentene. To promote coupling toluene was used as the solvent so that midway the sodium switched from amyl to benzyl (equation 3) and the process terminated on *n*-hexylbenzene[6,7]

$$C_5H_{11}Na + C_6H_5CH_3 \longrightarrow C_5H_{12} + C_6H_5CH_2Na \quad (3)$$

$$C_6H_5CH_2Na + C_5H_{11}Cl \longrightarrow C_6H_5CH_2\text{-}C_5H_{11} + NaCl \quad (4)$$

Therefore the principal process was a rapid cascade[8] of three reactions for the alkylation of toluene, a minor part fell through two levels to decane and a considerable diversion to disproportionation took place. The sodium reagents through which all processes were channeled[4,5] were solids, insoluble in the medium. The object of the work was to see how other solids or substances with which the sodium reagents could be mixed, might influence these courses.

This highly exothermic reaction was kept in bounds at 20° by dropwise addition of amyl chloride aided by a cold bath. All solids—the commercial halides, the salts made from alkali metal with alcohols, phenol and benzoic acid, and some non-ionic substances—were added before the sodium sand was made. Triethylamine, when used, was added just before the amyl chloride. A considerable excess of sodium metal over that needed for a completed Wurtz process—as calculated from equations (1) and (2)—ensured the rapid consumption of amyl chloride but also permitted termination of some of the reaction at the midway points, the organosodium intermediates, which were determined after subsequent carbonation to the corresponding acids. Hence four products were sought: decane and *n*-hexylbenzene, which measured two completed Wurtz couplings, and caproic and phenylacetic acids which represented the two organosodium intermediates. No other products were formed except from disproportionation, the amount of which was determined by difference. The sum of the two acids could not exceed 50% based on the amyl chloride and this quantity could only be realized if the incoming amyl chloride reacted exclusively with sodium metal, as in equation (1), until the metal was consumed and then reacted with the organosodium intermediates, as in equations (2) and (4). In two cases the yield reached 44% which is perhaps not surprising since the same technique was used as for good preparations of amylsodium[4,8] itself except that the temperature was 20° instead of −10°. But nearly all salts, and secondary alkoxides particularly, lowered the amount, in one case to 3%, which means that the amyl chloride then preferred to react with whatever organosodium compounds were present before it reacted with the metal. Similarly the sum of phenylacetic acid and *n*-hexylbenzene represented the switch of sodium from amyl to benzyl and this amount varied from 41 to 82%. *n*-Hexylbenzene, the principal product, ranged from 30 to 76%, a quantity more than doubled because of the facility[6,9] with which benzylsodium yields coupling products. The reproducibility in yields of *n*-hexylbenzene was better than for any other product, partly because it was probably the sole product from benzylsodium and partly because it was the end product of a cascading series. By contrast amylsodium gave two alternative hydrocarbon products, decane and the pentene–pentane pair, besides the change to benzylsodium which was usually favored because toluene was present in such abundance.

The specific influence of the salts is given in two tables. The first shows the effect in the absence of toluene, as represented by equations (1) and (2).

(1) The authors are greatly indebted to the Office of Rubber Reserve, Reconstruction Finance Corporation, for financial assistance of part of this work.

(2) Morton, Magat and Letsinger, THIS JOURNAL, **69**, 950 (1947).

(3) Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950).

(4) Morton, Davidson and Newey, THIS JOURNAL, **64**, 2240 (1942).

(5) Morton, Davidson and Hakan, *ibid.*, **64**, 2242 (1942).

(6) Morton and Fallwell, *ibid.*, **60**, 1429 (1938).

(7) Morton, Little and Strong, *ibid.*, **56**, 1339 (1943).

(8) Morton and co-workers, *ibid.*, **72**, 3785 (1950).

(9) Morton, Massengale and Gibb, *ibid.*, **63**, 324 (1941).

The two alkoxides decreased the yield of decane and amylsodium which means that they induced disproportionation in the Wurtz reaction. The potassium salt was more active than the sodium one.

TABLE I

EFFECT OF SALTS ON THE WURTZ REACTION IN PENTANE

Expt. no.	Added salt	Decane, %	Amyl sod., %	Total, %	Res.,[a] g.
1	None	29	44	73	1.4
2	$NaOC_3H_7$-iso	14	41	55	0.9
3	KOC_3H_7-iso	9	37	46	0.8

[a] Res. refers to the residue left after fractionation.

Table II gives the results obtained in toluene which comprised the bulk of the work. The arrangement is in the order of increasing yields of *n*-hexylbenzene (Column 3). For the first experiment listed (which is number 4 in the series) the yield was low because the medium was a 1:1 mole mixture of cumene with toluene and opportunity for the sodium shift was cut nearly in half. In all others toluene was the medium. From experiments 5 to 20, inclusive, the yields were only slightly different, if at all, from the four controls (7, 9, 10 and 12). That the alkali metal halides caused little effect can be attributed to their coarsely granular state as compared to the colloidal sodium chloride formed *in situ* by the reactions with amyl chloride. However, the cesium halides (No. 21 and 22) showed an activity definitely above the level of the four controls and the rest of that group. Beginning with Experiment 23 the sodium alkoxides as a class ranged higher. The secondary alkoxides in particular were effective in the order of 2-pentoxide > 2-octoxide > isopropoxide. As the quantity of sodium 2-pentoxide progressively increased in No. 34, 36, 38, 41 and 39 (0.17, 0.25, 0.38, 0.50 and 0.63, respectively, and No. 34 is included in this group because the *t*-pentoxide, also present, exerts only a comparatively small influence, as judged from No. 26) the yield of *n*-hexylbenzene increased to a maximum at No. 41 where a 1:1 ratio of sodium alkoxide to amyl chloride was used. Sodium *s*-octoxide did not cause a higher yield than the corresponding 2-pentoxide in spite of (or possibly because of) the fact that this salt was a little soluble in the toluene, but much difficulty was sometimes experienced in its use, notably in experiment No. 23, because of the tendency of the sodium sand to clump together and to thickening in general. The potassium salts appear largely from Experiments 35 onward. In all comparisons except for the benzoates, the potassium salts caused a higher yield than the corresponding sodium ones, amounting to 25% with the isopropoxides (No. 45 *vs.* 31) and 24% with the phenoxides (No. 35 *vs.* 8). In the single exception of the benzoate (No. 25 and 29) the difference was only 2%. The highest yield induced by any single alkoxide salt was by potassium isopropoxide in No. 45. Apparently the cation wielded a powerful influence in these reactions, since with these alkoxides potassium was more effective than sodium and with the halides the cesium salts surpassed the others.

Special attention can be directed to a few other matters of interest. The phenoxide ion (No. 8 and 35) virtually stopped the formation of decane but accelerated disproportionation. The *s*-octoxides in the experiments (No. 37 and 44), where least trouble with the physical condition of the alkoxide formation was experienced, reduced disproportionation to a low of 5 or 6%. Sodium fluoride in No. 5 seemed to suppress coupling in general and left the yield of total organosodium reagents the highest recorded in Table II. Triethylamine, a coördinating agent for cations, also increased the yield significantly.

While the work was not carried out to perfect a preparative method and while the proportions of reagents were not adjusted to permit that end (excess sodium was used), the results are none the less of real interest for synthesis. The best results hitherto obtained[6,7] at 75° in the absence of any alkoxide and with theoretical quantities of reagents was 61%. We have repeated this experiment at 75°, but in the presence of sodium isopropoxide, and obtained a yield of 74%. In the experiments at 20° (Expt. No. 46), however, the yield reached 76%, in spite of the fact that 6% of organosodium intermediate remained because excess sodium had been used.

The relationship between the increase in yields of *n*-hexylbenzene and the decreased yields in other products does not stand out clearly because of the diversity of reactions of amylsodium, as discussed before. The variations are eliminated by averaging all results in Table II (except for Expt. No. 4) roughly by quarters, as indicated by the four dividing lines. The averages, presented in Table III, show that the increase in hexylbenzene was accompanied by progressive changes in most other products, and suggest that this increase can be attributed to an improved conversion of amylsodium to benzylsodium because the total coupling increased nearly the same as the total sodium shift, as seen in line 5 (shift minus coupling) of the table. Earlier work[10] also has indicated that sodium isopropoxide aids the metalation of olefins. Disproportionation was the only process that showed no changes parallel to hexylbenzene. Actually a maximum was present in the third quarter and a minimum in the fourth. A maximum is perhaps not surprising because the alkoxides promoted disproportionation (Table I) as well as metalation. Not until the potassium salts and the best of the sodium salts were used did the preference for metalation show and a significant reduction in disproportionation appear. The amylsodium generally lagged behind the benzylsodium by approximately the same amount, 6 to 9%, in all quarters, which suggests that the ratio of reactivity of the two intermediates was not affected greatly by the added salts and that the main effect has been in the character of the reactions which the amylsodium underwent.

All these changes were induced by salts which are generally insoluble, nevertheless the effects are reproducible, particularly on the *n*-hexylbenzene. Part of their effect may be attributed to a dispersion of the sodium reagents over a larger surface

(10) Morton and Holden, THIS JOURNAL, **69**, 1675 (1947).

TABLE II

EFFECT OF SALTS AND OTHER MATERIALS ON THE ALKYLATION OF TOLUENE BY AMYL CHLORIDE[a] AND SODIUM

Expt. no.	Added material[b]	*n*-Hexylbenzene, %	Decane, %	Total coupling, %	Benzyl sod., %	Amyl sod., %	Total RNa, %	Total Na shift, %	Total products, %	Residue, g.
4[c]	None	16	25	41	18	14	32	34	73	2
5	NaF	30	11	41	33	11	44	63	85	2
6	C(Darco)	30	22	52	17	14	31	47	83	2
7	None	31	24	55	17	14	31	48	86	2
8	$NaOC_6H_5$	32	..	32	26	1	27	58	59	1
9	None	33	29	62	8	10	18	41	80	2
10	None	33	26	59	15	13	28	48	87	1
11	Cu(bronze)	33	7	40	23	13	36	56	76	1
12	None	34	18	52	18	14	32	52	84	2
13	NaI	34	11	45	25	10	35	59	80	3
14	KSCN	35	20	55	6	1	7	41	62	2
15	KBr[d]	35	12	47	22	11	33	51	80	2
16	NaCl	35	22	57	24	9	33	59	90	2
17	KBr	35	18	53	13	10	23	48	76	3
18	C(Spheron)	36	7	43	23	15	38	59	81	2
19	NaBr	36	17	53	17	13	30	53	83	2
20	KCl	37	14	51	17	11	28	54	79	3
21	CsBr	40	13	53	16	14	30	56	83	2
22	CsCl	42	19	61	19	13	32	61	93	2
23	$NaOC_8H_{17}$-*s*[e]	43	3	46	3	0	3	46	49	
24	$NaOC_3H_5$[f]	44	3	47	12	3	15	56	62	1
25	$C_6H_5CO_2K$	44	6	50	15	13	28	59	78	3
26	$NaOC_5H_{11}$-*t*	44	1	45	19	5	24	63	69	1
27	$NaOC_3H_7$-*n*	45	10	55	27	5	32	72	82	2
28	$NaOC_5H_{11}$-*n*	46	18	64	14	6	20	60	84	2
29	$C_6H_5CO_2Na$	46	1	52	6		1	52	83	3
30	AgI	47	21	68	10	4	14	57	82	3
31	$NaOC_3H_7$-iso	48	27	55	14	6	20	62	75	2
32	$N(C_2H_5)_3$	51	4	55	28	2	30	79	85	1
33	KOC_3H_7-*n*	51	15	66	3	5	8	54	74	2
34	$NaOC_5H_{11}$-*s*[g]	51	2	53	4	1	5	55	58	1
	$NaOC_5H_{11}$-*t*									
35	KOC_6H_5	54	4	58	9	1	10	63	68	1
36	$NaOC_5H_{11}$-s[h]	54	7	61	14	8	22	68	83	3
37	$NaOC_8H_{17}$-s[e]	55	7	62	33	0	33	88	95	2
38	$NaOC_5H_{11}$-*s*[i]	57	3	60	16	4	20	73	80	2
39	$NaOC_5H_{11}$-*s*[j]	58	4	62	8	2	10	66	72	2
40	KOC_5H_{11}-*n*[k]	65	10	75						
41	$NaOC_5H_{11}$-*s*	66	4	70	7	1	8	73	78	2
42	$NaOC_5H_{11}$-*s*	70	4	74	3	1	4	73	78	1
	$N(C_2H_5)_3$[l]									
43	KOC_5H_{11}-*s*	72	3	75	4	1	5	76	79	
44	KOC_8H_{17}-*s*	72	13	85	8	1	9	80	94	2
45	KOC_3H_7-iso	73	2	75	8	1	9	81	84	1
46	KOC_3H_7-iso	76	0	76	6	0	6	82	82	1
	$N(C_2H_5)_7$[l]									

[a] The yields are calculated on the amyl chloride, all of which was consumed in each reaction. The high-boiling residues, listed in the last column, were combined and refractionated. They proved to be almost entirely *n*-hexylbenzene. [b] One-half mole of the salt or other material was used in all cases unless otherwise specified. [c] The medium was a 1:1 mole mixture of cumene and toluene. [d] One mole of the salt was used. [e] The sodium *s*-octoxide was difficult to obtain free from large clumps. Hence physical factors in these two reactions were difficult to regulate and duplicate runs gave varying results. In No. 23, the condition was particularly bad. [f] C_3H_5 means $CH_2CH{=}CH_2$. [g] The quantities of the two salts in this experiment were 0.13 and 0.37 mole, respectively. [h] One-fourth mole of salt was used. [i] The quantity of salt was 0.383 mole. [j] The quantity of this salt was 0.633 mole. [k] Analysis was made only of the hydrocarbons. [l] Triethylamine, 0.5 mole, was used in addition to the 0.5 mole of salt present.

so that they were more available for reaction. But this view does not explain why the reactions were affected unequally as witnessed in Table I where disproportionation increased at the expense of coupling. Furthermore, copper bronze and two grades of carbon showed only a small amount of influence. Also, in previous work, the idea of mere increase in surface has been inadequate to explain the uniqueness of Alfin polymerization[2,3] (mentioned at the beginning of this paper) and par-

TABLE III

REACTION TRENDS AS INDICATED BY AVERAGING THE YIELDS FOR EACH QUARTER OF THE EXPERIMENTS FROM NO. 5 TO 44, INCLUSIVE

Product	Average yield in quarter No. 1, %	2, %	3, %	4, %
n-Hexylbenzene	33	39	49	66
Decane	18	11	11	5
Total coupling	49	50	59	71
Total sodium shift	52	56	62	77
Shift minus coupling	3	6	3	6
Benzylsodium	18	16	13	10
Amylsodium	11	10	4	1
Benzyl less amyl	7	6	9	9
Total sodium compounds	29	25	16	12
Total products isolated	78	77	74	83
Disproportionation	22	23	26	17

ticularly does not explain why butenylsodium[11] shows the special Alfin catalytic activity when a definite amount of sodium isopropoxide is used but has the activity destroyed when more of the same surface is used and does not show why allylsodium[11] with sodium 1-phenylethoxide shows a similar effect as more surface is used.

The view taken in this work and which really inspired the study has been that the size and polarity of the ions of the salts have a specific influence. To understand this point it must be remembered that the reaction probably takes place on a solid surface rather than in a non-polar solvent,[12] because these sodium reagents are insoluble aggregates or clusters of ions. For instance, the change from amylsodium to benzylsodium is from one insoluble salt to another insoluble salt. Both reagents will settle from the medium and leave it water-white, free from any trace of alkaline material. While some slight solubility of a reacting complex may occasionally occur (such a condition has indeed been assumed[13] in the addition of amylsodium to 1,1-diphenylethylene) and may even be a factor when triethylamine is present, the supposition of chemical reactivity by a reagent which is completely insoluble is in full accord with well-known chemical phenomena. The absorption of carbon dioxide by soda lime, the taking up of water vapor by solid drying agents, the reaction of an alkyl halide with sodium metal, and the adsorption of gases on carbon are well-known examples of the reaction of solid materials. Adsorption of gases on carbon is a particularly interesting comparison because forces of great magnitude[14] comparable to enormous compressions (12,000 atmospheres) are exerted in chemisorption. The reaction surface of these organoalkali metal reagents can accordingly be considered as irregular porous checkerworks of positive and negative ions upon which chemisorption takes place as the initial phase of a reaction. This adsorption is probably centered on the cation because a positive pole could exert an attraction for the electrons of the adsorbed material and many coördination compounds about the sodium cation do exist,[15] even with comparatively inactive salts. In this way the electrons in the adsorbed compound would suffer some displacement and a new anion would begin to form as the old anion is released for whatever activity is needed to conclude the reaction.

For such a system the role of the added salts becomes clear. They form part of the checkerwork environment within or on which the sodium reagent functions, that is, they are the true medium for the reaction rather than the liquid in which the solid reagents are suspended. The cations offer preferred centers for chemisorption and because of their position, size, or comparative activity, make possible a variety of chemisorptions—often very specific—not possible in the reagent itself. In this manner both cation and anion contribute to the process and the control by proper choice of a salt environment can be critical.

Experiments

Apparatus and Reaction Technique.—All reactions were carried out in a 1-l., 3-necked special flask with the high-speed stirring apparatus,[16] as used regularly in this Laboratory. Sodium metal (17.3 g. or 0.75 mole) was put in 500 ml. (4.7 mole) of sulfur-free toluene in the dry flask in an atmosphere of nitrogen. The temperature was raised to 108° with an external electric heater, which was then removed while the contents were stirred at full speed for one minute. The flask was allowed to cool, without stirring, to room temperature. A cellosolve bath cooled with pieces of solid carbon dioxide served to maintain the temperature at 20° during the reaction with amyl chloride.

When the inorganic salts or other solid material were used the dry granular commercial solid was ground in a mortar with pestle to break up the coarse particles and was added to the flask prior to making the sodium sand. Cesium bromide was supplied by the Dow Chemical Company.

The phenoxides, benzoates and alkoxides were made by addition of the acid or alcohol to the metal. If the sodium salt was to be made, the excess sodium was made into sand with the rest of the metal. The acid or alcohols was then added dropwise to the finely divided metal at 0° at a rate of not more than 0.5 ml. per minute lest the metal agglomerate. When the reaction had subsided the toluene suspension was heated cautiously to 108° and the sand remade by stirring for two minutes. The reaction with the last bit of alcohol was sometimes difficult and, in the cases of *t*-butyl alcohol and *s*-octoxide, was exceedingly so. Several days were required for this step in Experiment No. 21. In Experiment No. 29, a mixture was used but the reaction was still very slow. The potassium salts were made from the metal and the acid or alcohol in a separate container and then added to the sodium sand before reaction with the alkyl chloride.

The Darco carbon was 325 mesh regularly used for decoloration of organic compounds. The Spheron-9 carbon was a grade of carbon black used in tires. It was obtained through the courtesy of the Cabot Company. The copper was a commercial copper bronze used with lacquers.

n-Amyl chloride (61.0 ml. or 0.5 mole) which had been collected[17] from 106–108° was added dropwise at the rate of

(11) Morton, Welcher, Collins, Penner and Coombs, THIS JOURNAL, **71**, 481 (1949).

(12) Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 203.

(13) Morton and Wohlers, THIS JOURNAL, **69**, 167 (1947).

(14) Lamb and Coolidge, *ibid.*, **42**, 1146 (1920); Harkins and Ewing, *ibid.*, **43**, 1787 (1921).

(15) As a partial list, see Sidgwick and Plant, *J. Chem. Soc.*, **127**, 209 (1925); Sidgwick and Brewer, *ibid.*, 2379 (1925); Brady and Badger, *ibid.*, 952 (1932); Evans and Smiles, *ibid.*, 727 (1937); Dvorkovitz and Smiles, *ibid.*, 2022 (1938); McClement and Smiles, *ibid.*, 1016 (1937); Heppenstall and Smiles, *ibid.*, 899 (1938); Crawford, *ibid.*, 239 (1941); Ross and Morrison, *ibid.*, 1016 (1933); Speakman, *Nature*, **162**, 695 (1948); Beevers and Cochran, *ibid.*, **157**, 872 (1946); *Proc. Roy. Soc. (London)*, **A190**, 257 (1947).

(16) Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

(17) Since this work was started the amyl chloride purified by this method has occasionally proven unsatisfactory. Filtration through a four foot column which contains calcium chloride, alumina and calcium sulfate (Drierite) in successive equal sections removes the sharp odor present and gives a very suitable reagent.

1 ml. per minute while the stirrer was rotated from 5000–7000 r.p.m. The agitation was continued for 45 minutes longer, after which the contents were forced, *via* a delivery tube under pressure of nitrogen, into a 4-l. erlenmeyer flask one-third full of solid carbon dioxide.

Subsequently the excess sodium was eliminated from this mass by addition of 75 ml. of 95% ethanol. Water (500 ml.) was then added. Care was taken during these operations lest tiny bits of metallic sodium were yet present. An atmosphere of carbon dioxide was maintained by addition of pieces of solid carbon dioxide. After all traces of metal was gone, the mixture was warmed on a steam-bath to break up solid particles. The two layers were separated in a funnel. The organic layer was dried over calcium sulfate and the hydrocarbons analyzed by fractionation and measurement of refractive index. On the small scale used and with the low yields obtained the joint use of the two methods is desirable. With large yields separations are easily made with a good column. No amyl chloride was ever present and the complete removal of the halogen was shown by analyses for sodium chloride as silver chloride in representative experiments.

The aqueous layer was acidified and the acids removed by ether extraction. The ether extract was shaken with ammonium hydroxide and the aqueous layer heated on a steam-bath to remove excess ammonia. An aliquot portion was titrated. Another portion was acidified with sulfuric acid and steam distilled. The two acids came over at different rates and could be determined by the semidistillation values which are 0.946 and 0.048, respectively, for caproic and phenylacetic.

The water layer left from the original acidification was found to contain no butylmalonic acid upon extraction with ethyl acetate.

Examination of the combined residues left after the fractionation of the hydrocarbon fractions from forty experiments, representing the reaction of 690 g. of sodium metal with 2130 g. of amyl chloride in 20 l. of toluene, showed very little material other than *n*-hexylbenzene. Chromatographic adsorption over alumina gave only slight amounts of tar. Fractional distillation yielded 28.6 g. of the hexylbenzene, 5.1 g. of two much smaller fractions and 9.4 g. of residue. The last yielded no easily isolable acid after alkaline permanganate oxidation. If any dimetalation had resulted during the process or any other effect had occurred which could lead to a high-boiling compound, the quantity was less than 1%.

Reaction in Pentane and Cumene–Toluene.—For the pentane experiments, the sodium sand was made in decane. When cooled, the decane was removed in the usual way under nitrogen pressure, and the sand was washed three times each with 150 ml. of pentane. The decane that should be left would be negligible, and any error made would be on the side of a higher yield of decane. All operations otherwise were the same.

For the experiments in the 50–50 mole mixture of cumene–toluene, the sand was made in the mixture. The cumene used in this work was dried over sodium and then fractionated. All other operations were the same as before.

Reactions at Higher Temperature.—The process was in general the same except for the higher temperature and, in one case, different amounts of reagents. At 65° with one-quarter mole each of sodium isopropoxide and sodium, the yield of *n*-hexylbenzene was 73.6%. A trace of decane was found. The phenylacetic acid was 0.9%; caproic acid was 0.1%.

At 75° with sodium 2-pentoxide in the quantities regularly used at 20°, the yield of *n*-hexylbenzene was 49.2%. Those of decane, caproic acid and phenylacetic acid were 3.1, 0.03 and 0.5%, respectively. The residue was 1.4 g. At 60° the respective quantities were 48.4, 3.4, 0.1 and 0.9% and 1.3 g.

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The Synthesis of Substituted Penicillins and Simpler Structural Analogs. II. α-Acylamino β-Lactam-thiazolidines[1]

BY JOHN C. SHEEHAN AND JAMES J. RYAN[2]

The synthesis of several compounds containing the penicillin ring system, including the fused β-lactam-thiazolidine structure with an α-amino function, has been achieved by a rational method. In the key step, phthaloylglycyl chloride and 2-phenyl-2-thiazoline interact in the presence of triethylamine under high dilution conditions to yield 2-phenyl-α-phthalimido-2-thiazolidineacetic acid β-lactam. The chemical and physical properties of these synthetic β-lactam-thiazolidines correspond closely to the behavior of the penicillins. Oxidation with permanganate produced a sulfone and hydrolysis followed by mercuric chloride led to a carbonyl fragment, carbon dioxide and presumably thioethanolamine. Selective alkaline hydrolysis attacked the phthalimide group in preference to the β-lactam ring, and esterification with diazomethane of the acid thus produced led to α-(*o*-carbomethoxybenzamido)-2-phenyl-2-thiazolidineacetic acid β-lactam, a prototype of the penicillins. The infrared spectra of these analogs are similar to that of benzylpenicillin. The corresponding β-lactam-thiazolidine bearing a 3-nitrophthalimide substituent was also prepared and characterized.

The preceding communication[3] of this series described the synthesis of a group of α-acylamino monocyclic β-lactams. We are now reporting the preparation and reactions of several compounds containing the fused β-lactam-thiazolidine rings present in the β-lactam formula for the penicillins. In these compounds a rational synthesis of the combination of this ring system with an acylamino function alpha to the lactam carbonyl has been achieved for the first time.[4]

An important feature of the present work is the formation of a compound, by a synthesis specifically designed to yield a β-lactam, which undergoes two reactions (one of derivatization and one of degradation) exactly analogous to reactions of decisive significance in the chemistry of penicillin itself. Furthermore, the compound possesses an infrared spectrum in the critical range similar to that of benzylpenicillin.

Several reviews are available[5] which summarize the extensive efforts made during the war and early post-war periods toward the elucidation of the structure and the synthesis of the penicillins.

(1) This communication is from part of a thesis submitted by one of us (J. J. R.) to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of requirements for the Ph.D. degree, April, 1949.

(2) Bristol Laboratories Fellow, 1948–1949.

(3) J. C. Sheehan and J. J. Ryan, THIS JOURNAL, **73**, 1204 (1951).

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